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OPERATION INFORMATION

ONCOLOGY

GENERAL INFORMATION

THE 6TH DA NANG CITY CANCER PREVENTION CONFERENCE 2025

The 6th Da Nang City Cancer Prevention Conference will officially take place at Da Nang Oncology Hospital on April 24th and 25th, 2025. This scientific conference is organized biennially by Da Nang Oncology Hospital in collaboration with Vietnam Cancer Society, Vietnam National Cancer Hospital (Hanoi), Ho Chi Minh City Oncology Hospital, and other cancer prevention institutions nationwide. The event is expected to attract the participation of hundreds of experts, physicians, researchers, and medical units from across the country.

Cancer prevention plays a pivotal role in safeguarding public health. Measures such as early screening, adopting healthy lifestyles, and accessing advanced treatment methods can significantly reduce the risk of disease and increase survival rates for patients. The 2025 Cancer Prevention Conference will serve as an important forum for medical professionals, researchers, and policymakers to update information, exchange experiences, and share scientific research activities across clinical and paraclinical fields, as well as new advancements in epidemiology, screening, early detection, and specialized cancer treatment.

Approximately 600 delegates are expected to attend the conference, including leading healthcare experts, cancer specialists, representatives from Departments of Health, hospitals, universities, institutes, centers and other medical establishments nationwide. The conference will also welcome international oncology experts from countries such as Italy, South Korea, Japan and Taiwan.

The conference will focus on specialized oncology topics including "Gastrointestinal Lung Breast - Gynecological - Urological - Hematological Cancers, Radiation Therapy, Nuclear Medicine, Pathology, Molecular Biology, Nursing and Palliative Care". These themes will provide an overview of cancer prevention and control efforts in Vietnam, cancer diagnosis, treatment, patient care, as well as global medical advancements and treatment practices in developed countries such as Italy, South Korea, Japan and Taiwan.

There are 127 reporters with 161 scientific reports, both domestic and international. Through this conference, participants will gain new insights into treatment directions, appropriate research orientations, updated information, and new collaborative opportunities in cancer diagnosis and treatment contributing to the overall enhancement of cancer care quality.

RESULTS OF CHEMOTHERAPY PACLITAXEL - CARBOPLATI TREATMENT IN METASTATIC THYMIC CARCINOMA AT VIETNAM NATIONAL CANCER HOSPITAL

Bui Xuan Thang[1*], Nguyen Thi Thai Hoa[1], Vu Ha Thanh[1], Nguyen Thi Thuy Hang[1], Nguyen Van Cao[1], Doan Thi Tuyet[1], Dao Khanh Linh[1], Truong Cong Minh[1], Nguyen Tuan Anh[1], Le Xuan Ha[2]

ABSTRACT

Objective: Evaluation of clinical and paraclinical characteristics and treatment results of Paclitaxel-Carboplatin in metastatic thymic carcinoma at Vietnam National Cancer Hospital.

Subjects and Methods: A retrospective study with longitudinal follow-up on patients diagnosed with metastatic thymic carcinoma (AJCC 8th edition), treated with the Paclitaxel-Carboplatin chemotherapy regimen from 2020 to 2024 at Vietnam National Cancer Hospital.

Results: The study included 20 patients with an average age of 56.4 years; 65% were male and 35% were female. ECOG 0 accounted for 70% and ECOG 1 for 30%. The predominant histological type was squamous cell carcinoma (70%). The treatment results showed a response rate of 45% and a disease control rate (DCR) of 75%. The median progression-free survival (mPFS) was 8.7 months after a follow-up of 15.6 months. Hematologic toxicity related to the regimen included anemia in 55% of patients (grade 3 in 5%) and neutropenia in 55% (grade 3 in 10%). Non-hematologic toxicity was commonly observed in the peripheral nervous system (40%) and elevated AST/ALT levels (45%), mainly grades 1 and 2.

Conclusion: The combination of paclitaxel and carboplatin is an effective treatment option for metastatic thymic carcinoma in patients who have not previously received systemic therapy.

Keywords: Thymic carcinoma; Metastasis; Paclitaxel-Carboplatin.

1. INTRODUCTION

Thymic carcinoma is a rare malignant tumor located in the anterior mediastinum, accounting for approximately 5÷36% of all malignant thymic neoplasms[1-3]. Due to its rarity, only a limited number of patients have been analyzed in published studies to date. Complete surgical resection remains the most effective treatment, significantly improving survival. Chemoradiotherapy plays a supportive role postoperatively in some cases or is used when the disease is unresectable due to extensive local invasion. However, approximately 20÷30% of patients are diagnosed at advanced stages, with widespread metastasis, rendering local treatment unfeasible[4]. In such cases, systemic chemotherapy becomes crucial. Several studies have shown the efficacy of cisplatin-based combination therapies, such as ADOC (cisplatin, doxorubicin, vincristine,

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and cyclophosphamide) and CODE (cisplatin, vincristine, doxorubicin, and etoposide) in treating thymic tumors[5-6]. Although these regimens have shown promising response rates, most patients in those studies were diagnosed with thymoma rather than thymic carcinoma and high rates of severe toxicity were reported. In contrast, newer anticancer agents-such as irinotecan, paclitaxel, docetaxel, gemcitabine, and vinorelbine-developed in the 1990s exhibit different mechanisms of action from older agents like vindesine, vinblastine, and etoposide. As a result, platinum-based combination regimens with these newer agents have been proposed for epithelial-origin solid tumors, including thymic carcinoma. A phase II clinical trial conducted across 21 cancer centers in Japan between 2008 and 2011 evaluated paclitaxel-carboplatin in patients with stage IV thymic carcinoma. The trial reported an overall response rate of 36% and a median progression-free survival (PFS) of 7.5 months[7]. Another study conducted in China in 2014 reported a median PFS of 3.5 months and a median overall survival (OS) of 24 months[8].

To date, no studies in Vietnam have evaluated the treatment of metastatic thymic carcinoma. Therefore, we conducted this study with the following objectives:

- To assess the clinical and paraclinical characteristics of patients with metastatic thymic carcinoma treated with the paclitaxel–carboplatin regimen at Vietnam National Cancer Hospital.

- To evaluate the treatment outcomes in this patient group.

2. PATIENTS AND METHODS

2.1. Study subjects

A total of 20 patients with metastatic thymic carcinoma who received Paclitaxel-Carboplatin chemotherapy at Vietnam National Cancer Hospital from 2020 to 2024.

Inclusion criteria

Histologically confirmed thymic carcinoma, classified according to the 2015 WHO classification.

Stage IV disease based on the AJCC 8th edition.

Age ≥18 years.

ECOG performance status of 0 or 1.

No prior chemotherapy.

Received at least 2 cycles of the Paclitaxel Carboplatin regimen.

Adequate liver, renal and bone marrow function for chemotherapy.

Complete medical records available.

Exclusion criteria

Diagnosis of a second primary cancer.

Pregnant or breastfeeding women.

Presence of life-threatening comorbidities (e.g., decompensated heart, liver, or kidney failure).

Discontinuation of treatment for non-medical reasons (not due to disease progression or intolerance to side effects).

2.2. Research methods

Study design: Descriptive case series.

Sampling method: Convenience sampling of 20 patients.

3. RESULTS

3.1. Clinical and paraclinical characteristics

Patient Characteristics	N = 20 (%)
Age	
Average (X ± SD)	56,4 ± 8,7 (years)
Gender	
Male	13 (65%)
Female	7 (35%)

Performance Status (ECOG)	
PS 0	15 (75%)
PS 1	5 (25%)
Histopathology	
Squamous cell carcinoma	14 (70%)
Carcinoma, NOS	2 (10%)
Lymphoepithelioma-like carcinoma	1 (5%)
Large cell neuroendocrine carcinoma	1 (5%)
Disease Stage	
Stage IVA	8 (40%)
Stage IVB	12 (60%)
Myasthenia Status	
Present	1 (5%)
Absent	19 (95%)

Comment: The average age of patients was 56.4 years, with a male predominance (65%). The most common histological subtype was squamous cell carcinoma (70%). The most frequent metastatic sites were pleura, bone and lung. One patient (5%) was diagnosed with grade 2 myasthenia gravis.

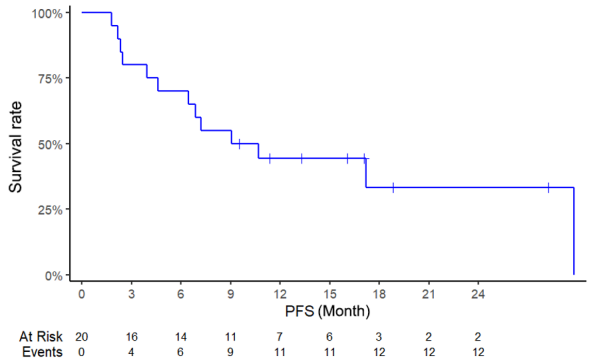
3.2. Treatment Outcomes

3.2.1. Overall response rate (ORR)

Response	N	%
Complete response	0	0
Partial response	9	45
Stable disease	6	30
Progressive disease	5	25
ORR (%)	45%	
DCR (%)	75%	

Comment: Partial response was achieved in 45% of patients, with stable disease observed in 30%. Disease progression occurred in 25% of patients. The overall response rate was 45%, and the disease control rate (partial response + stable disease) reached 75%.

3.2.2. Progression-free survival (PFS)



Comment: With a median follow-up duration of 15.6 months, the median progression-free survival (PFS) was 8.7 months.

3.2.3. Adverse events of the paclitaxel-carboplatin regimen

Toxicity	Adverse Events (%)				
	Total (n=20)	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic Toxicity					
Leukopenia	11 (55%)	6 (30%)	3 (15%)	2 (20%)	0
Neutropenia	8 (40%)	4 (20%)	2 (20%)	2 (20%)	0
Thrombocytopenia	4 (20%)	3 (15%)	1 (5%)	0	0
Anemia	11 (55%)	8 (40%)	2 (10%)	1 (5%)	0

Toxicity	Adverse Events (%)				
	Total (n=20)	Grade 1	Grade 2	Grade 3	Grade 4
Non-Hematologic Toxicity					
Peripheral Neuropathy	8 (40%)	7 (35%)	1 (5%)	0	0
Elevated AST/ALT	9 (45%)	7 (35%)	2 (10%)	0	0
Nausea/Vomiting	5 (25%)	4 (20%)	1 (5%)	0	0

Comment: The most commonly observed hematologic toxicities were anemia and leukopenia, predominantly at Grade 1–2. Thrombocytopenia was less frequent, and no cases of febrile neutropenia or bleeding due to thrombocytopenia were reported. Among non-hematologic toxicities, peripheral neuropathy and elevated liver enzymes (AST/ALT) were the most frequently encountered, mostly mild (Grade 1). Importantly, no Grade 4 toxicity was recorded in any of the patients.

4. DISCUSSION

Thymic carcinoma, particularly in its metastatic stage, presents a major therapeutic challenge, as patients are often ineligible for local treatments such as surgery or radiotherapy. Moreover, no standardized chemotherapy regimen has yet been established for this stage of the disease.

In our study, 20 patients diagnosed with metastatic thymic carcinoma were treated with the Paclitaxel carboplatin regimen. The average patient age was 56.4 years, with a predominance of male patients (65%). Histologically, squamous cell carcinoma was the most common subtype (70%), consistent with global epidemiological data on thymic carcinoma. Notably, our cohort also included one case of large cell neuroendocrine carcinoma and one case of lymphoepithelioma-like carcinoma, highlighting the histological heterogeneity in this rare malignancy. Histopathological subtype has been considered a key prognostic factor in thymic carcinoma, with squamous cell histology associated with better treatment responses, while other subtypes may be less sensitive to chemotherapy. In our series, pleural and pulmonary metastases were commonly observed, with 60% of patients classified as stage IVB, underscoring the aggressive and poor-prognosis nature of the disease. Additionally, one patient (5%) presented with myasthenia gravis (Grade 2), further complicating the clinical picture.

Our findings showed a partial response rate of 45%, which is higher than previously reported by Igawa (2010) and Lenma (2008), who documented partial response rates of 36% and 28%, respectively. Disease stabilization was observed in 30% of patients, and only 25% showed progressive disease, indicating encouraging disease control using the Paclitaxel carboplatin combination. However, no complete responses were achieved, reflecting the ongoing challenge in managing advanced thymic carcinoma.

The median progression-free survival (PFS) was 8.5 ± 1.0 months, aligning with prior studies, such as Furugen (2011) reporting 8.6 months, Igawa (2010) 7.9 months and Hirai (2015) 7.5 months.

Historically, anthracycline-based chemotherapy regimens were considered standard in treating thymic epithelial tumors, with Loehrer et al. reporting a 50% response rate and a median overall survival of 37.7 months in patients treated with PAC. However, cardiotoxicity, prior mediastinal radiation, advanced patient age, and comorbid pulmonary conditions have limited the use of anthracyclines, leading to increasing interest in non-anthracycline regimens, such as Paclitaxel carboplatin, which is now widely adopted. While response rates have not markedly

improved, these regimens offer better tolerability profiles.

In our study, the toxicity profile of the Paclitaxel carboplatin regimen was manageable. The most common hematologic adverse events were anemia and leukopenia, primarily Grade 1–2, with no cases of febrile neutropenia reported. Thrombocytopenia was less frequent, and no bleeding events were observed. Among non-hematologic toxicities, peripheral neuropathy and elevated AST/ALT levels were the most common, again primarily Grade 1. Importantly, no Grade 4 toxicity was recorded, suggesting an acceptable safety profile. These findings are consistent with previous studies, such as the Phase II multicenter trial by Hirai (2015) and the study by Song (2014), which reported similar toxicity patterns.

5. CONCLUSION

5.1. Clinical and paraclinical characteristics

Mean age: 56.4 ± 8.7 years, male (65%), female (35%), ECOG PS: 75% with PS 0, 25% with PS 1.

Histology: Predominantly squamous cell carcinoma (70%), Stage: 40% stage IVA, 60% stage IVB, myasthenia gravis was observed in one patient prior to treatment.

5.2. Treatment outcomes

Objective response rate (ORR): 45% (no complete responses), Disease control rate (DCR): 75%, Median progression-free survival (mPFS): 8.7 months.

Common toxicities: Hematologic: Leukopenia (40%), anemia (55%), mostly Grade 1–2; Non-hematologic: Peripheral neuropathy (40%), elevated AST/ALT (45%), mostly Grade 1–2.

REFERENCES

[1]. Hsu CP, Chen CY, Chen CL, et al. Thymic carcinoma. Ten years' experience in twenty patients. *J Thorac Cardiovasc Surg*. 1994;107(2):615-620.

[2]. Suster S, Rosai J. Thymic carcinoma. A clinicopathologic study of 60 cases. *Cancer*. 1991;67(4):1025-1032. doi:10.1002/1097-0142(19910215)67:4<1025::aid-cncr2820670427>3.0.co;2-f

[3]. Wick MR, Scheithauer BW, Weiland LH, Bernatz PE. Primary thymic carcinomas. *Am J Surg Pathol*. 1982;6(7):613-630. doi:10.1097/00000478-198210000-00003

[4]. Liu HC, Hsu WH, Chen YJ, et al. Primary thymic carcinoma. *Ann Thorac Surg*. 2002;73(4):1076-1081. doi:10.1016/s0003-4975(01)03607-4

[5]. Koizumi T, Takabayashi Y, Yamagishi S, et al. Chemotherapy for advanced thymic carcinoma: clinical response to cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC chemotherapy). *Am J Clin Oncol*. 2002;25(3):266-268. doi:10.1097/00000421-200206000-00012

[6]. Yoh K, Goto K, Ishii G ichiro, et al. Weekly chemotherapy with cisplatin, vincristine, doxorubicin, and etoposide is an effective treatment for advanced thymic carcinoma. *Cancer*. 2003;98(5):926-931. doi:10.1002/cncr.11606

[7]. Hirai F, Yamanaka T, Taguchi K, et al. A multicenter phase II study of carboplatin and paclitaxel for advanced thymic carcinoma: WJOG4207L. *Ann Oncol*. 2015;26(2):363-368. doi:10.1093/annonc/mdu541

[8]. Song Z. Chemotherapy with paclitaxel plus carboplatin for relapsed advanced thymic carcinoma. *Journal of Thoracic Disease*. 2014;6(12). doi:10.3978/j.issn.2072-1439.2014.11.18

[9]. Lemma GL, Lee JW, Aisner SC, et al. Phase II Study of Carboplatin and Paclitaxel in Advanced Thymoma and Thymic Carcinoma. *J Clin Oncol*. 2011;29(15):2060-2065. doi:10.1200/JCO.2010.32.9607

[10]. Loehrer PJ, Kim K, Aisner SC, et al. Cisplatin plus doxorubicin plus cyclophosphamide in metastatic or recurrent thymoma: final results of an intergroup trial. The Eastern Cooperative Oncology Group, Southwest Oncology Group, and Southeastern Cancer Study Group. *J Clin Oncol*. 1994;12(6):1164-1168. doi:10.1200/JCO.1994.12.6.1164

METASTASIS TO BREAST FROM OVARIAN CANCER CONCURRENTLY DIAGNOSIS: A RARE CASE REPORT AND REVIEW OF LITERATURE

Le Tri Chinh[1], Truong Van Hop[1,2*], Nguyen Thanh Long[1], Pham Van Quan[2], Tran Viet Hoang[1], Nguyen Ba Dat[1], Tran Thanh Long[1], Pham Thi Dieu Ha[1], Phung Thi Huyen[1], Nguyen Van Tuyen[1]

ABSTRACT

Metastasis of breast cancer originating from other organs is exceedingly uncommon, accounting for merely 0.33÷6.3% of malignant breast tumors, predominantly stemming from melanoma, sarcoma, lung cancer, and renal cancer. Compared to primary breast carcinoma, metastatic breast cancer generally has a less favorable prognosis. In clinical practice, precise identification of the primary organ is imperative for devising an optimal treatment regimen. Particularly, metastasis of ovarian cancer to the breast at the time of diagnosis is even more infrequent. This article delineates a clinical case illustrating the diagnosis and initial therapeutic outcomes of ovarian cancer metastasis to the breast and reviews pertinent features in the medical literature.

Key words: Ovarian cancer; breast metastasis.

1. INTRODUCTION

Metastasis to the breast from other organs is extremely rare, accounting for approximately 0.33–6.3% of all malignant breast tumors. Most of these cases originate from contralateral breast cancer, melanoma, sarcoma, lung cancer and renal cell carcinoma [1]. Metastasis to the breast from primary ovarian carcinoma is even rarer, with the first case reported globally in 1907 [2]. According to a study by Hadju and Urban on 4,051 patients with malignant breast tumors, the rate of tumors originating from female genital organs was 0.17%, and primary ovarian cancer accounted for only 0.07% [3]. The prognosis for breast metastases is typically very poor, and treatment approaches vary significantly depending on the site of the primary tumor. Therefore, accurate identification of the primary site is crucial for developing an appropriate treatment plan.

Typically, ovarian cancer spreads within the peritoneal cavity, as well as via the lymphatic and hematogenous routes. Common metastatic sites include the peritoneal cavity and retroperitoneal lymph nodes, while extra-abdominal organ metastases-especially to the breast-are rare. On average, breast metastases are detected about two years after the diagnosis of primary ovarian cancer [4]. Our case involves breast metastasis detected at the time of initial diagnosis, which is an extremely rare presentation globally.

Clinical Case

A 49-year-old female patient, PARA 2002, with no significant past medical history and no family history of cancer, presented to the hospital

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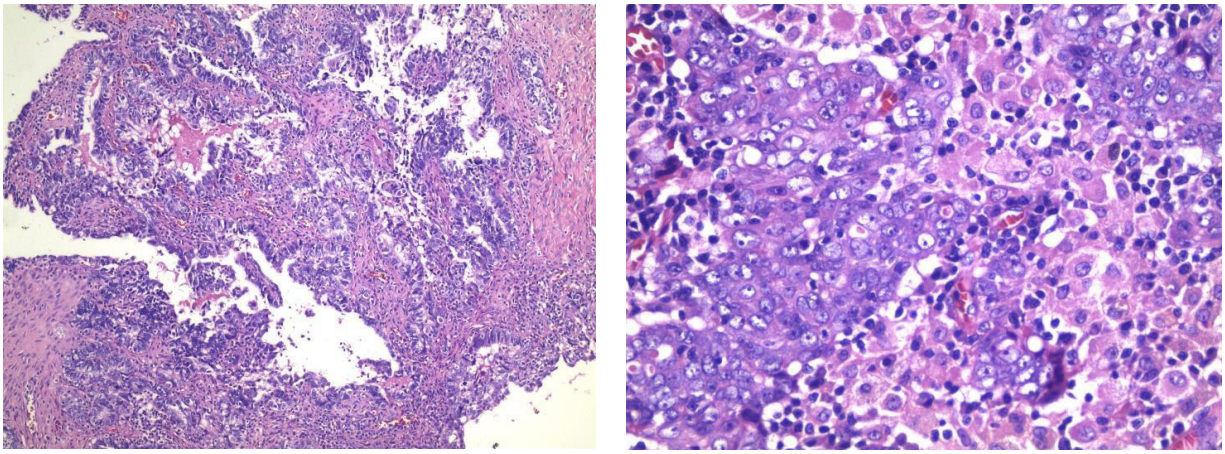
after detecting a lump in her left breast. Clinical examination revealed a firm, poorly mobile mass in the upper outer quadrant of the left breast, measuring 3×3 cm. Additionally, a firm left inguinal lymph node measuring 3×4 cm was palpated. No abnormalities were noted in other organs. Breast ultrasound and mammography revealed a 29×25 mm mass classified as BIRADS 4B. A 6 mm left axillary lymph node was observed with preserved hilar structure.



Microscopic image of the lesion in the right ovarian tumor

Cytological analysis showed malignant epithelial cells in both the left breast tumor and left inguinal lymph node, while the left axillary lymph node was benign. A biopsy of the left breast tumor and left inguinal lymph node was performed. Histopathological results indicated grade III invasive carcinoma in the breast and metastatic carcinoma in the inguinal lymph node. The initial diagnosis was left breast cancer with metastasis to the left inguinal lymph node. To assess metastases in other areas, the patient underwent a whole-body CT scan and bone scintigraphy. Imaging revealed a well-defined right ovarian mass measuring 38×52 mm. Multiple enlarged lymph nodes were observed along the abdominal aorta, bilateral pelvic vessels, and left groin, with the largest measuring 39×52 mm and showing loss of hilar architecture. No abnormalities were found in other regions. Gastroscopy and colonoscopy were also performed and yielded normal results. At this point, three differential diagnoses were considered: (1) Primary breast cancer, (2) Primary ovarian cancer, (3) Synchronous primary cancers of both the breast and ovary. To distinguish between these possibilities, immunohistochemistry (IHC) was performed on both the left breast tumor and the left inguinal lymph node specimens. Results showed both lesions were positive for estrogen receptor (ER), negative for progesterone receptor (PR), negative for human epidermal growth factor receptor 2 (HER2), positive for GATA binding protein 3 (GATA3), positive for p53, positive for Wilms' tumor 1 (WT1), and positive for paired box gene 8 (PAX8). This immunoprofile is consistent with high-grade serous carcinoma of ovarian origin. Thus, the definitive diagnosis was stage IV ovarian carcinoma with metastases to the left breast, pelvic lymph nodes, para-aortic lymph nodes, and left inguinal lymph node.

The patient received neoadjuvant chemotherapy with a regimen of Paclitaxel 175 mg/m² and Carboplatin AUC 5, administered every three weeks for three cycles. This regimen is known to be effective against both breast cancer and ovarian cancer. After three cycles, the left breast tumor decreased in size from 29×25 mm to 7×11 mm;

multiple lymph nodes along the para-aortic, bilateral pelvic chains, and left inguinal region (initially up to 39×53 mm) were reduced to 16×19 mm; the right ovarian mass decreased from 38×52 mm to 33×35 mm; and the tumor marker CA125 declined significantly from 2,817 U/mL to 57.3 U/mL.

The patient was evaluated as having a partial response to neoadjuvant chemotherapy and was subsequently indicated for interval debulking surgery. Intraoperative findings included: A left breast lesion measuring 1×2 cm, cystic and degenerative in nature; A left inguinal lymph node measuring 1.5×2 cm, firm; A right ovarian tumor measuring 3×4 cm; Peritoneal implants in the pelvic cavity with nodular masses up to 2 cm in size; Enlarged, soft bilateral pelvic and para-aortic lymph nodes measuring 1–2 cm. The diaphragmatic peritoneum, paracolic gutters, and mesentery appeared smooth and uninvolved. The patient underwent the following procedures: Total hysterectomy, Bilateral salpingo-oophorectomy, Omentectomy, Pelvic peritonectomy, Excision of the left inguinal lymph node, Left breast tumor resection. Postoperative histopathology findings: The right ovarian tumor was confirmed to be high-grade serous carcinoma, grossly presenting as a thin-walled cystic lesion containing yellowish fluid, measuring 5×3.5×3 cm. Microscopic examination showed tumor cells arranged in solid sheets and papillary structures, with areas of degeneration. Metastatic carcinoma was identified in the right pelvic, para-aortic and left inguinal lymph nodes, with some areas showing signs of tumor degeneration. No residual malignancy was detected in the left breast tumor or pelvic peritoneum. The greater omentum, left adnexa, and entire uterus were free of tumor cells. Postoperative recovery was uneventful. The patient is currently planned for adjuvant therapy following surgery.

2. DISCUSSION

Malignant breast tumors are predominantly primary breast carcinomas, with most secondary breast malignancies originating from the contralateral breast [5]. Advanced-stage ovarian cancer typically presents with widespread peritoneal involvement or retroperitoneal lymph node metastasis within the abdominal cavity. Distant metastases are rare, though the disease can occasionally spread to the liver, pleura, and lungs, with such cases generally associated with poor prognosis [6].

Metastasis of primary ovarian cancer to the breast is extremely rare. In a study of 4,051 patients with breast malignancies, the incidence of ovarian cancer metastasizing to the breast was only 0.07% [3]. Since the first reported case by Sitzenfrey in 1907 [2], a literature review by Tempfer et al. in 2016 identified over 110 reported cases [7], and by 2020, the number had increased to 120 cases, according to Caruso et al [8].

Unilateral breast involvement is more common than bilateral metastases in ovarian cancer. In our case, metastasis was confined to the left breast. According to a 2022 study by Arif Musa et al., only 10 cases of bilateral breast metastases from primary ovarian cancer have been reported.

The median time to breast metastasis detection after a primary ovarian cancer diagnosis is approximately two years. In contrast, our patient presented with breast metastasis at the time of initial diagnosis, which is extremely rare. According to Ferrari et al. (2020), only 18 cases of synchronous breast metastases at the time of ovarian cancer diagnosis had been reported [4].

Our case was histopathologically identified as high-grade serous carcinoma (HGSC) of the ovary. This histological subtype accounts for approximately 72% of ovarian cancer metastases to the breast, according to Antuono et al. [2]. Among the patients in the Ferrari study with breast metastases at the time of ovarian cancer diagnosis, 61% were HGSC [4].

Differentiating between primary and metastatic breast tumors is crucial, as it directly impacts both prognosis and treatment strategies. Typically,

metastatic breast tumors present as well-defined masses without architectural distortion, as was seen in our case. On mammography, metastatic lesions often appear as solid, well-circumscribed masses without spiculations or skin retraction. On ultrasound, ovarian metastases to the breast may show lobulated margins, well-defined borders, and posterior acoustic enhancement. Due to the psammoma bodies (calcifications) seen in ovarian carcinoma, calcifications on imaging may not reliably distinguish primary breast cancer from ovarian metastases [2].

Histopathology and immunohistochemistry (IHC) are critical in differentiating between primary breast carcinoma and ovarian metastasis to the breast. Both tumors are commonly positive for cytokeratin 7 and estrogen receptor (ER). Wilms' tumor 1 (WT1) nuclear expression is present in about 70% of ovarian carcinomas, but in less than 10% of breast cancers. Paired box gene 8 (PAX8) is another useful marker, being positive in 87% of ovarian cancers and consistently negative in breast cancers. Both primary and metastatic breast tumors may show GATA3 positivity in 80–90% of cases, though this rate is lower in triple-negative breast cancers (around 67%). GATA3 can also be expressed in 86% of urothelial carcinomas but is rarely seen in ovarian cancers. p53 mutation marker, frequently positive in ovarian carcinoma, is a key factor in distinguishing the origin of the malignancy [9]. In our case, IHC staining showed positivity for ER, PAX8, WT1, GATA3, and mutant p53, supporting a diagnosis of metastatic ovarian serous carcinoma.

Our patient underwent three cycles of neoadjuvant chemotherapy, with a partial clinical response, followed by maximal cytoreductive surgery, and is planned to continue with adjuvant chemotherapy. According to various studies, the overall survival following diagnosis of breast metastasis from ovarian carcinoma is limited, ranging from 13 days to 3.5 years, with most patients succumbing to the disease within one year [10].

3. CONCLUSION

This is an extremely rare clinical case of ovarian cancer metastasizing to the breast, identified at the time of initial diagnosis a phenomenon seldom reported both in Vietnam and globally. Accurate determination of the primary site of metastasis is of paramount importance, as it directly influences the patient's prognosis and therapeutic strategy. Diagnosis should be based on a combination of clinical presentation, radiological findings, and, most critically, the use of histopathology and immunohistochemistry, which play a pivotal role in establishing a definitive diagnosis and distinguishing between primary breast cancer and metastasis from ovarian origin.

REFERENCES

[1]. Abbas, J. and associates (2013), I*ntramammary metastases: comparison of mammographic and ultrasound features*, Eur J Radiol. 82(9), tr. 1423-30.

[2]. Caruso, G. and associates (2020), *Ovarian Cancer Metastasis to the Breast: A Case Report and Review of the Literature*, Case Rep Oncol. 13(3), tr. 1317-1324.

[3]. Cormio, G. and associates (2003), *Distant metastases in ovarian carcinoma*, Int J Gynecol Cancer. 13(2), tr. 125-9.

[4]. Dueno, S. and associates (2024), *Metastasis of serous ovarian carcinoma to the breast: a case report and review of the literature*, J Med Case Rep. 18(1), tr. 127.

[5]. Ferrari, F. and associates (2020), *Extra-abdominal ovarian cancer presenting with breast metastases at diagnosis: Case report and literature review*, Eur J Obstet Gynecol Reprod Biol. 255, tr. 211-221.

[6]. Klein, R. L. and associates. (2010), *Ovarian cancer metastatic to the breast presenting as inflammatory breast cancer: a case report and literature review*, J Cancer. 1, tr. 27-31.

[7]. Lee, A. H. (2007), *The histological diagnosis of metastases to the breast from extramammary malignancies*, J Clin Pathol. 60(12), tr. 1333-41.

[8]. Moore, D. H. and associates (1998), *Gynecologic cancers metastatic to the breast*, J Am Coll Surg. 187(2), tr. 178-81.

[9]. Musa, A. and associates (2022), *Metastatic spread of serous ovarian carcinoma to the bilateral breasts: a rare presentation*, BMJ Case Rep. 15(11).

[10]. Tempfer, C. B. and associates (2016), *Metastasis of ovarian cancer to the breast: A report of two cases and a review of the literature*, Oncol Lett. 11(6), tr. 4008-4012.

GAMMA KNIFE STEREOTACTIC RADIOSURGERY COMBINED WITH TARGETED THERAPY FOR BRAIN METASTASES IN NON-SMALL CELL LUNG CANCER WITH EGFR GENE MUTATIONS

Phan Thanh Duong*, Nguyen Duc Lien

ABSTRACT

Objectives: Our study aims to evaluate the outcome of Gamma Knife radiosurgery combined TKIs for brain metastasis of non-small cell lung cancer with EGFR gene mutations.

Methods: We analyzed 35 patients with brain metastatic non-small cell lung cancer with EGFR gene mutations from July 2019 to May 2024. Selected patients have brain metastases from 1 to 10 tumors, size ≤ 3cm, KPS score ≥ 60, EGFR gene mutation, first-generation TKI treatment. Patients were treated by stereotactic radiosurgery using Leksell Gamma Knife ICON unit (Elekta AB) with dose of 20 – 24, 18 – 20Gy for lesions measuring < 2, 2.1 – 3 cm, respectively. Patients take st generation TKIs (erlotinib or gefitinib) 1 tablet per day. Patients were assessed for clinical symptoms and imaging response according to RANO criteria at 6, 12 months and survival outcomes.

Results: In our study, cerebral progression-free survival rate at 12 months was 100%, 24 months was 65,6%. Overall survival rate at 12 months was 84%, 24 months was 57,9%, overall survival time was 28 ± 3,7 months.

Conclusion: Combination Gamma Knife radiosurgery with TKIs is an effective treatment for brain metastasis of non-small cell lung cancer with EGFR gene mutations.

Key words: Radiosurgery; brain metastases; non-small cell lung cancer; EGFR gene mutations; TKIs.

1. INTRODUCTION

Lung cancer (LC) is one of the most common malignancies and remains the leading cause of cancer-related death worldwide. According to the International Agency for Research on Cancer (IARC), in 2018, there were approximately 2.09 million new cases and 1.76 million deaths globally. In Vietnam, these figures were estimated at 23.67 thousand new cases and 20.71 thousand deaths[1]. A characteristic feature of advanced-stage lung cancer is its tendency to metastasize to the brain, with approximately 10% of patients diagnosed with advanced non-small cell lung cancer (NSCLC) presenting with brain metastases[2]. Among NSCLC patients, those with brain metastases tend to have a higher rate of EGFR mutations compared to patients without brain metastases. Conversely, among NSCLC patients with EGFR mutations, the incidence of brain metastases (70%) is significantly higher than in the EGFR wild-type group[3]. Historically, brain metastases were considered a poor prognostic factor, with patients rapidly

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deteriorating due to neurological symptoms and having a median overall survival of only 4-6 weeks without treatment. However, with advancements in medical science particularly the emergence of targeted therapies for patients with genetic mutations and the development of local treatments such as stereotactic radiosurgery (SRS), treatment outcomes have markedly improved in terms of both survival and symptom control. Our study aims to evaluate the treatment outcomes of non-small cell lung cancer patients with EGFR mutations and brain metastases treated with a combination of stereotactic radiosurgery and tyrosine kinase inhibitors (TKIs).

2. SUBJECTS AND RESEARCH METHODS

2.1. Study Subjects

2.1.1. Inclusion Criteria

- Non-small cell lung cancer (NSCLC) with brain metastases.

- Number of brain metastatic lesions: 1-10, with each lesion's maximum diameter ≤ 3 cm.

- Presence of EGFR mutation.

- Karnofsky Performance Status (KPS) ≥ 60.

- First-time stereotactic radiosurgery (SRS).

- Liver, kidney and bone marrow functions within acceptable limits.

2.1.2. Exclusion criteria

- Patients previously treated with whole-brain radiotherapy.

- Patients who underwent surgical resection of brain metastases.

- Patients with co-existing cancers or severe acute/chronic illnesses with near-term mortality risk.

2.1.3. Study Period and location

- Study period: From July 2019 to May 2024.

- Location: Vietnam National Cancer Hospital, Vietnam.

2.2. Research Methods

2.2.1. Study design

- Clinical interventional study without a control group.

2.2.2. Sample size

- Convenience sampling method.

- A total of 35 patients were included in the study.

2.2.3. Study procedure

- Patients underwent clinical examination and laboratory testing before treatment

- Stereotactic radiosurgery (SRS) was performed using the Leksell Gamma Knife ICON system (Elekta AB, Sweden). Radiation dose based on RTOG 90-05 protocol, depending on tumor size, number, and location:

+ < 2 cm: 20-24 Gy;

+ 2–3 cm: 18-20 Gy.

- Patients were treated with tyrosine kinase inhibitors (TKIs):

- Erlotinib (Tarceva): 150 mg, 1 tablet/day.

- Or Gefitinib (Bigefinib, Iressa): 250 mg, 1 tablet/day.

- Duration of TKI treatment: minimum of 3 months.

- Follow-up assessment every 3 months: MRI (or contrast-enhanced CT) of the brain, contrast-enhanced CT of the chest and abdomen.

2.2.4. Evaluation Criteria

- Tumor response: assessed based on RANO (Response Assessment in Neuro-Oncology) criteria.

+ Complete Response: all lesions disappear, no corticosteroids required, non-target lesions resolved, clinical condition stable or improved

+ Partial Response: ≥30% reduction in total diameter of target lesions, non-target lesions non-progressive, corticosteroid dose stable or reduced, clinical condition stable or improved

+ Stable Disease: reduction in target lesion size <30% or increase <20%, non-target lesions non-progressive, corticosteroid dose stable or reduced, clinical condition stable or improved

+ Progressive Disease: any of the following: ≥20% increase in target lesion size, progression in non-target lesions, appearance of new lesions, worsening clinical condition.

- Survival analysis: Kaplan–Meier method: OS (Overall Survival), iPFS (Intracranial Progression-Free Survival).

+ Key time points:

• Date of Gamma Knife SRS initiation.

• Date of disease progression per objective response.

• Date of death.

• Date of last follow-up.

• End of study date.

+ Overall Survival (OS): time from treatment initiation to either death or last follow-up.

+ Intracranial Progression-Free Survival (iPFS): time from treatment initiation to brain metastasis progression (increased lesion size or new lesions).

2.3. Data Processing

- All data were coded and processed using SPSS version 20.0.

- Descriptive statistics included mean, median, standard deviation, minimum and maximum values.

- Comparisons of proportions were performed using the Chi-square (χ^2) test.

- Statistical significance was considered at $p < 0.05$.

3. RESULTS

3.1. Patient Characteristics

Table 1. Patient Characteristics

Variable	Result
Total number of patients	35
Age	
Mean	57,5 ± 9,1
Range	32 - 71
Gender	
Male	18 (51,4%)
Female	17 (48,6%)
Neurological symptoms	
Present	27 (77,1%)
Absent	8 (22,9%)
Karnofsky Performance Status	
≥ 90	21 (60%)
≤ 80	14 (40%)
Number of brain metastases	
1 lesion	11 (31,4%)
2 - 5 lesions	20 (57,1%)
6 - 10 lesions	4 (11,4%)
Extracranial metastases	
Present	14 (40%)
Absent	21 (60%)

Remarks: The mean age of the study population was 57.5±9.1 years. The male-to-female ratio was 1.06. A total of 27 patients (77.1%) presented with neurological symptoms. Karnofsky Performance Status (KPS) was ≥ 90 in 21 patients (60.0%). Brain metastases were limited to a single lesion in 31.4% of patients. The rate of extracranial metastases was 40%.

3.2. Treatment Outcomes

3.2.1. Overall Survival (OS)

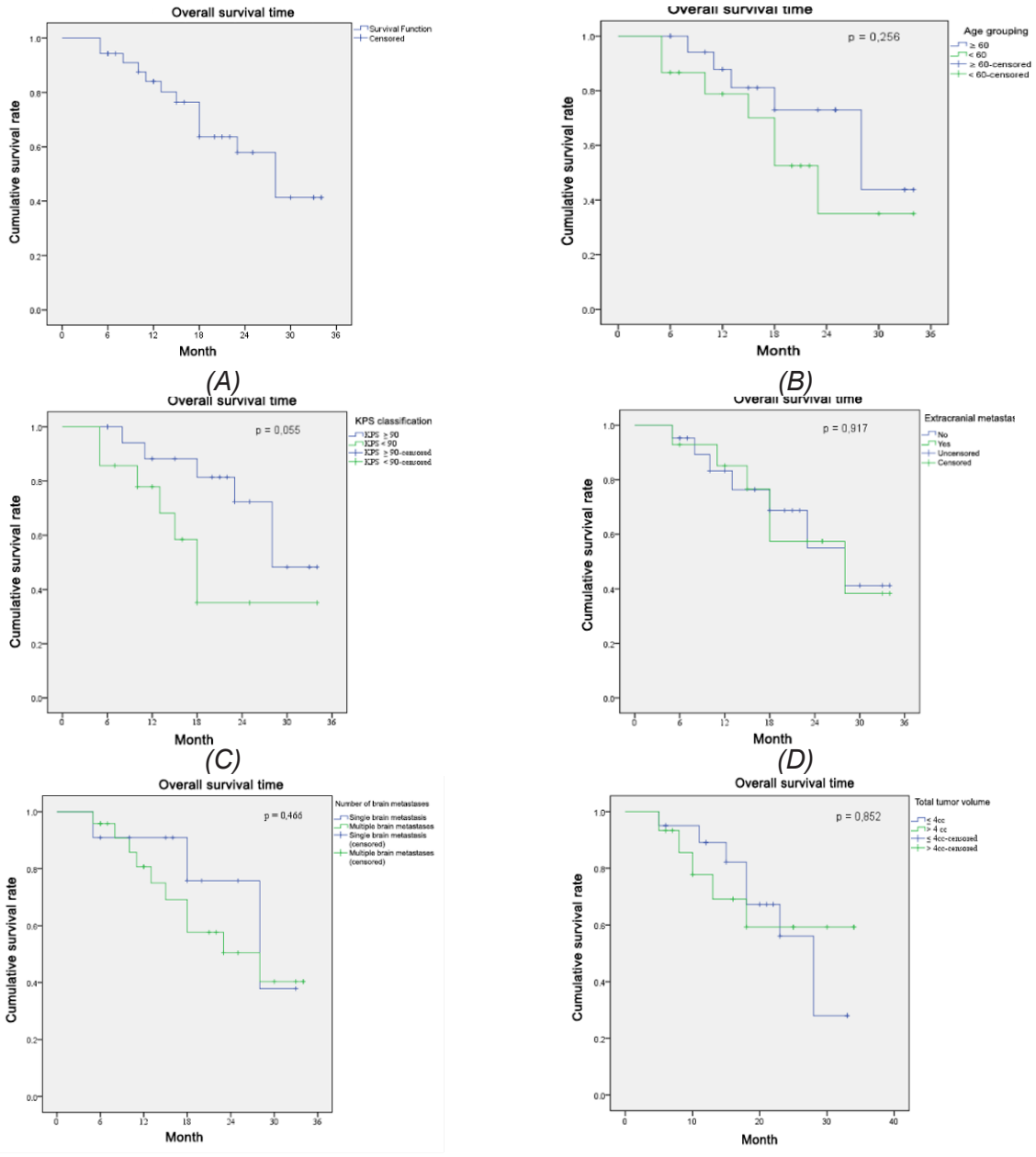
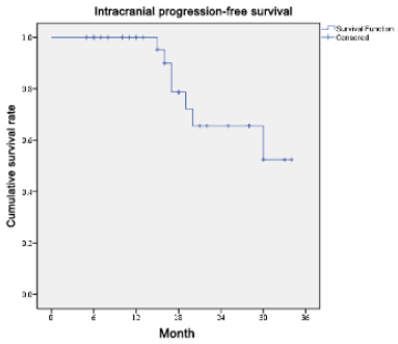


Figure 1. Overall survival (A) and associated factors. (B) Survival by age. (C) Survival by karnofsky performance status (KPS). (D) Survival by presence of extracranial metastases. (E) Survival by number of brain metastases. (F) Survival by total tumor volume

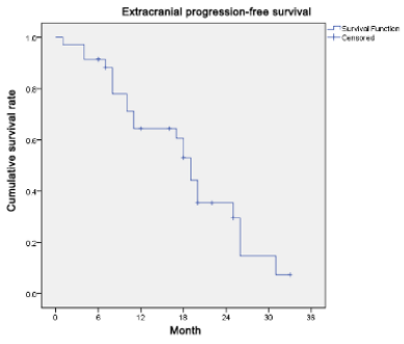
Comments: The median overall survival was 28 ± 3.7 months. The overall survival rates were 84% at 12 months and 57.9% at 24 months. There was no statistically significant association between overall survival and the following factors: Age, Karnofsky Performance Status (KPS), Presence of extracranial metastases, Number of brain metastases, Total tumor volume.

3.2.2. Progression-Free Survival (PFS)

Observation: The median intracranial progression-free survival was 27.8 ± 1.9 months. The intracranial PFS rates at 12 months and 24 months were 100% and 65.6%, respectively. The median extracranial progression-free survival was 19 ± 1.2 months. The extracranial PFS rates at 12 months and 24 months were 64.4% and 35.4%, respectively.



(G)



(H)

Figure 2. Progression-Free Survival: (G) Intracranial. (H) Extracranial

4. DISCUSSION

The main treatment strategies for brain metastases include surgery, whole-brain radiotherapy (WBRT), and stereotactic radiosurgery (SRS), used either alone or in combination. To date, the optimal treatment strategy remains a matter of debate. Since the advent of first-generation TKIs, brain metastases from lung cancer have become a major focus of therapeutic research. It is undeniable that TKIs with their advantages of low molecular weight, favorable lipid/water ratio, and good permeability have achieved significant results in treating brain metastases compared to traditional therapies. Some authors suggest that TKIs can be used as a standard initial treatment for asymptomatic brain metastases in EGFR-mutant NSCLC patients, with radiotherapy reserved for symptom onset or disease progression. In contrast, other studies support early combination with local therapies such as radiotherapy to improve local control, alleviate local symptoms, enhance the depth of systemic treatment, and thereby extend patient survival[4]. A major concern raised in previous studies is the adverse cognitive effects associated with radiotherapy, especially WBRT. However, most of those studies involved WBRT. The combination of stereotactic radiosurgery and TKIs offers a promising treatment strategy that enhances local control, prolongs survival and minimizes adverse effects.

Regarding intracranial control, Oda's study reported distant brain metastasis recurrence rates of 34% at 1 year and 53% at 2 years, with local control rates of 97% and 95% at 1 and 2 years, respectively[5]. Another study by Dohm on 174 NSCLC patients with brain metastases treated with SRS within 3 months of systemic therapy initiation showed significantly improved intracranial control with TKIs compared to conventional chemotherapy (HR = 0.4; 95% CI: 0.25–0.76; p = 0.04) and also when SRS was given prior to systemic therapy (HR = 0.6; 95% CI: 0.3–0.9; p = 0.03). Local control also improved significantly when patients received SRS prior to (HR = 0.4; 95% CI: 0.2–0.9; p = 0.03) or concurrently with (HR = 0.3; 95% CI: 0.1–0.6;

p = 0.003) systemic therapy[6]. These results are consistent with our findings and other reports, indicating improved control of distant brain metastases when SRS is administered before or during TKI therapy. In our study, intracranial progression-free survival was 100% at 12 months and 65.6% at 24 months.

A 2018 retrospective study by Yomo et al. on 133 EGFR-mutant lung adenocarcinoma patients with brain metastases treated with Gamma Knife SRS followed by TKIs reported 1- and 2-year overall survival (OS) rates of 74% and 52%, respectively, with a median OS of 24.8 months. These results are significantly better than earlier studies, suggesting an increase in survival from 7 months (1985-2005) to 12 months (2006-2014)[5]. Another multi-center retrospective analysis by Magnuson et al. on 351 EGFR-mutant NSCLC patients with brain metastases compared groups treated with SRS followed by TKIs, WBRT followed by TKIs, or TKIs followed by either SRS or WBRT upon progression. The best OS was observed in the group receiving SRS followed by TKIs, with a median survival of 44 months, while avoiding the cognitive decline associated with WBRT[7]. The survival outcomes in our study are consistent with these findings. The 1- and 2-year OS rates were 84% and 57.9%, respectively, with a median OS of 28 months.

5. CONCLUSION

Gamma Knife radiosurgery combined with TKIs is an effective treatment approach for patients with EGFR-mutant non-small cell lung cancer.

REFERENCES

[1]. GOLOBOCAN. Incidence, Mortality and Prevalence by cancer site.

[2]. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 15 2004;22(14):2865-72. doi:10.1200/JCO.2004.12.149

[3]. Ge M, Zhuang Y, Zhou X, Huang R, Liang X, Zhan Q. High probability and frequency of EGFR mutations in non-small cell lung cancer with brain metastases. *Journal of neuro-oncology*. Nov 2017;135(2):413-418. doi:10.1007/s11060-017-2590-x

[4]. Zhuang H, Shi S, Chang JY. Treatment modes for EGFR mutations in patients with brain metastases from non-small cell lung cancer: controversy, causes, and solutions. *Translational lung cancer research*. Aug 2019;8(4):524-531. doi:10.21037/tlcr.2019.07.03

[5]. Yomo S, Oda K. Impacts of EGFR-mutation status and EGFR-TKI on the efficacy of stereotactic radiosurgery for brain metastases from non-small cell lung adenocarcinoma: A retrospective analysis of 133 consecutive patients. *Lung cancer*. May 2018;119:120-126. doi:10.1016/j.lungcan.2018.03.013

[6]. AE D, J T, MN M, et al. Clinical Outcomes of Non-Small Cell Lung Cancer Brain Metastases Treated with Stereotactic Radiosurgery and Immune Checkpoint Inhibitors, EGFR Tyrosine Kinase Inhibitors, Chemotherapy and Immune Checkpoint Inhibitors, or Chemotherapy Alone. *Int J Radiat OncolBiolPhys*. 2021;111(3, Supplement):567.

[7]. Magnuson WJ, Lester-Coll NH, Wu AJ, et al. Management of Brain Metastases in Tyrosine Kinase Inhibitor-Naive Epidermal Growth Factor Receptor-Mutant Non-Small-Cell Lung Cancer: A Retrospective Multi-Institutional Analysis. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. Apr 1 2017;35(10):1070-1077. doi:10.1200/JCO.2016.69.7144

SURVIVAL OUTCOMES AND SOME RELATED FACTORS IN THE TREATMENT OF RELAPSED/REFRACTORY B-CELL NON-HODGKIN LYMPHOMA WITH R-GEMOX REGIMEN AT VIETNAM NATIONAL CANCER HOSPITAL

Do Huyen Nga[1*], Hoang Thi Tra My[1,2], Le Phong Thu[2], Nguyen Thanh Tung[1]

ABSTRACT

Objective: To evaluate the survival outcomes and some related factors of R-GEMOX chemotherapy regimen in the treatment of relapsed/refractory B-cell non-Hodgkin lymphoma at Vietnam National Cancer Hospital from 2019 to 2024.

Subjects and methods: A cross-sectional descriptive study was conducted on 83 patients with relapsed/refractory B-cell non-Hodgkin lymphoma treated with RGEMOX regimen at the Hematologic oncology department, Vietnam National Cancer Hospital from May 2019 to June 2024. Results: The average age was 59.9; the male/female ratio was 1; The overall response rate was 51.8%, of which the complete response rate was 20.5%; partial response was 31.3%; The rate of stable disease was 4.8%; the rate of progression disease was 43.4%; The median progression-free survival of the study was 13 months. The median overall survival of the study was 21 months. Refractory was an independent prognostic factor for PFS ($p<0.05$) and response after treatment was an independent prognostic factor for progression-free survival and overall survival with $p<0.001$.

Conclusion: R-GEMOX regimen prolongs progression-free survival as well as overall survival and is safe for patients with relapsed/refractory B-cell non-Hodgkin lymphoma without high-dose chemotherapy indications.

Key words: R/R NHL (Relapsed/Refractory B-cell non-Hodgkin lymphoma).

1. INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is a group of malignant neoplasms of lymphoid tissue. This is one of the most common cancers in the world as well as in Vietnam. According to the report of the Global Cancer Organization (GLOBOCAN) in 2020, the age-standardized incidence of NHL in both sexes in the world is 5.8/100,000 people. The disease ranks 11th among cancers in the world. In Vietnam, the age-standardized incidence rate for both sexes is 10.07/100,000 people and is one of the 13 most common cancers today. NHL is one of the cancers that can be cured. With the advancement of diagnostic methods of pathology, immunohistochemistry, cell biology, and molecular biology, it has helped to classify histopathological types in detail and accurately. With the development of treatment methods such as chemotherapy, radiotherapy, monoclonal antibodies, some forms of NHL can be cured with a 5-year survival rate of 30-

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55%. However, a significant proportion of patients are still resistant to treatment or relapse after initial treatment.

Multi-chemotherapy is a major step forward in the treatment of relapsed/refractory non-Hodgkin lymphoma. To date, high-dose chemotherapy (HDT) with hematopoietic stem cell transplantation is the treatment of choice for patients with relapsed/refractory rapidly progressive non-Hodgkin lymphoma that is sensitive to chemotherapy[1]. For relapsed/refractory indolent non-Hodgkin lymphoma, this approach also appears superior to conventional salvage chemotherapy[2]. The R-GEMOX regimen was created as a lifesaver for patients with relapsed/refractory B-cell non-Hodgkin lymphoma who are not eligible for high-dose chemotherapy. The unique synergistic effects and toxicity profiles of rituximab, gemcitabine, and oxaliplatin (R-GemOx) suggest that combination regimens containing these three agents may have advantages in the treatment of relapsed/refractory B-cell non-Hodgkin lymphoma compared with conventional regimens in terms of efficacy, safety, and tolerability[3,4].

2. SUBJECT AND STUDY METHOD

2.1. Subject

a. Selection criteria

All patients diagnosed with relapsed/refractory B-cell non-Hodgkin lymphoma at Vietnam National Cancer Hospital met the following selection criteria:

- From 18 years old with a diagnosis of relapsed/refractory non-Hodgkin lymphoma (Relapsed disease is when the disease progresses again after achieving a complete response for at least 6 months/ refractory disease is when the disease does not respond to the most recent treatment regimen).

- Immunohistochemistry results confirm the diagnosis of non-Hodgkin lymphoma, CD 20 (+).

- Not meeting the criteria or refusing high-dose chemotherapy + stem cell transplantation.

- Liver and kidney function and blood count tests are at the threshold allowing treatment.

- Patients agree to receive chemotherapy with the R-GEMOX regimen.

b. Exclusion criteria

- Signs of active HBV, HCV, HIV.

- Toxicity ≥ grade 3 due to previous chemotherapy.

- Pregnant or lactating women.

2.2. Study method

A cross-sectional prospective study was conducted on 83 patients with relapsed/refractory B-cell non-Hodgkin lymphoma from May 2019 to June 2024 at the Hematologic Oncology Department - Vietnam National Cancer Hospital.

Treatment regimen: R-GEMOX[5].

Drug	Dose	Route	Day
Rituximab	375 mg/m^2	IV	1 +15
Gemcitabine	1000 mg/m^2	IV	1 + 15
Oxaliplatin	100 mg/m^2	IV	1 + 15
Frequency: 28 days **Cycles:** 6			

2.3. Data analysis and research ethics

The information was encoded and processed using SPSS 23.0 software.

The study was approved by the Ethics Council of Thai Nguyen University of Medicine and Pharmacy and approved by the Ethics Council of Vietnam National Cancer Hospital.

3. RESULT

Table 1. General characteristics of research subjects

Characteristics		n	%
Age	≤ 40	8	9.6
	41 - 60	29	34.9
	61 - 75	42	50.6
	>75	4	4.8
Sex	Men	41	49.4
	Female	42	50.6
ECOG	0	43	51.8
	1	38	45.8
	2	2	2.4
B symptom	Yes	16	19.3
Extranodal lesion		38	45.8
Size of lesion	Median (min - max) cm	4.2 (1-16)	
Bulky > 7,5 cm		17	20.5

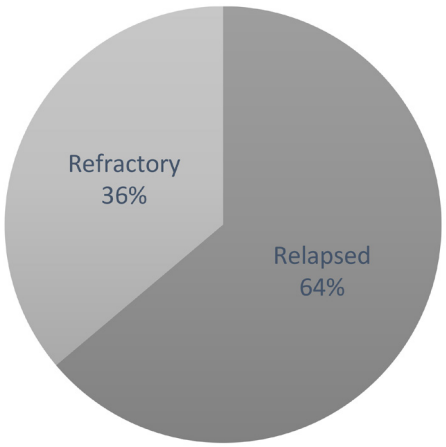


Figure 1. Relapsed and refractory rates

Comment: Of the 83 patients studied, 64% relapsed and 36% were refractory to previous regimens.

Table 2. Interim and End-of-treatment response rate

Response Category (n=83)	Interim n (%)	End-of-treatment n (%)
Complete response (CR)	13 (15.7)	17 (20.5)
Partial response (PR)	54 (65.1)	26 (31.3)
Stable disease (SD)	3 (3.6)	4 (4.8)
Progression disease (PD)	13 (15.7)	36 (43.4)
Overall response rate (CR+PR)	67 (80.8)	43 (51.8)

Comments: At the interim assessment, 13 patients had complete response (15.7%), partial response (65.1%). 13 patients progressed, and 3 patients did not respond (19.3%). At the end-of-treatment assessment, the complete response rate was 20.5%; partial response rate was 31.3%, and 43.4% of patients progressed.

Progression-free survival and overall survival

In our study, the average follow-up time was 18.3 months (shortest 1 month, longest 48 months), 56 patients had recurrence and 45 patients died.

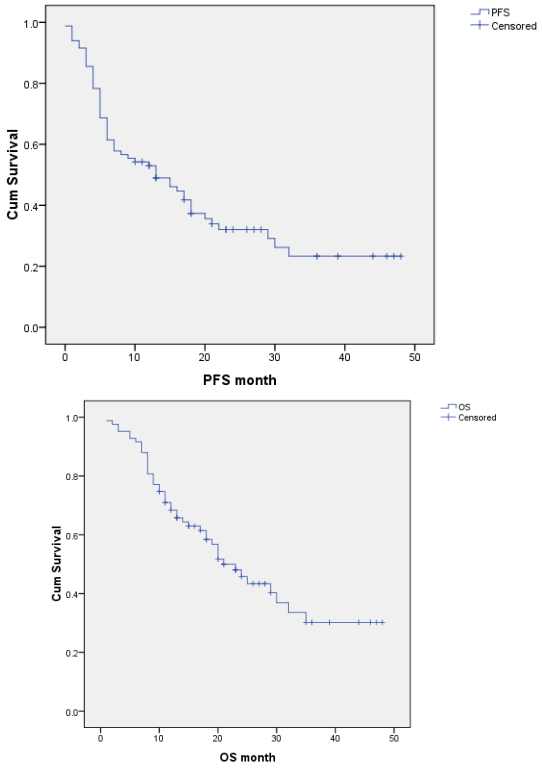
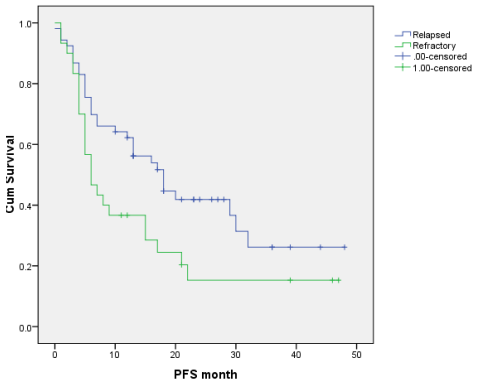


Figure 2. Progression-free survival and overall survival

Comment: The median progression-free survival of the study was 13 months. The median overall survival of the study was 21 months.



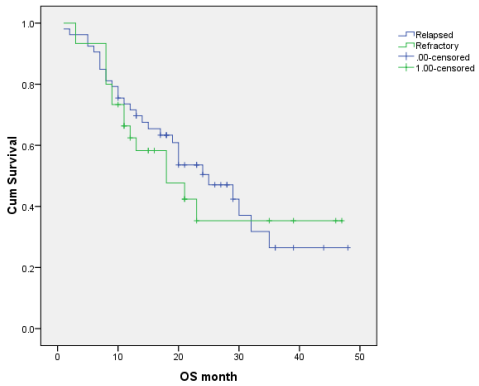


Figure 3. Association between relapsed or refractory and progression-free survival and overall survival

Comment: Refractory is an independent prognostic factor for PFS ($p<0.05$) but has no prognostic significance for OS ($p>0.05$).

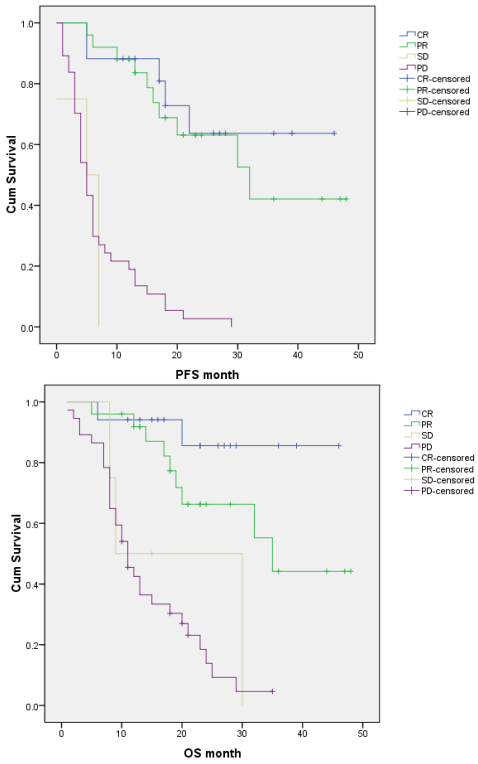


Figure 4. Association between treatment response and progression-free survival and overall survival

Comment: Treatment response is an independent prognostic factor for progression-free survival and overall survival with p<0.001.

4. DISCUSSIONS

4.1. General characteristics of patients

According to statistics in the world, patients with diffuse large B-cell lymphoma have an average age of 64 and the male ratio accounts for 55%. Our study is mostly patients with diffuse large B-cell lymphoma (87.5%) with the average age of the study being 59.9; the male/female ratio = 1.

T. El Gnaoui's study (2007) on 46 patients with relapsed/refractory B-cell lymphoma showed an average age of 64, the male/female ratio = 2[3]. Clarisse Cazelles' study (2021) conducted on 196 patients with relapsed/refractory diffuse large B-cell lymphoma showed a mean age of 72, male/female ratio = 1.2[6].

4.2. Clinical characteristics

General condition and syndrome B

At the time of admission, the majority of patients had PS=1, accounting for 45.8%. The rate of syndrome B was 19.3%. Research by T. El Gnaoui (2007) showed that the rate of PS 0-1 accounted for 67%; PS > 2 accounted for 33%[3]. Clarisse Cazelles's study (2021) showed that the proportion of patients with PS 0-1 accounted for 66% and patients with PS ≥ 2 accounted for 34%[6].

4.3. Response rate

Our study found that after 3 cycles, 13 patients had a complete response (15.7%), and 65.1% had a partial response. There were 13 patients who progressed, and 3 patients had stable disease (19.3%). After 6 cycles, the complete response rate was 20.5%; partial response was 31.3%; 4.8% had stable disease, and 43.4% of the patients progressed. Clarisse Cazelles's study (2021) showed that the interim response rate was 54% and the complete response rate was 23%. The end-of-treatment response rate was 38% and the complete response rate was 33%[6]. T. El Gnaoui's study (2007) showed that the complete response rate was 50%; the partial response rate was 33%; and the disease progression rate was 17%[3]. Thus, the response rate in our study was higher than that of Clarisse Cazelles, possibly because most patients received the RGEMOX regimen in line 2, while in this author's study, patients underwent more regimens before RGEMOX.

4.4. Overall survival and progression-free survival and associated factors

In our study, the median follow-up time was 18.3 months (shortest 1 month, longest 48 months), 56 patients had relapses and 45 patients died. The median progression-free survival time of the study was 13 months. The median overall survival time of the study was 21 months. The study by Clarisse Cazelles (2021) showed a median progression-free survival time of 5 months and an overall survival time of 10 months[6]. T. El Gnaoui's study (2007) showed that the overall survival rate at 2 years was 66%; the disease-free survival rate was 43%[3]. Refractory was an independent prognostic factor for PFS (p<0.05) and treatment response was an independent prognostic factor for PFS and OS with p<0.001.

5. CONCLUSION

Through our study, we found that the RGEMOX regimen applied in the treatment of relapsed/refractory B-cell non-Hodgkin lymphoma without high-dose chemotherapy achieved a final overall response rate of 51.8%, with acceptable safety profile, the median progression-free survival was 13 months, and the overall survival was 21 months.

REFERENCES

[1]. Philip T, Guglielmi C, Hagenbeek A et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. . *N Engl J Med*. 1995;333:1540–1545.

[2]. Schouten HC, Qian W, Kvaloy S et al. High-dose therapy improves progressionfree survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. *J Clin Oncol* 2003;21:3918–3927.

[3]. T. El Gnaoui, J. Dupuis, K. Belhadj et al. Rituximab, gemcitabine and oxaliplatin: an effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy. *Annals of Oncology*. 2007:1363–1368.

[4]. Fossa A, Santoro A, Hiddemann W et al. Gemcitabine as a single agent in the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma. *J Clin Oncol*. 1999;17:3786–3792.

[5]. Andrew D.Z. et al. NCCN Clinical practice guidelines in Oncology - B-Cell lymphomas. *NCCN*. 2020:12-65.

[6]. Clarisse Cazelles, Karim Belhadj, Hélène Vellemans et al. Rituximab plus gemcitabine and oxaliplatin (R-GemOx) in refractory/ relapsed diffuse large B-cell lymphoma: a real-life study in patients ineligible for autologous stem-cell transplantation. *Leuk Lymphoma*. 2021;62(9):2161-2168.

CORRELATION BETWEEN HER2-LOW EXPRESSION WITH CLINICOPATHOLOGIC CHARACTERISTICS AND ITS PROGNOSTIC VALUE IN EARLY-STAGE TRIPLE-NEGATIVE BREAST CANCER AT VIETNAM NATIONAL CANCER HOSPITAL

Phung Thi Huyen[1], Nguyen Thi Hoa[1], Hoang Thi Hoai[2], Nguyen Thanh Long[1*], Nguyen Dinh Thach[1]

ABSTRACT

Background: HER2-low expression impacts on clinical features and prognosis in early-stage triple-negative breast cancer (TNBC) remain unclear. Our aim was to evaluate its prognostic value and correlation with clinicopathological characteristics in this population.

Methods: A retrospective study of 126 patients with early-stage TNBC who did not undergo neoadjuvant systemic therapy in Vietnam National Cancer Hospital from January 2018 to December 2019, HER2 expression was evaluated using the 2018 ASCO/CAP guidelines, Tumor-infiltrating lymphocyte scores (TILs) assessment were assessed based on the guide of an international TILs research group in 2014, using 40% as the cut-off.

Results: Among the 126 patients, with a median age of 54.7±11.4 years, 74.6% were HER2-0 and 25.4% were HER2-low. Compared to HER2-0 tumors, HER2-low tumors were associated with higher age (p=0.02), lower Ki67 score (p=0.05), and lower tumor-infiltrating lymphocyte (p=0.005). During a median follow-up of 54 months, the univariate analysis revealed that patients with HER2-low tumors had a worse overall survival (OS) compared to those with HER2-0 tumors (83.3% vs. 69.6%, p=0.04). However, in the multivariate analysis, HER2 expression did not show a significant association with OS. Instead, independent predictors of OS were identified as tumor-infiltrating lymphocyte scores scores (TILs) (p=0.02; HR=0.17; 95%CI 0.04-0.77) and nodal status (p=0.002; HR=3.8; 95%CI 1.6-9.1).

Conclusions: This study suggests that HER2-low expression is associated with a lower immune response and worse survival outcome in early-stage TNBC patients compared to HER2-0 tumors. Further investigations is needed to explore the potential of more refined classification and novel strategies that may improve the prognosis for HER2-low TNBC patients.

Keywords: Breast cancer; triple negative; Her2-low; Her2-0; TILs.

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1. INTRODUCTION

Breast cancer is the most common cancer among women, with an increasing number of cases and being one of the leading causes of cancer-related mortality [1]the American Cancer Society estimates the numbers of new cancer cases and deaths that will occur in the United States in the current year and compiles the most recent data on cancer incidence, mortality, and survival. Incidence data were collected by the Surveillance, Epidemiology, and End Results Program; the National Program of Cancer Registries; and the North American Association of Central Cancer Registries. Mortality data were collected by the National Center for Health Statistics. In 2017, 1,688,780 new cancer cases and 600,920 cancer deaths are projected to occur in the United States. For all sites combined, the cancer incidence rate is 20% higher in men than in women, while the cancer death rate is 40% higher. However, sex disparities vary by cancer type. For example, thyroid cancer incidence rates are 3-fold higher in women than in men (21 vs 7 per 100,000 population. Triple-negative breast cancer (TNBC) is a subtype characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), accounting for 15-20% of all breast cancer cases. TNBC is associated with rapid disease progression and a poorer prognosis compared to other subtypes [2]. Since TNBC is defined by the absence of hormone receptors and HER2 negativity, endocrine therapy and HER2-targeted therapy are not applicable. Chemotherapy remains the mainstay of treatment, with an emerging role for immunotherapy [3]. The HER2-negative group includes the HER2-0 subgroup (score 0 on immunohistochemistry (IHC)) and the HER2-low subgroup (HER2 1+ on IHC or HER2 2+ on IHC with a negative Dual-ISH or FISH result). Studies have suggested differences in prognosis between HER2-low and HER2-0 cases. The DESTINY-Breast04 clinical trial demonstrated that trastuzumab deruxtecan is highly effective in metastatic HER2-low breast cancer [4].

Thus, it has been hypothesized that the risk of recurrence and treatment efficacy may vary between HER2-low and HER2-0 cases in early-stage TNBC. These findings support the use of HER2 status as a prognostic factor and the development of new treatment strategies for TNBC in the future. Such insights may contribute to personalized treatment approaches for TNBC patients.

In Vietnam, the impact of low HER2 expression on tumor clinical characteristics and prognostic value in early-stage TNBC has not been extensively studied. Therefore, this study aims to evaluate the association between HER2 expression, clinical characteristics, and prognostic value in early-stage TNBC among Vietnamese patients.

2. METHODS

2.1. Study subjects

This retrospective study was conducted on 126 patients diagnosed with non-metastatic triple-negative breast cancer (TNBC) based on surgical specimens at Vietnam National Cancer Hospital from January 2018 to December 2019. HER2 expression was evaluated according to the 2018 ASCO/CAP guidelines and tumor-infiltrating lymphocytes (TILs) were assessed based on the 2014 guidelines of the International TILs Working Group, using a threshold of 40%.

2.2. Inclusion criteria

- Female patients who underwent surgery as the initial treatment (without prior neoadjuvant therapy) and were histopathologically confirmed to have primary breast carcinoma based on surgical specimens.

- No history of second primary cancer.

- Complete medical records with sufficient data for the study. Availability of histopathological slides and paraffin blocks meeting the requirements for hematoxylin and eosin (HE) staining and immunohistochemistry (IHC).

- Patients confirmed to have negative estrogen receptor (ER), progesterone receptor (PR), and HER2 status (IHC 0+, 1+ or 2+ with a negative FISH/Dual-ISH result) in surgical specimens.

2.2. Exclusion criteria

Incomplete medical records lacking necessary information for the study.

2.3. Research methods

A cross-sectional descriptive study was conducted to determine HER2 status, the proportion of tumor-infiltrating lymphocytes, and their association with histopathological characteristics and survival outcomes in TNBC.

2.4. Study procedure

- Identify patients diagnosed with TNBC from January 2018 to December 2019.

- Review medical records and collect relevant data for the study.

- Record histopathological findings based on HE and IHC staining for ER, PR, HER2, Ki67 and assess TILs.

- Evaluate HER2 expression according to the 2018 ASCO/CAP guidelines and assess TILs using the 2014 International TILs Working Group criteria, with a cutoff threshold of 40%.

3. RESULTS

3.1. Association between HER2 status and clinical, paraclinical characteristics and tumor-infiltrating lymphocytes (TILs)

Table 1. Association between HER2 status and clinical, paraclinical characteristics

Characteristics	HER2-0 (n=94)	HER2-low (n=32)	p-value
Age (years), Mean ± SD	53.3 ± 11.0	58.6 ± 10.8	0.02
Tumor Stage (T-stage)			0.30
- T1 (%)	48 (51.1)	13 (40.6)	
- T2-3 (%)	46 (48.9)	19 (59.4)	
Nodal Status			0.22
- Negative (%)	67 (71.3)	26 (81.3)	
- Positive (%)	27 (28.7)	6 (18.8)	
Histological Grade			0.19
- Grade 1-2 (%)	40 (42.6)	19 (58.4)	
- Grade 3 (%)	54 (57.4)	13 (40.6)	
Ki67 (%)			0.05
- ≤ 50% (%)	24 (25.5)	14 (43.8)	
- > 50% (%)	70 (74.5)	18 (56.3)	
Vascular Invasion			0.06
- No (%)	91 (96.8)	28 (87.5)	
- Yes (%)	3 (3.2)	4 (12.5)	
TILs, No. (%)			0.005
- Low (%)	46 (48.9)	26 (81.3)	
- High (%)	48 (51.1)	6 (18.8)	

Our study included 126 patients, with a mean age of 54.7 ± 11.4 years. The mean age was 53.3 ± 11.0 years in the HER2-0 group and 58.6 ± 10.8 years in the HER2-low group. Among the participants, 74.6% had HER2-0 expression, while 25.4% had HER2-low expression (HER2 1+ on IHC or HER2 2+ on IHC with a negative Dual-ISH or FISH result). A total of 51.1% of HER2-0 cases and 40.6% of HER2-low cases were diagnosed at T1 stage. Most patients in both groups were node-negative after surgery (71.3% in HER2-0 vs. 81.3% in HER2-low).

Compared to HER2-0 patients, HER2-low patients were significantly older (58.6 ± 10.8 years vs. 53.3 ± 11.0 years, p = 0.02) and had lower Ki67 expression (p = 0.05). Additionally, TIL levels were significantly lower in the HER2-low group compared to HER2-0 (p = 0.005). These differences were statistically significant (p < 0.05). Other factors, such as tumor stage, nodal status, histological grade, and vascular invasion, did not show statistically significant differences between HER2-0 and HER2-low groups (p > 0.05).

3.2. Association between HER2 status and overall survival (OS)

The median follow-up time in our study was 54 months. Univariate analysis showed that patients with HER2-low tumors had a lower 5-year overall survival (OS) rate compared to those with HER2-0 tumors (69.6% vs. 83.3%, p = 0.04). However, in multivariate analysis, HER2 expression was not a statistically significant independent predictor of OS. Instead, independent prognostic factors for OS included TILs (p = 0.02; HR = 0.17; 95% CI 0.04-0.77) and lymph node metastasis (p = 0.002; HR = 3.8; 95% CI 1.6-9.1).

Table 2. Multivariate analysis of factors associated with overall aurvival (OS)

Factor	p-value	HR	95% CI
Age (≤50 vs. >50 years)	0.17	1.88	0.77-4.61
Ki67 (≤20% vs. >20%)	0.84	0.89	0.30-2.70
Lymph Node Metastasis (Negative vs. Positive)	0.002	3.84	1.61-9.10
Tumor Stage (T1 vs. T2-3)	0.08	2.31	0.88-6.06
TILs (Low vs. High)	0.02	0.17	0.04-0.77
Vascular Invasion (No vs. Yes)	0.85	0.83	0.88-6.42
HER2 Status (0 vs. Low)	0.08	2.55	1.05-6.16

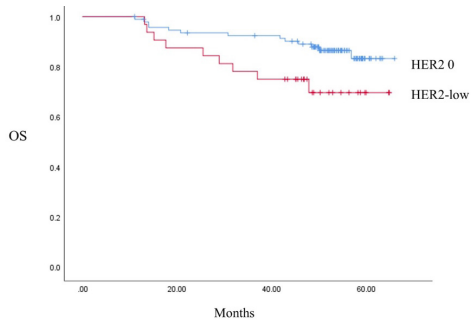

Figure 1. Kaplan-Meier survival curve based on HER2 Status

4. DISCUSSION

Triple-negative breast cancer (TNBC) is associated with rapid disease progression and a poorer prognosis compared to other subtypes [2]. Studies have shown differences in prognosis between HER2-low and HER2-0 groups [5]. Therefore, we focused on investigating the relationship between HER2 status and clinical, pathological characteristics, as well as survival outcomes in patients with early-stage TNBC. In our cohort, 25.4% of patients exhibited HER2-low

expression (HER2 1+ by IHC or HER2 2+ by IHC with a negative Dual-ISH or FISH result), a rate similar to the findings of Tomomi et al [6].

HER2-low was identified as a poor prognostic factor in both univariate and multivariate analyses for disease-free survival (DFS) in stage I TNBC in Tomomi's study. In our study, univariate analysis showed that patients with HER2-low tumors had a lower 5-year overall survival (OS) rate compared to those with HER2-0 tumors. Consistent with previous research, our study also demonstrated a better prognosis in patients with high tumor-infiltrating lymphocytes (TILs) [7].

We found a correlation between TILs and HER2 status. The TILs level was higher in the HER2-0 group compared to the HER2-low group ($p = 0.005$). According to Xi et al., TNBC with HER2-0 status exhibits a more active immune tumor microenvironment than the HER2-low group, as indicated by macrophage polarization and the accumulation of a large number of CD8+ T cells [8]. Additionally, in TNBC patients, HER2-low tumors have a lower pathological complete response rate than HER2-0 tumors and are associated with a weaker immune response [9]. This study suggests that HER2-low expression is associated with a lower intratumoral immune response and worse survival outcomes in patients with early-stage TNBC compared to the HER2-0 group.

5. CONCLUSION

This study suggests that HER2-low expression is associated with a lower intratumoral immune response and poorer survival outcomes in patients with early-stage TNBC compared to the HER2-0 group.

REFERENCES

[1]. Siegel RL, Miller KD, Jemal A (2017) Cancer statistics, 2017. CA Cancer J Clin 67:7–30. https://doi.org/10.3322/caac.21387

[2]. Dent R, Trudeau M, Pritchard KI, et al (2007) Triple-Negative Breast Cancer: Clinical Features and Patterns of Recurrence. Clin Cancer Res 13:4429-4434. https://doi.org/10.1158/1078-0432.CCR-06-3045

[3]. Cardoso F, Kyriakides S, Ohno S, et al (2019) Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 30:1194–1220. https://doi.org/10.1093/annonc/mdz173

[4]. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. New England Journal of Medicine. https://www.nejm.org/doi/full/10.1056/NEJMoa2203690. Accessed 27 Jul 2024

[5]. Almstedt K, Heimes A-S, Kappenberg F, et al (2022) Long-term prognostic significance of HER2-low and HER2-zero in node-negative breast cancer. Eur J Cancer Oxf Engl 1990 173:10–19. https://doi.org/10.1016/j.ejca.2022.06.012

[6]. Sanomachi T, Okuma HS, Kitadai R, et al (2023) Low HER2 expression is a predictor of poor prognosis in stage I triple-negative breast cancer. Front Oncol 13:1157789. https://doi.org/10.3389/fonc.2023.1157789

[7]. De Jong VMT, Wang Y, Ter Hoeve ND, et al (2022) Prognostic Value of Stromal Tumor-Infiltrating Lymphocytes in Young, Node-Negative, Triple-Negative Breast Cancer Patients Who Did Not Receive (neo)Adjuvant Systemic Therapy. J Clin Oncol Off J Am Soc Clin Oncol 40:2361–2374. https://doi.org/10.1200/JCO.21.01536

[8]. Hu X, Yang P, Chen S, et al (2023) Clinical and biological heterogeneities in triple-negative breast cancer reveals a non-negligible role of HER2-low. Breast Cancer Res 25:34. https://doi.org/10.1186/s13058-023-01639-y

[9]. Van den Ende NS, Smid M, Timmermans A, et al (2022) HER2-low breast cancer shows a lower immune response compared to HER2-negative cases. Sci Rep 12:12974. https://doi.org/10.1038/s41598-022-16898-6

FIRST-LINE CHEMOTHERAPY OUTCOMES IN A PATIENT WITH RELAPSED METASTATIC NON-SMALL CELL LUNG CANCER HARBORING AN EGFR EXON 20 INSERTION MUTATION

Tran Thi Hau*, Do Hung Kien, Dao Minh The

ABSTRACT

Introduction: Non-small cell lung cancer (NSCLC) with exon 20 insertion mutations accounts for 4-10% of all NSCLC patients with EGFR mutations. The primary treatment for NSCLC patients with recurrent metastatic EGFR exon 20 insertion mutations remains platinum-based doublet chemotherapy. However, there are very few studies in Vietnam evaluating the effectiveness of this treatment. Therefore, this study was conducted to evaluate the effectiveness of this therapy in the mentioned patient group.

Subjects and Methods: This is a retrospective cross-sectional descriptive study on 36 NSCLC patients with recurrent metastatic EGFR exon 20 insertion mutations treated with platinum-based doublet chemotherapy from January 2019 to June 2024 at Vietnam National Cancer Hospital to evaluate treatment outcomes and adverse effects of the regimen in this patient group.

Results: The response rate of the regimen was 25%, and the disease control rate was 66.7%. The median progression-free survival (PFS) was 7.0 months. The median overall survival (OS) was 17.6 months. The majority of patients experienced at least one adverse effect, accounting for 80.6%. The most common adverse effects were neutropenia (in 58% of patients), peripheral neuropathy (44%), anemia (48%), and nausea (42%). The most common grade 3 or higher adverse effects were neutropenia (25%), thrombocytopenia (6%) and anemia (8%). Dose reductions and drug discontinuations due to adverse effects were reported in 17% and 8% of patients, respectively.

Conclusion: First-line treatment with platinum-based doublet chemotherapy for recurrent/metastatic NSCLC patients with exon 20 insertion mutations is an effective treatment method with manageable toxicity.

Keywords: Non-small cell lung cancer; EGFR exon 20 insertion; platinum-based doublet chemotherapy.

I. INTRODUCTION

Lung cancer (LC) is the most common malignancy and the leading cause of cancer-related mortality worldwide. Non-small cell lung cancer (NSCLC) accounts for the majority (85%) of all primary lung malignancies. The epidermal growth factor receptor (EGFR), a member of the human epidermal receptor (HER) family, plays a vital role in cellular proliferation, metabolism, and evasion of apoptosis. EGFR exon 20 insertion mutations (EGFRex20ins) comprise approximately 4% to 10% of EGFR-mutated NSCLC and about 2% of all NSCLC cases. These mutations are more frequently observed in females, non-smokers or light smokers,

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and are typically associated with adenocarcinoma histology. EGFRex20ins is also characterized by a high rate of initial brain metastases and a pattern of bone metastasis similar to that seen with classical EGFR-activating mutations.

Over the past 20 years, EGFR tyrosine kinase inhibitors (EGFR-TKIs) have become an effective treatment option for NSCLC patients harboring EGFR mutations. However, unlike common EGFR mutations, EGFRex20ins responds poorly to first- and second-generation EGFR-TKIs such as afatinib, erlotinib, and gefitinib, with response rates around 10% and a median progression-free survival (PFS) of only 1 to 3 months. Even when osimertinib was administered at a doubled dose (160 mg instead of 80 mg) in a study involving 21 patients previously treated with EGFR-TKIs, outcomes were still suboptimal: the objective response rate was 25%, median PFS was 9.7 months, and median duration of response was 5.7 months. Similarly, immune checkpoint inhibitors, either as monotherapy or in combination with chemotherapy, have shown poor efficacy in patients with EGFRex20ins, with response rates ranging from 0% to 25% and median PFS of only 2 to 3 months. The monoclonal antibody amivantamab, in combination with platinum-based chemotherapy, has demonstrated improved survival in NSCLC patients harboring EGFRex20ins. However, this drug has not yet been approved by the Ministry of Health in Vietnam.

Therefore, for most patients with relapsed or metastatic NSCLC carrying EGFRex20ins mutations, platinum-based chemotherapy remains the standard treatment option. However, in Vietnam, clinical research on treatment outcomes in this patient group remains limited. Therefore, we conducted this study with two objectives:

- To evaluate the outcomes of first-line chemotherapy in patients with relapsed or metastatic NSCLC harboring EGFR exon 20 insertion mutations.

- To assess the adverse effects of this treatment regimen in the study population.

2. SUBJECTS AND METHODS

2.1. Subjects

This study included 36 patients diagnosed with relapsed or metastatic non-small cell lung cancer (NSCLC) harboring EGFR exon 20 insertion mutations, who received first-line platinum-based doublet chemotherapy at Vietnam National Cancer Hospital from January 2019 to June 2024.

Inclusion Criteria:

- Confirmed diagnosis of relapsed/metastatic NSCLC according to AJCC 8th edition.

- Presence of EGFR exon 20 insertion mutation, without accompanying mutations, as determined by next-generation sequencing (NGS) or Real-time PCR using the Cobas EGFR Mutation Test v2.

- Measurable lesions on imaging (MRI, CT scan). Patients with asymptomatic or stable brain metastases after treatment were also eligible.

- Received at least 2 and up to 6 cycles of platinum-based doublet chemotherapy.

- Age > 18 years, any sex, with an ECOG performance status (PS) of 0 or 1.

- Adequate organ function: White blood cell count (WBC) ≥ 4 G/L; Platelet count (PLT) ≥ 100 G/L; Hemoglobin ≥ 100 g/L; AST/ALT ≤ 2× upper limit of normal (ULN); Total bilirubin ≤ 1.5× ULN; Creatinine ≤ 1.5× ULN; Complete and accessible medical records.

Exclusion Criteria:

- Patients with a second primary malignancy.

- Contraindications to treatment drugs, such as severe liver or kidney dysfunction or drug hypersensitivity.

- Uncontrolled brain metastases.

- Patients who had received treatment for metastatic disease prior to the study.

- Patients unwilling to cooperate or lost to follow-up.

2.2. Methods

- Study design: Retrospective cross-sectional descriptive study.

- Study period and location: From January 2019 to June 2024 at Vietnam National Cancer Hospital.

- Sampling method: Convenience sampling; 36 eligible patients were included.

- Data Collection:

+ Clinical and paraclinical information collected included: Age, sex, reason for admission, smoking status, performance status, tumor characteristics, lymph node involvement, metastatic sites, histopathological type, and EGFR mutation testing method.

+ Overall Response Rate (ORR): Percentage of patients achieving partial or complete response; Disease Control Rate (DCR): Percentage of patients with complete response, partial response, or stable disease; Progression-Free Survival (PFS): Time from study enrollment to disease progression or death from any cause; Overall Survival (OS): Time from enrollment to death from any cause.

+ Treatment toxicity: Hematologic, hepatic, renal, gastrointestinal toxicities were assessed according to CTCAE version 4.0.

- Study Procedure:

+ Step 1: Select patients based on inclusion criteria.

+ Step 2: Collect clinical and laboratory data.

+ Step 3: Administer chemotherapy regimens: Pemetrexed 500 mg/m² + Carboplatin AUC 5, every 3 weeks; or Paclitaxel 200-225 mg/m² + Carboplatin AUC 6, every 3 weeks.

+ Step 4: Evaluate treatment outcomes: Tumor response assessed using RECIST 1.1 (2009), Survival analysis using the Kaplan Meier method, Toxicity assessed per CTCAE v4.0. Patients were evaluated every 2–3 cycles or earlier if abnormalities were noted.

- Data Analysis:

Data were entered and analyzed using SPSS version 22.0. Descriptive statistics (percentages, means, standard deviations) were used. Survival estimates were calculated using the Kaplan Meier method.

2.3. Ethical considerations

All patients in the study voluntarily participated. The study was conducted solely for the purpose of improving treatment quality, with no other objectives. Patients who met the inclusion criteria were thoroughly and clearly informed about available treatment options, the treatment process, advantages and disadvantages of each regimen, and potential risks. All personal and medical information was kept strictly confidential.

3. RESULTS

3.1. Clinical characteristics of the study population

Table 1. Characteristics of the study population

Characteristic	Number of Patients (n)	Percentage (%)
Age		
Mean age: 59,61		
> 65 years	12	33,3
≤ 65 years	24	66,7

Characteristic	Number of Patients (n)	Percentage (%)
Gender		
Male	28	77,8
Female	8	22,2
Smoking History		
Non-smokers	10	27,8
Smokers	26	72,2
ECOG		
0	19	52,8
1	17	47,2
Histology		
Adenocarcinoma	33	91,7
NSCLC, NOS	3	8,3
EGFR testing method		
PCR	13	36,1
NGS	23	63,9
Metastatic sites		
Brain	13	36,1
Lung	8	22,2
Pleura	12	33,3
Liver	3	8,3
Bone	18	50
Adrenal gland	6	16,7
Chemotherapy regimens		
Pemetrexed - carboplatin	19	52,8
Paclitaxel - carboplatin	17	47,2
Number of chemotherapy cycles		
2 cycles	6	16,7

Characteristic	Number of Patients (n)	Percentage (%)
3 cycles	5	13,9
4 cycles	10	27,8
5 cycles	4	11,1
6 cycles	11	30,6

Remarks: The average age of the study population was 59.61 years; the male-to-female ratio was 3,5/1. A majority of patients had a history of smoking (72.2%). ECOG performance status 0 was the most common (52.8%). Bone was the most frequent metastatic site (50%), followed by brain metastases (36.1%). Liver metastases were the least common (8.3%). Adenocarcinoma was the most prevalent histological type (91.7%). The most commonly used chemotherapy regimen was pemetrexed - carboplatin (52.8%). NGS was the most frequently used EGFR testing method (63.9%).

3.2. Treatment outcomes

Table 2. Treatment response

Treatment response	Number of patients (n) and percentage (%)	Paclitaxel-carboplatin	Pemetrexed-carboplatin
Complete Response	0 (0)	0 (0)	0 (0)
Partial Response	9 (25)	3 (17,6)	6 (31,6)
Stable Disease	15 (41,7)	8 (47,1)	7 (36,8)
Progressive Disease	12 (33,3)	6 (35,3)	6 (31,6)

Remarks: The overall response rate (ORR) was 25%. The disease control rate (DCR) was 66.7%. The response rate for the paclitaxel-carboplatin regimen was 17.6%, while for the pemetrexed-carboplatin regimen it was 31.6%.

Observation: The median progression-free survival time is 7 months. The shortest progression-free survival time is 2 months, while the longest is 27 months.

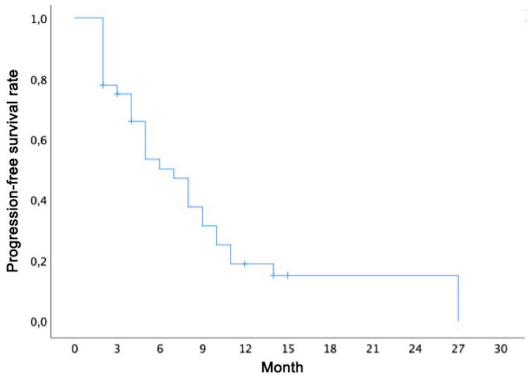

Figure 1. Progression-Free survival time

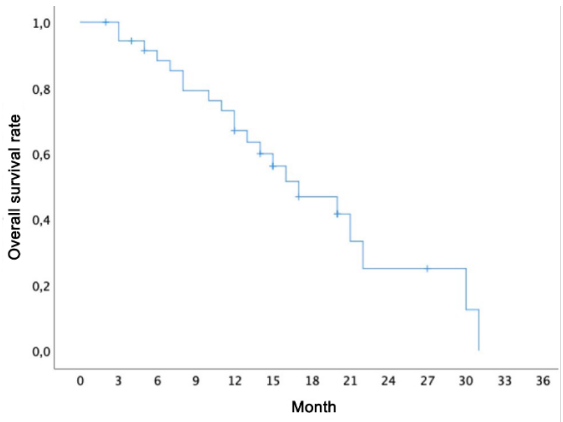

Figure 2. Overall Survival Time

Observation: The median overall survival time is 17 months. The shortest overall survival time is 3 months, and the longest is 31 months.

3.3. Adverse effects of the treatment regimen

Table 3. Adverse effects of the treatment regimen

Adverse Effect	All Grades	Grade ≥ 3
Leukopenia	58% (n=21)	25% (n=9)
Anemia	38% (n=14)	8% (n=3)
Thrombocytopenia	36% (n=13)	6% (n=2)
Vomiting	22% (n=8)	0% (n=0)
Nausea	42% (n=15)	0% (n=0)
Fatigue	17% (n=6)	0% (n=0)
Elevated AST	36% (n=13)	0% (n=0)
Elevated ALT	36% (n=13)	0% (n=0)
Elevated Creatinine	14% (n=5)	0% (n=0)
Peripheral Neuropathy	44% (n=16)	6% (n=2)
Dose reduction due to toxicity	17% (n=6)	
Discontinued due to side effects	8% (n=3)	

Observation: The majority of patients (80.6%) experienced at least one adverse effect. The most common side effects were leukopenia (58%) and peripheral neuropathy (44%), followed by anemia (38%) and nausea (42%). The most frequent grade ≥ 3 toxicities were leukopenia (25%) and anemia (8%). Dose reduction and treatment discontinuation due to toxicity occurred in 17% and 8% of patients, respectively.

4. DISCUSSION

In our study, the average age was 59.61 years. The majority of patients were under 65 years old, accounting for 66.7%. Most patients were male (77.8%). Adenocarcinoma was the predominant histological subtype, found in 91.7% of patients. Bone, brain, and pleura were the most common sites of metastases, accounting for 50%, 36.1%, and 33.3%, respectively. The most commonly used chemotherapy regimen was pemetrexed–carboplatin, administered to over half of the patients, and nearly one-third of patients underwent up to 6 treatment cycles. The characteristics of our patient population show both similarities and differences compared to other studies. Most studies indicate that patients with EGFR exon 20 insertions (EGFRex20ins) are generally 60 years old or younger. Caicun and colleagues reported a mean age of 61, with most patients being under 65 (63%)[5]. Similarly, in Morita's study, the median age was 60[6]. In Shah's study, the figure was also 60 [7]. Clearly, EGFRex20ins seems to occur more commonly in a younger population. However, our study shows a reversed gender distribution, with males being predominant. This contrasts with other studies where exon 20 insertions are more frequently found in females[5,6]. This discrepancy might be due to the small sample size in our study, which may not fully represent the population of NSCLC patients with EGFR exon 20 insertion mutations. Regarding metastatic sites, in our study, EGFRex20ins tended to spread to the bone, brain, and pleura. According to Morita's study, bone metastases (21.6%) were the most common among patients with exon 20 insertions, followed by the central nervous system (CNS) (13.0%) and liver (17.4%)[6]. In a study conducted in China, Yang also reported that bone and lung were the most common metastatic sites, accounting for 40.6% and 40%, respectively, followed by pleura and brain at 36.4% and 23%[8].

In terms of chemotherapy, more than half of our patients received pemetrexed-platinum-based regimens. A multicenter study by Su demonstrated that patients treated with pemetrexed-based chemotherapy had a longer median progression-free survival (PFS) compared to those who did not (5.5 vs. 3.0 months, p = 0.0026)[9]. Data from 66 patients showed a median overall survival (OS) of 24.7 months. Patients receiving pemetrexed-based chemotherapy tended to have longer OS than those who did not (25.0 vs. 19.6 months, P = 0.0769)[9]. However, for advanced NSCLC in general, paclitaxel carboplatin and pemetrexed carboplatin regimens produce similar outcomes, although pemetrexed-based regimens tend to be better tolerated[10]. Our study showed an objective response rate (ORR) of 25% and a disease control rate of 66.7%. The PFS was 7.0 months, and OS was 17 months. In a retrospective study at Stanford University, the objective response rate to platinum doublet chemotherapy was 44% (8 partial responses, 10 stable disease), with an average tumor burden reduction of 22% (SD: 15.6). PFS was 7.1 months (95% CI, 6.3–13.7)[7]. A Japanese study on 85 patients with exon 20 insertions showed that pemetrexed-containing regimens provided better PFS (6.2 vs. 2.7 months, p < 0.0001) and OS (28 vs. 13.9 months, p = 0.016) compared to non-pemetrexed regimens[10]. According to Morita's study, the ORR and median PFS of first-line platinum chemotherapy in patients with exon 20 insertions were 11.8% (95% CI: 1.5–36.4) and 8.9 months (95% CI: 5.0–17.3), respectively [6]. Compared to other treatment approaches, a recent study comparing chemotherapy versus chemotherapy plus amivantamab in NSCLC patients with EGFRex20ins found significantly longer PFS in the amivantamab-combination group (HR = 0.40; 95% CI: 0.30 to 0.53; P < 0.001)[5]. After 18 months, PFS was observed in 31% of patients receiving amivantamab-combination therapy, compared to 3% in the chemotherapy-only group. PFS was 12.9 months (95% CI: 11.4–16.7) for the combination group versus 6.9 months (95% CI: 6.2–8.3) in the chemo-only group (HR = 0.38; 95% CI: 0.29–0.51). Objective responses were reported in 73% (95% CI: 65–80) of the combination group and 47% (95% CI: 39–56) of the chemo-only group (RR = 1.50; 95% CI: 1.32–1.68; P < 0.001)[5].

Our study found that most patients experienced at least one adverse event. The most common adverse events were neutropenia (58%), peripheral neuropathy (44%), anemia (38%) and nausea (42%). The most frequent grade ≥3 adverse events were neutropenia (25%), thrombocytopenia (6%), and anemia (8%). Adverse events led to dose reductions in 17% of patients and treatment discontinuation in 8%. These results are consistent with previous studies. One study on EGFRex20ins also showed that most patients experienced at least one adverse event. The most commonly reported events were anemia (55%), neutropenia (45%), and nausea (42%) in the chemotherapy group. Febrile neutropenia occurred in 2% of patients receiving chemotherapy. The most frequent grade 3 toxicities were neutropenia (23%), anemia (12%) and thrombocytopenia (10%). Serious adverse events occurred in 31% of patients in the chemotherapy group. Adverse events leading to dose interruption, dose reduction, and discontinuation occurred in 36%, 23% and 10% of patients, respectively. Death within 30 days after the last dose of study drug occurred in 4 patients (3%) [5]. Compared to advanced-stage NSCLC patients treated with paclitaxel carboplatin, serious adverse events leading to hospitalization occurred in 13.1% of patients. The rates of peripheral neuropathy, nausea and vomiting, and hematologic toxicity were 69.9%, 44.3%, and 67.1%, respectively. Interstitial lung disease occurred in 8 patients receiving paclitaxel carboplatin (1.4%), one of whom died[5].

5. CONCLUSION

Based on our study of 36 patients with advanced recurrent metastatic non-small cell lung cancer (NSCLC) harboring EGFR exon 20 insertion mutations who received first-line platinum-based

doublet chemotherapy at Vietnam National Cancer Hospital from January 2019 to June 2024, we conclude the following:

- The objective response rate (ORR) of the regimen was 25%, and the disease control rate (DCR) was 66.7%.

- The median progression-free survival (PFS) was 7.0 months.

- The median overall survival (OS) was 17.6 months.

- Most patients experienced at least one adverse event, the most common being neutropenia (58%), peripheral neuropathy (44%), anemia (48%) and nausea (42%). The most frequent grade ≥3 adverse events were neutropenia (25%), thrombocytopenia (6%), and anemia (8%). Dose reductions and treatment discontinuations due to toxicity occurred in 17% and 8% of patients, respectively.

REFERENCES

[1]. Beau-Faller M, Prim N, Ruppert AM, et al. Rare EGFR exon 18 and exon 20 mutations in non-small-cell lung cancer on 10 117 patients: a multicentre observational study by the French ERMETIC-IFCT network. *Ann Oncol*. 2014;25(1):126-131. doi:10.1093/annonc/mdt418

[2]. Yang JCH, Sequist LV, Geater SL, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol*. 2015;16(7):830-838. doi:10.1016/S1470-2045(15)00026-1

[3]. Van Veggel B, Madeira R Santos JFV, Hashemi SMS, et al. Osimertinib treatment for patients with EGFR exon 20 mutation positive non-small cell lung cancer. *Lung Cancer*. 2020;141:9-13. doi:10.1016/j.lungcan.2019.12.013

[4]. Negrao MV, Reuben A, Robichaux JP, et al. Association of EGFR and HER-2 exon 20 mutations with distinct patterns of response to immune checkpoint blockade in non-small cell lung cancer. *JCO*. 2018;36(15_suppl):9052-9052.doi:10.1200/JCO.2018.36.15_suppl.9052

[5]. Amivantamab plus Chemotherapy in NSCLC with EGFR Exon 20 Insertions | NEJM. Accessed November 24, 2023. https://www.nejm.org/doi/full/10.1056/NEJMoa2306441

[6]. Morita C, Yoshida T, Shirasawa M, et al. Clinical characteristics of advanced non-small cell lung cancer patients with EGFR exon 20 insertions. *Sci Rep*. 2021;11:18762. doi:10.1038/s41598-021-98275-3

[7]. Shah MP, Aredo JV, Padda SK, et al. EGFR exon 20 Insertion NSCLC and Response to Platinum-Based Chemotherapy. *Clin Lung Cancer*. 2022;23(2):e148-e153. doi:10.1016/j.cllc.2021.07.001

[8]. Yang G, Li J, Xu H, et al. EGFR exon 20 insertion mutations in Chinese advanced non-small cell lung cancer patients: Molecular heterogeneity and treatment outcome from nationwide real-world study. *Lung Cancer*. 2020;145:186-194. doi:10.1016/j.lungcan.2020.03.014

[9]. Xu CW, Wang WX, Wang D, et al. Pemetrexed-based chemotherapy for non-small-cell lung cancer patients with EGFR exon 20 insertion mutation: a multicenter study. *Transl Lung Cancer Res*. 2020;9(5):1853-1861.doi:10.21037/tlcr-20-382

[10]. Wu JY, Yu CJ, Shih JY. Effectiveness of Treatments for Advanced Non-Small-Cell Lung Cancer With Exon 20 Insertion Epidermal Growth Factor Receptor Mutations. *Clin Lung Cancer*. 2019;20(6):e620-e630. doi:10.1016/j.cllc.2019.06.018

THE EFFECTIVENESS OF THE CELL BLOCK TECHNIQUE IN THE CYTOLOGICAL DIAGNOSIS OF PLEURAL EFFUSION AT HA DONG GENERAL HOSPITAL FROM 2021 TO 2024

Le Dinh Chinh[1*], Ngo Van Lang[2], Nguyen Thi Hanh[1], Nguyen Ha Trang[3], Le Thi Tham[4]**

ABSTRACT

Aims: (1) Compare the results of cell block examination and cell smear cytology in diagnosing malignant pleural effusion at the Pathology Department of Ha Dong General Hospital from 2021 to 2024. (2) Identify factors associated with cytological diagnosis using the cell block technique for pleural effusion.

Materials and Methods: A cross-sectional descriptive study was conducted on 176 pleural effusion samples at the Pathology Department of Ha Dong General Hospital from October 2021 to May 2024.

Results: The cell block technique detected malignancy in 22.1% of samples and suspected malignancy in 5.7%, whereas the cell smear technique identified malignancy in 7.4% and suspected malignancy in 2.3%. The cell block method detected more malignant and suspicious cases than the cell smear method ($p<0.05$). The concordance rate between the two techniques was 79.6%. The malignancy rate was higher in males than in females ($p<0.05$) and was significantly higher in cases with fluid volume >500mL ($p<0.05$).

Conclusion: The cell block technique identified more malignant and suspicious cases than the cell smear technique in diagnosing malignant pleural effusion. A significant association was found between gender, fluid volume, and cytological diagnosis using the cell block technique.

Keywords: Pleural effusion; Cell block; Cell smear; Conventional smear cytology.

1. INTRODUCTION

Pleural effusion is a common clinical manifestation of various diseases, particularly malignant conditions. Determining the underlying cause of pleural effusion plays a crucial role in guiding diagnosis and treatment. Among these causes, cancer is one of the leading contributors to pleural effusion, especially in elderly patients and those with a history of malignancy [1]. Cytological examination of pleural fluid is a minimally invasive method with high clinical value and is widely used to detect malignant cells in the fluid. The cell smear technique is a common and easy-to-perform method; however, it has several limitations, such as uneven cell distribution, potential cell loss during processing, and difficulty in identifying cellular structures in a background of abundant proteinaceous

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material [2]. In recent years, the cell block technique has been increasingly applied due to its ability to preserve tissue architecture, allowing for special staining techniques and immunohistochemistry, which support differential diagnosis particularly in cases where cells are suspicious or difficult to interpret [3], [4]each case was objectively analysed for cellularity, arrangement (acini, papillae, cell balls, and proliferation spheres. Although applied at Ha Dong General Hospital since October 2021, no study has evaluated its actual effectiveness in cancer diagnosis on pleural effusion samples at this hospital. Therefore, this study was conducted with two objectives: (1) Compare the results of cell block examination and cell smear cytology in diagnosing malignant pleural effusion at Ha Dong General Hospital. (2) Identify factors associated with cytological diagnosis using the cell block technique.

2. STUDY SUBJECTS AND METHODS

2.1. Study subjects

Pleural effusion samples sent to the Pathology Department from October 2021 to May 2024. Inclusion criteria: Pleural effusion samples indicated for both cell block and cell smear techniques at the Pathology Department with complete patient records.Exclusion criteria: Coagulated specimens.

2.2. Study period and location

The study was conducted from February 2024 to September 2024. Data were collected from October 2021 to May 2024 at the Pathology Department of Ha Dong General Hospital.

2.3. Research methods

2.3.1. Study design

A cross-sectional descriptive study was conducted.

2.3.2. Sample size and selection

The study used a total sample approach. A total of 176 pleural effusion samples meeting inclusion and exclusion criteria were collected from October 2021 to May 2024.

2.4. Research variables

Cell block and cell smear diagnosis results were classified into three categories: 1) Benign: No abnormal or suspicious malignant cells. 2) Malignant: Presence of abnormal cells meeting malignant criteria. 3) Suspicious for malignancy: Presence of abnormal proliferative cells insufficient for malignancy diagnosis.

2.5. Research process

- Step 1: Collect patient information: age, gender, effusion aspiration site from medical records.

- Step 2: Record fluid volume and color through direct observation or medical records

- Step 3: Process specimens using cell block and cell smear techniques per Ministry of Health protocols [5]. Cell blocks were embedded, sectioned, and stained with Hematoxylin-Eosin. Suspicious cases underwent immunohistochemical staining.

- Step 4: Record cytological diagnosis results. All diagnoses were performed by certified pathologists. Suspicious cases were reviewed by a pathology board for confirmation.

- Step 5: Data entry into Excel software.

- Step 6: Data analysis, report compilation, discussion, and conclusion formulation.

2.6. Data analysis and processing

Data were entered into Excel and analyzed using SPSS 26.0. Frequency and percentage statistics were used. Chi-square and Fisher's exact tests assessed differences, with statistical significance at $p<0.05$.

2.7. Ethical considerations

The study was approved by the Ha Dong General Hospital Scientific Committee and hospital leadership. Data were collected honestly and

objectively, solely for research purposes. Patient confidentiality was strictly maintained.

3. RESULTS

3.1. General characteristics of study subjects

The study population mainly belonged to the >70 age group (50%). The proportion of males was higher than that of females. Yellow-colored fluid had the highest proportion (48.3%). The majority of submitted fluid samples fell within the >250-500 mL range (46%) (Table 1).

Table 1. General characteristics of the study population

Characteristics	Number (n)	Percentage (%)
Age group		
≤50	28	15.9
51-60	16	9.1
61- 70	44	25.0
>70	88	50.0
Gender		
Male	111	63.1
Female	65	36.9
Fluid color		
Red	43	24.4
Serosanguinous	48	27.3
Yellow	85	48.3
Fluid volume		
<50 mL	22	12.5
50 - 250 mL	56	31.8
>250 - 500 mL	81	46.0
>500 mL	17	9.7
Total	176	100

3.2. Comparison of cell block and cell smear results in pleural effusion diagnosis

According to Table 2, the results of the cell block test on pleural effusion samples showed that 39 samples were malignant, accounting for 22.1%; 10 samples were suspicious for malignancy, accounting for 5.7%; and 127 samples were benign, accounting for 72.2%. Benign samples had the highest proportion.

Table 2. Comparison of cytological diagnosis results between the cell block and cell smear techniques on pleural effusion samples

Cell Smear	Cell Block				p
	Malignant n (%)	Suspicious n (%)	Benign n (%)	Total n (%)	
Malignant	13 (7.4)	0 (0)	0 (0)	13 (7.4)	<0.001**
Suspicious	4 (2.3)	0 (0)	0 (0)	4 (2.3)	
Benign	22 (12.4)	10 (5.7)	127 (72.2)	159 (90.3)	
Total	**39 (22.1)**	**10 (5.7)**	**127 (72.2)**	**176 (100)**	

***Fisher's-exact test*

The results of the cell smear test showed that 13 samples were malignant, accounting for 7.4%; 4 samples were suspicious for malignancy, accounting for 2.3%; and 159 samples were benign, accounting for 90.3%. Benign samples had the highest proportion.

A comparison of the cell block and cell smear test results on 176 pleural effusion samples showed that 140 cases had the same diagnostic results on both methods (accounting for 79.6%). Among them, 11 cases were malignant, 127 cases were benign, and there were no suspicious cases (with corresponding rates of 7.4%, 72.2% and 0%, respectively).

There were 36 cases with differing results between cell smear and cell block (accounting for 20.4%). Among them, 4 suspicious cases and 22 benign cases on cell smear were diagnosed as malignant on cell block (accounting for 2.3% and 12.4%, respectively). Additionally, 10 benign cases on cell smear were diagnosed as suspicious on cell block (accounting for 5.7%).

Cell block identified more malignant and suspicious cases than cell smear. The results were statistically significant with $p<0.05$.

3.3. Factors associated with cell block cytological diagnosis

Table 3. Factors associated with cytological diagnosis results using the cell block technique for pleural effusion (n=176)

Related Factors	Diagnosis Results			p
	Malignant n (%)	Suspicious n (%)	Benign n (%)	
Age group				
≤50	2 (7.1)	2 (7.1)	24 (85.8)	0.308**
51-60	4 (25.0)	1 (6.3)	11 (68.7)	
61-70	13 (29.6)	1 (2.3)	30 (68.2)	
>70	20 (22.7)	6 (6.8)	62 (70.5)	
Gender				
Male	19 (17.1)	4 (3.6)	88 (79.3)	**0.020***
Female	20 (30.8)	6 (9.2)	39 (60.0)	

Related Factors	Diagnosis Results			p
	Malignant n (%)	Suspicious n (%)	Benign n (%)	
Fluid color				
Red	8 (18.6)	3 (7.0)	32 (74.4)	0.638**
Serosanguinous	8 (16.7)	3 (6.2)	37 (77.1)	
Yellow	23 (27.1)	4 (4.7)	58 (68.2)	
Fluid volume				
<50 mL	5 (22.7)	4 (18.2)	13 (59.1)	**0.030****
50 - 250 mL	16 (28.6)	2 (3.6)	38 (67.8)	
>250 - 500 mL	13 (16.1)	2 (2.5)	66 (81.4)	
>500 mL	5 (29.4)	2 (11.8)	10 (58.8)	

**Chi-square*
***Fisher's-exact test*

Table 3 shows that:

There is a statistically significant association between gender and the cytological diagnosis results of the cell block technique for pleural effusion ($p<0.05$). The rates of malignancy and suspicious cases are higher in females than in males.

There is a statistically significant association between fluid volume and the cytological diagnosis results of the cell block technique for pleural effusion ($p<0.05$). The rates of malignancy and suspicious cases are higher in samples with a volume >500 mL compared to other samples.

The rates of malignancy and suspicious cases are higher in red-colored fluid samples than in other samples. However, this result is not statistically significant ($p>0.05$).

There is no statistically significant association between age group and the cytological diagnosis results of the cell block technique for pleural effusion ($p>0.05$).

4. DISCUSSION

Our study, conducted on 176 pleural effusion samples, showed that the majority of samples were obtained from patients over 70 years old. Male patients outnumbered female patients, with corresponding rates of 63.1% and 36.9%. Yellow-colored fluid had the highest proportion (48.3%), while red-colored fluid had the lowest proportion (24.4%). Our results are similar to those of Nguyen Quang Thi (2022), in which yellow-colored fluid accounted for the majority (61.3%) [6]the rate of malignancy and suspected malignancy accounted for 27.7%. The cell block technique was highly effective in the cytodiagnosis of some body cavity effusions with the success rate of 98.2%. The majority of cases that did not form a cell block were pleural fluid (78.1%. According to Ozcakar et al. (2010), a study on 390 cancer patients with pleural effusion concluded that in cases of pleural effusion with a history of cancer, bloody effusion is not significant in predicting the malignant nature of the effusion. The proportion of malignant cells found in bloody and non-bloody effusions was equivalent [7].

In our study, the majority of pleural effusion samples received from departments had a volume of >250–500 mL (46.0%), while 12.5% of the samples had a volume of <50 mL. There is still considerable debate regarding the optimal fluid volume required for the best diagnostic results. Determining whether a sample is benign or a false negative can be challenging in cases with low fluid volume. The Ministry of Health has recommended collecting 50–250 mL of fluid to obtain an adequate number of cells for diagnosis. [5]. In practice, we have received all pleural effusion samples indicated for the cell block test and observed that the larger the fluid volume, the more cellular sediment is obtained. With more cellular sediment, we have a stronger basis for diagnosis.

The cell smear technique was developed in the early 20th century, with the primary goal of facilitating the microscopic observation of cells. However, over time, researchers have recognized that the cell block technique can enhance the detection of malignant cells and provide more detailed information on cellular structures [2]. This method also facilitates more advanced analyses, such as immunohistochemistry, aiding in the early detection and accurate diagnosis of malignant diseases [3]. In our study, 72.2% of the samples were benign, 22.1% were malignant, and 5.7% were suspicious (Table 2). These proportions are consistent with previous studies, which indicate that the majority of cases are diagnosed as benign [2], [4], [8], [9]. According to Table 2, the concordance rate between cell smear and cell block results was 79.6%, while the discrepancy rate was 20.4%. The detection rates of malignancy and suspicious cases were higher with the cell block technique compared to the cell smear technique (22.1% and 5.7% vs. 7.4% and 2.3%, respectively). This difference was statistically significant with $p<0.05$. Our results are also consistent with other studies worldwide [4], [8], [9]. According to S.H. Kumar et al. (2020), the highest diagnostic concordance between the cell block and cell smear techniques was observed in synovial fluid (4/4, 100%) and pericardial fluid (1/1, 100%), followed by pleural fluid (38/40, 95%) and peritoneal fluid (33/39, 84.6%). The sensitivity and specificity of the cell smear technique compared to the cell block technique in effusion diagnosis were 86% and 100%, respectively [9]. According to S. S. Sabitha Rani et al. (2021), the lower malignancy detection rate of the cell smear technique compared to the cell block technique is due to the dispersed nature of cells in cell smears, with cellular morphology being obscured by a background of red blood cells, numerous inflammatory cells, necrotic debris, and reactive mesothelial cells. The cell block technique enhances the effectiveness of malignancy diagnosis by 6.66% compared to the cell smear technique [4].

Our study results showed a statistically significant association between gender and fluid volume with the cell block test results for pleural effusion ($p<0.05$). The study found that the malignancy diagnosis rate was higher in females than in males, and the malignancy rate was higher in the >500 mL group compared to other groups. There was no statistically significant association between age group and fluid color with the cell block test results (Table 3). According to several studies, malignant pleural effusion is commonly associated with lung cancer and breast cancer [9], [10]. Breast cancer occurs more frequently in females than in males because the ovaries in females produce higher levels of estrogen and progesterone. These hormones play a crucial role in the development of breast glandular tissue and cell division. Their continuous presence throughout the menstrual cycle can stimulate abnormal cell growth, increasing the risk of cancer [11].

Multiple studies have demonstrated a correlation between certain characteristics of pleural effusion and malignancy [12]. However, there is no evidence that pleural fluid volume directly determines the

malignancy rate. Malignant pleural effusion often occurs in advanced or metastatic cancer stages, potentially due to angiogenesis leading to increased vascular permeability. This condition typically indicates that the patient may be in a severe disease stage with a poor prognosis [12]. On the other hand, a larger volume of pleural effusion results in a higher amount of cellular sediment, improving the ability to observe abnormal cells and increasing the likelihood of malignancy diagnosis.

Regarding color, pleural effusion can vary significantly in appearance depending on the underlying cause. For example, red or bloody fluid may suggest the presence of cancer or trauma, whereas clear or pale yellow fluid may indicate benign causes such as heart failure or cirrhosis. Although color alone is not a definitive indicator of malignancy, certain appearances, such as turbid or bloody fluid, may suggest a higher likelihood of cancer presence [12].

5. CONCLUSION

The cell block technique identified more malignant and suspicious cases than the cell smear technique in diagnosing malignant pleural effusion. A significant association was found between gender, fluid volume and cytological diagnosis using the cell block technique.

REFERENCES

[1]. J. M. Porcel and R. W. Light, Diagnostic approach to pleural effusion in adults, *Am. Fam. Physician*, vol. 73, no. 7, pp. 1211–1220, Apr. 2006.

[2]. L. G. Koss and M. R. Melamed, *Koss' Diagnostic Cytology and Its Histopathologic Bases*, 5th ed. Lippincott Williams & Wilkins, 2006.

[3]. M. Thapar, R. K. Mishra, A. Sharma, V. Goyal, and V. Goyal, Critical analysis of cell block versus smear examination in effusions, *J. Cytol.*, vol. 26, no. 2, pp. 60–64, Apr. 2009, doi: 10.4103/0970-9371.55223.

[4]. S. S. S. Rani and I. S. Vamshidhar, "Efficacy of Cell Block Technique in the Cytodiagnosis of Malignant Serous Effusions," *Maedica*, vol. 16, no. 1, pp. 16–21, Mar. 2021, doi: 10.26574/maedica.2020.16.1.16.

[5]. Ministry of Health, *Guidelines for Technical Procedures in Pathology and Cytology*. Hanoi: Medical Publishing House, 2016.

[6]. Nguyen Quang Thi *et al.*, Efficacy of cell block technique in the cytodiagnosis of some body cavityeffusions at the 108 Military Central Hospital, *J. 108 - Clin. Med. Phamarcy*, vol. 17, no. 8, pp. 156–162, Aug. 2022, doi: 10.52389/ydls.v17iDB8.1316.

[7]. Ozcakar, B *et al.*, Does pleural fluid appearance really matter? The relationship between fluid appearance and cytology, cell counts, and chemical laboratory measurements in pleural effusions of patients with cancer, *J. Cardiothorac. Surg.*, vol. 5, pp. 1–5, 2010.

[8]. S. S. S. Rani, I. S. Vamshidhar, N. A. John, and J. John, Diagnosis of Pleural Fluid Effusions by Cell Block and Pleural Biopsy - A Comparative Study, *J. Cytol.*, vol. 39, no. 4, pp. 169–173, 2022, doi: 10.4103/joc.joc_91_21.

[9]. S. H. KUMAR, S. S, D. SHETTY, and R. RAO, Clinicopathological Study of 117 Body Fluids: Comparison of Conventional Smear and Cell Block Technique, *Curr. Health Sci. J.*, vol. 46, no. 4, pp. 336–343, 2020, doi: 10.12865/CHSJ.46.04.03.

[10]. U. Shivakumarswamy, S. U. Arakeri, M. H. Karigowdar, and B. Yelikar, Diagnostic utility of the cell block method versus the conventional smear study in pleural fluid cytology, *J. Cytol. Indian Acad. Cytol.*, vol. 29, no. 1, pp. 11–15, 2012, doi: 10.4103/0970-9371.93210.

[11]. V. Atashgaran, J. Wrin, S. C. Barry, P. Dasari, and W. V. Ingman, Dissecting the Biology of Menstrual Cycle-Associated Breast Cancer Risk, *Front. Oncol.*, vol. 6, Dec. 2016, doi: 10.3389/fonc.2016.00267.

[12]. Ali Saeed Wahla, Mateen Uzbeck, Yaser Abu El Sameed, and Zaid Zoumot, Managing malignant pleural effusion | Cleveland Clinic Journal of Medicine, *Cleveland Clinic Journal of Medicine*, vol. 86, no. 2, pp. 95–99, 2019, doi: https://doi.org/10.3949/ccjm.86a.17095.

NEW INCIDENCE TRENDS OF BREAST CANCER AND DIAGNOSTIC METHODS FOR HER2 IN VIETNAM IN YEAR 2010-2022

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ABSTRACT

Aims: 1) Describe the trend in new incidence of breast cancer (BC) in the world and in Vietnam and 2) Describe the trend in diagnosis of HER2 in BC patients.

Materials and Methods: A number of studies and reports on the trend of cancer incidence of BC and diagnosis of HER2 in the period 2010-2022 in the world and in Vietnam. Synthesize and analyze data collected from 20 studies and articles on major online medical databases inclusive Medline/Pubmed, Web of Science, CI5 and GLOBOCAN; Domestic Medical Journal; Documents, Research Works, Thesis, Data Reported at International and Domestic Meeting. Zotero 6.0 software was used to manage and cite collected documents.

Results*:* 20 studies and reports in the world and in Vietnam were selected for the study, including seven documents on new trends of BC by time and geography, 13 documents on new trends for diagnosis of HER2. The incidence of BC tends to increase in the world and in Vietnam. Vietnam has a lower incidence rate than the world, but has a high mortality rate from cancer (10.5 deaths/26.4 new cases/100,000 population) equivalent to nearly 40%, common aged 50-59. Immunohistochemistry (IHC) is chosen as the routine test in the diagnosis of BC and FISH is the gold standard for evaluating HER2 gene amplification with a sensitivity of up to 98% with a specificity of 100%.

Conclusion: Vietnam is in the trend of increasing the incidence of BC in the world, mainly in the age group 50-59 during menopause, the mortality rate due to cancer is high, accounting for about 40% of all cases. new. The diagnosis of HER2 in BC is confirmed, the first test is IHC, FISH/CISH techniques.

Keywords: Breast cancer; HER2; diagnosis; Vietnam; IHC; FISH/CISH.

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1. INTRODUCTION

Breast cancer (BC) is the most common cancer in women. It has surpassed lung cancer to become the leading cause of cancer worldwide, with 2.3 million new cases in 2022, accounting for 11.7% of all new cancer cases and 25.8% of all cancers in women. In Vietnam, it is estimated that there were 182,563 new cases and 122,690 deaths due to BC. For every 100,000 people, 159 are newly diagnosed, and 106 die from BC [1]. BC manifests in various subtypes. Advances in early diagnosis, intervention, and new treatment methods have improved survival rates and prognoses. Among these, targeted therapy has emerged as a key treatment option for HER2-positive BC patients. HER2 (Human Epidermal Growth Factor Receptor 2) is one of the four members of the EGFR (Epidermal Growth Factor Receptor) family, which includes four receptors: EGFR, HER2, HER3, and HER4. *HER2* gene amplification is observed in approximately 20–30% of BC patients. HER2-positive BC is a highly aggressive subtype characterized by an overexpression of the HER2 protein on the cancer cell surface beyond normal thresholds. This subtype tends to grow faster, metastasize earlier, and recur more quickly [2,3]. However, in Vietnam, no studies have yet addressed the trends in new BC diagnoses or the methods for diagnosing HER2 in patients. Therefore, we conducted this review with two objectives: 1) To describe the trends in new BC cases globally and in Vietnam. 2) To describe the trends in diagnostic methods for identifying HER2 in BC patients.

2. STUDY SUBJECTS AND METHODS

2.1. Study subjects

The study reviewed various research and reports on the trends in incidence, diagnosis, and treatment of breast cancer (BC) during the 2010-2022 period globally and in Vietnam.

2.2. Search strategy

2.2.1. Databases

Relevant studies were searched in medical databases such as Medline/PubMed, Web of Science, CI5 and GLOBOCAN, as well as in domestic medical journals. Additional resources included research reports, theses, conference presentations and publications from both national and international sources. Data were updated until July 2022.

2.2.2. Search terms

English terms used for the search in titles or abstracts were: ([Breast cancer OR Breast carcinoma] AND [Incidence OR Epidemiology OR Epidemic OR Trend]) OR ([Breast cancer OR Breast carcinoma] AND [HER2 testing OR HER2 determination]).

2.3. Literature Selection

2.3.1. Inclusion Criteria

- Studies and reports with data published globally from 2010 to the end of July 2022.

- Studies and reports presenting BC incidence rates, including crude and age-standardized rates.

- Studies and reports on HER2 diagnostic techniques.

- Languages: English and Vietnamese.

2.3.2. Exclusion Criteria

- Studies and reports focusing on BC incidence in specific subpopulations rather than the general population.

- Studies and reports without clear population data for standardization.

2.3.3. Selection and Management Process

Literature from the databases underwent two rounds of classification:

- Round 1: Screening titles and abstracts, excluding studies based on the exclusion criteria.

- Round 2: Full-text review of articles that passed the first round. The Zotero 6.0 software was used for managing and citing the collected literature.

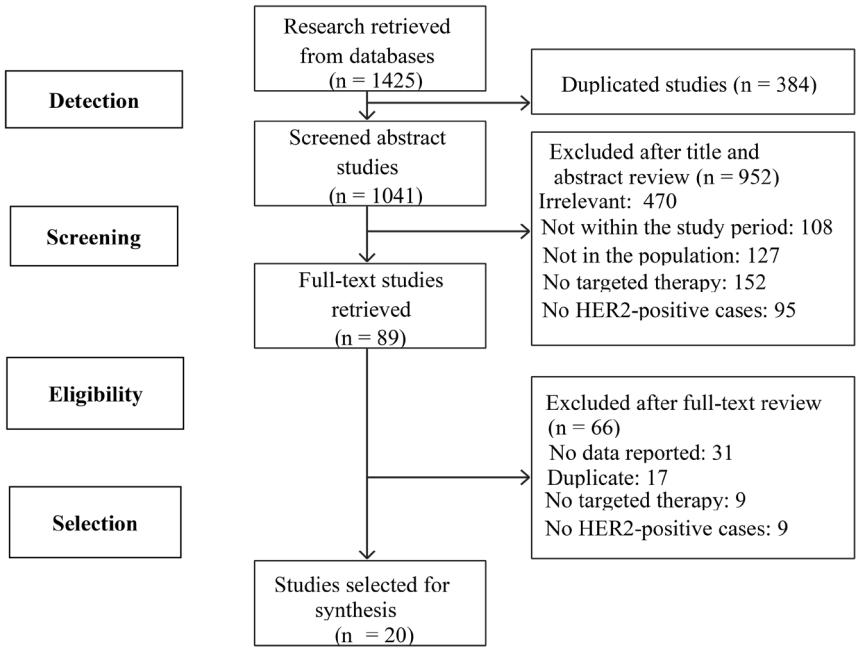

Figure 1. Search and selection results of studies

2.4. Screening results

Through comprehensive literature searches, 1,425 abstracts were identified from electronic databases that met the study's inclusion criteria. After removing 384 duplicates and excluding 952 studies that did not align with the objectives, population, or research issues, 89 full-text articles remained for further review. Of these, 66 articles were excluded due to the following reasons:

- No data reporting (31 articles).
- Duplication (17 articles).
- No targeted therapy (9 articles).
- No HER2-positive data (9 articles).
- Ultimately, 20 articles met the inclusion criteria for synthesis and analysis.

2.5. Characteristics of selected studies

According to Diagram 1, a total of 20 studies were selected to present research findings based on two objectives, including 7 studies on the trends of new breast cancer incidence by time and geography and 13 studies on HER2 diagnostic trends.

2.6. Data Analysis

Data were analyzed using SPSS version 25 software (IBM, USA).

3. RESULTS

3.1. Trends in new breast Cancer incidence worldwide and in Vietnam

In 2020, the global incidence rate of breast cancer was 47.8 cases per 100,000 people, with Australia having the highest incidence rate at 95.5 cases per 100,000, while Southeast Asia had the lowest at 41.2 cases per 100,000 [1]. Moreover, the age-standardized incidence rate of breast cancer per 100,000 population showed an increasing trend, rising from 43.4 cases per 100,000 in 2012 to 47.8

cases per 100,000 in 2020. However, there were variations in incidence rates across different regions. Specifically, Australia had the highest incidence rate, increasing from 85.5 cases per 100,000 in 2012 to 94.2 cases per 100,000 in 2018 and 95.5 cases per 100,000 in 2020. Conversely, Southeast Asia had the lowest incidence rates over the years, recorded at 34.8, 38.1, and 41.2 cases per 100,000 in 2012, 2018 and 2020, respectively.

The rate of increase in new breast cancer incidence also varied across regions worldwide. North America experienced the highest increase, from 67.6 cases per 100,000 in 2012 to 89.4 cases per 100,000 in 2020, whereas Western Asia had the lowest increase, from 43.8 cases per 100,000 in 2012 to 46.6 cases per 100,000 in 2020 [1,4,5,6] (Figure 2).

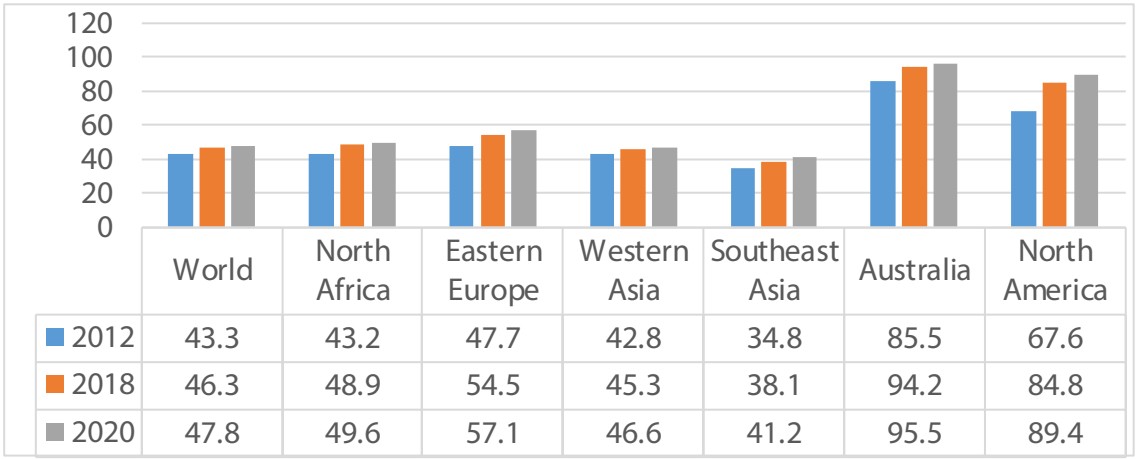

Figure 2. Age-Standardized Incidence Rates of Breast Cancer in Various Regions Worldwide [1, 4, 5, 6]

According to the report published in 2020, Vietnam recorded 21,555 new cases of breast cancer, accounting for 25.8% of all common cancers in women [7]. During the period from 2010 to 2020, the number of new cases showed an increasing trend over the years, with a sharp rise between 2018 and 2020, averaging approximately 3,163 new cases per year. The age-standardized incidence rate per 100,000 population increased but was not consistent across the years. Specifically, in 2010, the rate was 29.9 cases per 100,000 population, which decreased to 26.4 cases per 100,000 in 2018 but then rose to 34.2 cases per 100,000 in 2020 (Table 1).

Table 1. New breast cancer incidence rates in Vietnam (2010-2020) [7]

Year	2010	2018	2020
Number of new cases	12,533	15,229	21,555
Age-standardized incidence rate per 100,000 population	29.9	26.4	34.2

The age group under 30 had the lowest incidence rate of breast cancer, specifically 1.5%, 1.3%, and 1.1% in 2014, 2016 and 2018, respectively. The highest incidence rate was observed in the 50–59

age group, with rates of 33.1%, 27.3%, and 34.8% in 2014, 2016 and 2018, respectively. The incidence rate of breast cancer increased with age, with the highest concentration in the 50-59 age group, while cases were rare in those under 30 [2,8] (Table 2).

Table 2. New breast cancer incidence rates by age group (2014-2018) [2, 8].

Age Group	Year		
	2014	2016	2018
< 30	1.5	1.3	1.1
30-39	10.9	13.7	9.8
40-49	24.3	25.7	22.8
50-59	33.1	27.3	34.8
60-69	22.3	21.5	31.5
>70	7.9	10.5	

3.2. Trends in HER2 diagnosis in breast cancer patients

Different HER2 diagnostic techniques for breast cancer patients have their own advantages and limitations. Immunohistochemistry (IHC) can only detect protein expression on the cell membrane, while gene and protein expression are not always consistent. Therefore, FISH/CISH techniques have been implemented to accurately assess the amplification level of the *HER2* gene.

The issue of specimen collection is also a concern in simplifying the process. In previous techniques such as IHC and FISH/CISH, most tests were performed using paraffin-embedded tissue samples. However, tissue samples have certain limitations and cannot be repeatedly tested multiple times. Therefore, future techniques are being developed to use blood samples, such as the ELISA method [9] (Table 3).

Table 3. HER2 Diagnostic Techniques [2, 9]

No.	Diagnostic Technique	FDA Approved	Method	Sample Type	Target	Advantages	Disadvantages
1	IHC CTA	No	IHC (CB-11 + 4D5 antibody)	Paraffin-embedded tissue	HER2 protein on the cell surface	Simple, low cost	Affected by factors such as fixation time and method; subjective due to semi-quantitative scoring
2	IHC HercepTest	Yes	IHC polypclonal goat antibody)				
3	IHC Pathway	Yes	IHC (CB-11 replaced with 4B5 in 2008)				

No.	Diagnostic Technique	FDA Approved	Method	Sample Type	Target	Advantages	Disadvantages
4	FISH Inform	Yes	FISH (HER2 probe)	Paraffin-embedded tissue	*HER2* gene on chromosome 17	More accurate than IHC, less affected by pre-analytical factors	Higher cost and more time-consuming than IHC
5	FISH PathVysion	Yes	FISH (HER2 + CEP17 probe)				
6	FISH HER2 PharmDX	Yes	FISH (HER2 + CEP17 probe)				
7	CISH SpotLight	Yes	FISH (HER2 probe)	Paraffin-embedded tissue	*HER2* gene on chromosome 17	Lower cost and faster than FISH; easy signal assessment	Difficult to evaluate in areas with high amplification levels
8	SISh Enzmet	No	FISH (HER2 + CEP17 probe)			Fully automated, easy signal assessment	Requires additional hybridization to evaluate CEP17 separately to overcome chromosome 17 polysomy
9	mRNA OncotyeDX	No	RT-PCR	Fresh/frozen tissue	mRNA	Can assess RNA levels and quantify expression	False negatives due to RNA degradation in tissue samples
10	mRNA	No	RT-PCR; microarray				
11	Dimerization HERmark	No	VeraTag capillary electrophoresis	Paraffin-embedded tissue	Protein dimers	Simple, accurate, quantifiable	Expensive and time-consuming
12	ELISA serum HER2 Advia Centaur	Yes	Sandwich immnoassay	Serum sample	Protein (serum)	Easy to perform, fast, uses serum samples	Results may be affected in patients undergoing Trastuzumab treatment

4. DISCUSSION

Globally, the incidence of breast cancer has shown an increasing trend across all regions. However, the rate of increase varies among continents. In 2020, Australia had the highest incidence rate, with 95.5 cases per 100,000 population, while Southeast Asia had the lowest, with 41.2 cases per 100,000 [1]. From 2012 to 2020, North America experienced the highest increase in new breast cancer cases, with a growth rate of 21.8 cases per 100,000 population. This suggests that breast cancer incidence is influenced by various factors, including socioeconomic conditions, lifestyle, cultural habits and exposure to carcinogens.

Furthermore, developed countries tend to have high breast cancer incidence rates but significantly lower mortality rates (Australia: 12.1 deaths per 100,000, North America: 12.5 deaths per 100,000) [1]. This reflects the fact that while lifestyle factors in these countries-such as processed food consumption, low birth rates, and short breastfeeding duration-may contribute to an increased risk of breast cancer, their advanced healthcare systems ensure effective early screening, diagnosis, and treatment, leading to higher early detection rates and lower mortality.

Conversely, in regions like North Africa and Western Asia, women's health issues are often overlooked, making breast cancer a leading cause of mortality due to late-stage detection. Notably, approximately 20% of breast cancer cases worldwide are attributed to modifiable risk factors, including alcohol consumption, smoking, obesity, and physical inactivity. Therefore, reducing the burden of breast cancer requires promoting healthier lifestyles and habits.

Vietnam follows a similar trend of increasing breast cancer incidence as seen globally. Between 2010 and 2020, the incidence rate rose from 29.9 to 34.2 cases per 100,000 population. Although Vietnam does not belong to the group of countries with the highest incidence rates and has a lower incidence rate than the global average, it has a high breast cancer mortality rate (10.5 deaths per 26.4 new cases per 100,000 population), equivalent to nearly 40% [6]. This high mortality rate may be due to late-stage diagnosis, poor prognosis, and ineffective treatment. Therefore, breast cancer screening and early detection are crucial, as early-stage diagnosis leads to simpler treatment, higher treatment efficacy, and lower costs.

Immunohistochemistry (IHC) is the most widely used diagnostic method for determining HER2 protein overexpression on breast cancer cell surfaces, with approximately 80% of breast cancer patients in the U.S. diagnosed with HER2 status using IHC. IHC has advantages such as simplicity, ease of implementation, low cost, and broad applicability in diagnostic laboratories. However, IHC results rely on a semi-quantitative scoring system, which introduces subjectivity and reduces accuracy.

To overcome these limitations, fluorescence in situ hybridization (FISH) is used to detect HER2 gene amplification through fluorescently labeled probes. FISH can incorporate chromosome 17 centromere (CEP17) probes for quality control. Currently, three FDA-recommended FISH techniques with equivalent diagnostic value include FISH Inform, which detects HER2 alone and FISH PathVysion and FISH PharmDX, which use dual probes for HER2 and CEP17 centromere detection. Among these, FISH is considered an objective scoring method, offering high accuracy in detecting *HER2* gene amplification, making it the gold standard with a sensitivity of 98% and a specificity of 100% [9]. When IHC results are equivocal (IHC 2+), additional FISH testing is required for confirmation. However, FISH has some drawbacks, including the need for a fluorescence microscope, higher costs and longer processing times compared to IHC.

The introduction of chromogenic in situ hybridization (CISH) and silver-enhanced in situ hybridization (SISH) has integrated the advantages of both IHC and FISH. These methods detect *HER2* gene copy number using a single HER2 probe labeled with chromogenic or silver stains, eliminating the need for fluorescence microscopy. CISH and FISH have shown a high concordance rate of 97–99% [9].

In Vietnam, IHC remains the first-line diagnostic test for determining HER2-positive breast cancer. If the IHC result is 2+, confirmatory FISH/CISH testing is required.

5. CONCLUSION

Vietnam is experiencing an increasing trend in new breast cancer cases, similar to the global pattern. The disease is most commonly diagnosed in women aged 50–59 during menopause, and the mortality rate is high, accounting for approximately 40% of new cases. The primary diagnostic test for HER2-positive breast cancer is IHC, with FISH/CISH used for confirmation when the IHC result is 2+, offering a sensitivity of 98% and a specificity of 100%.

REFERENCES

[1]. Hyuna Sung, Jacques Ferlay, Rebecca L Siegel, et al (2021), *Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries*, CA Cancer J Clin, 71(3), 209-249.

[2]. Dang Cong Thuan, Le Trong Lan, Nguyen Tran Bao Song, et al. (2018), *Study on HER2 Status and Its Relationship with Prognostic Factors in Invasive Breast Carcinoma*, Hue journal of medicine and pharmacy, 8(4), 13-22.

[3]. Hafiz Muhammad Asif, Sabira Sultana, Saeed Ahmed, et al (2016), *HER-2 Positive Breast Cancer - a Mini-Review*, Asian Pac J Cancer Prev, 17(4), 1609-1615.

[4]. J Ferlay, M Colombet, I Soerjomataram, et al (2019), *Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods*, Inter J Cancer, 144, 1941-53.

[5]. Jacques Ferlay, Isabelle Soerjomataram, Rajesh Dikshit, et al (2015), *Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012*, Inter J Cancer, 136, E359-386.

[6]. Freddie Bray, Jacques Ferlay, Isabelle Soerjomataram, et al (2018), *Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries*, CA Cancer J Clin, 68(6), 394-424.

[7]. WHO, International Agency for Research on Cancer. Viet Nam Source: Globocan 2020, 2021 March.

[8]. Nguyen Thi Mai Lan (2020), *Study on the Incidence of Breast Cancer in Women in Hanoi from 2014 to 2016*, Doctoral Dissertation, Hanoi Medical University, 78-79.

[9]. Sejal Shah, Beiyun Chen (2010), *Testing for HER2 in Breast Cancer: A Continuing Evolution*, Pathology Res Int, 2011, 903202.

THE UTILITY OF 18F-FDG PET/CT IN DETECTING RECURRENT BREAST CANCER AND ITS CORRELATION WITH SOME CLINICAL CHARACTERISTICS

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ABSTRACT

Objective: To evaluate the role of 18F-FDG PET/CT in detecting recurrent breast cancer lesions and its association with various clinical characteristics.

Materials and Methods: A cross-sectional descriptive study was conducted on 32 patients at Vietnam National Cancer Hospital who were diagnosed with recurrent breast cancer based on histopathological confirmation and subsequently underwent 18F-FDG PET/CT for evaluation.

Results: The mean age of the 32 female patients was 53.7 years (range: 39-74 years). The most common histopathological subtype was infiltrating duct carcinoma, not otherwise specified (59.4%). Recurrence was most commonly detected in stage II (43.8%) and stage III (34.4%), with 56.3% of cases presenting with lymph node metastases prior to treatment. The most common sites of recurrence were the lymph nodes (53.1%) and chest wall (18.8%). The median time to recurrence detection was 25 months. 18F-FDG PET/CT accurately identified recurrent disease in 28 cases (sensitivity: 87.5%), with a mean SUVmax of 10.2. Additionally, metastatic lesions in other locations were detected in 15 out of 28 cases. Higher SUVmax values were observed in patients with advanced-stage disease, lymph node metastases, ER-negative status, PR-negative status, and HER2-positive tumors. No significant difference in SUVmax was observed among different histopathological subtypes.

Conclusion: 18F-FDG PET/CT demonstrates high sensitivity in detecting recurrent breast cancer lesions and reveals variations in SUVmax values associated with clinical and paraclinical characteristics. However, given the limited sample size, further studies with larger cohorts are required to validate these findings.

Keywords: Recurrent breast cancer; 18F-FDG PET/CT; clinical - paraclinical characteristics.

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1. INTRODUCTION

Breast cancer (BC), as defined by the World Health Organization (WHO), is a malignant disease characterized by the uncontrolled proliferation of breast glandular cells, leading to tumor formation. According to GLOBOCAN 2022, breast cancer ranks as the second most common cancer worldwide, with 2,296,840 new cases, and the fourth leading cause of cancer-related mortality, accounting for 666,103 deaths[1].

Recurrent breast cancer occurs in approximately 20% of breast cancer patients and is often associated with a poor prognosis. The median survival time for patients with recurrent breast cancer ranges from 9 to 36 months; however, early detection of recurrence can improve survival outcomes[2, 3].

In addition to conventional imaging modalities such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), several studies have demonstrated that 18F-FDG PET/CT is a highly accurate diagnostic tool for detecting recurrent breast cancer, with a reported sensitivity of 90-97% and specificity of 71-93%[4-7]. The interpretation of 18F-FDG PET/CT findings is influenced by multiple factors, particularly clinical and paraclinical characteristics. Therefore, patient stratification based on these factors is crucial for optimizing imaging indications and ensuring accurate diagnosis. However, limited research has been conducted on the correlation between clinical characteristics and imaging findings on 18F-FDG PET/CT in recurrent breast cancer. Thus, this study aims to evaluate the role of 18F-FDG PET/CT in detecting recurrent breast cancer lesions and its association with specific clinical and paraclinical characteristics.

2. PATIENTS AND METHODS

2.1. Patients

This study included 32 female patients diagnosed with recurrent breast cancer based on histopathological findings. All patients had completed curative treatment at least six months prior and were identified with suspected recurrent lesions on ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) at Vietnam National Cancer Hospital between April 2023 and November 2023. Suspicious lesions were confirmed by cytological or histopathological examination, and all patients underwent 18F-FDG PET/CT for disease evaluation.

- The study excluded patients who had two or more distinct primary cancers.

2.2. Methods

- Study design: Cross-sectional descriptive study.

- Sampling method: Convenience sampling.

- Data analysis: Data were processed using Excel 2016 and SPSS 26. One-way ANOVA was applied to analyze differences between groups.

- 18F-FDG PET/CT Imaging Protocol:

+ 18F-FDG was produced by the cyclotron (HIC-KOTRON13) and PET/CT was performed using the PET/CT system (GE Discovery IQ).

+ The 18F-FDG PET/CT imaging procedure was conducted following the EANM (EARL standards). All patients were instructed to fast for at least 6 hours before imaging. At the time of the tracer injection, patients should have had a blood glucose level of less than 140 mg/dL. Before and after injection, patients were kept lying comfortably in a quiet, dimly lit room. Image acquisition was started 45-60 minutes after intravenous administration of FDG (0.15 mCi/kg body weight).

- Image Interpretation:

+ Two nuclear medicine specialists independently reviewed the images.

+ Lesions presenting with abnormal anatomical findings on CT and abnormal FDG uptake on PET

were classified as malignant.

+ SUVmax was determined based on a 1 mL region of interest (ROI) at the site of recurrence on 18F-FDG PET/CT.

- Histopathological and immunohistochemical classification followed the 2012 WHO classification system, while disease staging was conducted according to the AJCC 8th edition [8, 9].

3. RESULTS

3.1. Characteristics of the patients

The study included 32 female patients with recurrent breast cancer. The mean age was 53.7 ± 1.6 years, ranging from 39 to 74 years. The median time to recurrence was 25 months. The earliest recurrence was observed at 7 months, while the latest recurrence occurred at 212 months post-treatment.

Table 1. Histopathological characteristic initial pre-treatment

Histopathological type	Percentage (%)	No. of patients (n)
Infiltrating duct carcinoma, NOS	59,4	19
Lobular carcinoma, NOS	6,3	2
Other histological types	34,4	11
Total	100	32

Table 2. Immunohistochemical characteristics initial pre-treatment

	Positive		Negative	
	Percentage (%)	Number of patients (n)	Percentage (%)	Number of patients (n)
ER (Estrogen receptor)	62,5	20	37,5	12
PR (Progesteron receptor)	46,9	15	53,1	17
HER-2	37,5	12	62,5	20

Table 3. Staging initial pre-treatment

Staging initial pre-treatment	Percentage (%)	No. of patients (n)
Stage I	21,8	7
Stage II	43,8	14
Stage III	34,4	11
Stage IV	0	0
Lymph node metastasis status before treatment		
Lymph node metastasis	56,3	18
No lymph node metastasis	43,8	14

Comment: In the present study, the majority of patients had invasive ductal carcinoma, no special type (59.4%). The most common immunohistochemical profile was ER-positive (62.5%), PR-negative (53.1%) and HER-2-negative (62.5%). The most frequently observed disease stages before treatment were Stage II (43.8%) and Stage III (34.4%). Lymph node metastasis was present in 56.3% of patients before treatment.

Table 4. Recurrent disease locations

Recurrence site	Percentage (%)	No. of patients (n)
Lymph nodes	53,1	17
Chest wall	18,8	6
Lungs	9,4	3
Liver	9,4	3
Bones	9,4	3
Total	100	32

Comment: The most common recurrence sites in this study were lymph nodes (53.1%) and chest wall (18.8%).

3.2. The role of 18F-FDG PET/CT in diagnosing recurrent breast cancer

Table 5. Role of 18F-FDG PET/CT in diagnosing recurrent breast cancer

	No. of patients recurrence	Total no. of patients (n)	Sensitivity (%)
18F-FDG PET/CT	28	32	87,5%
Histopathology	32	32	
Additional lesions detected on 18F-FDG PET/CT	15/28 patients		
Mean SUVmax: 10,2 ± 0,9			

Comment: 18F-FDG PET/CT demonstrated a high sensitivity (87.5%) in detecting recurrent breast cancer with the mean SUVmax of recurrent lesions was 10.2 ± 0.9, indicating a high metabolic activity in these lesions. Additional, metastatic lesions were detected in 53.6% of cases using 18F-FDG PET/CT.

3.3. Correlation between 18F-FDG PET/CT and clinical, paraclinical characteristics

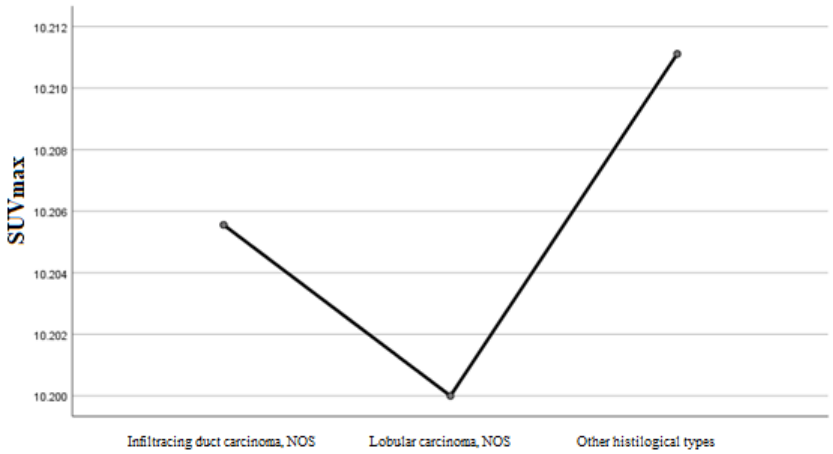


Figure 1. Correlation between SUVmax and histopathological characteristics

Comment: The SUVmax values for the three histopathological subtypes were 10.2 ± 1.2, 10.2, and 10.2 ± 1.8, respectively. There was no significant difference in SUVmax among the different histopathological subtypes on 18F-FDG PET/CT.

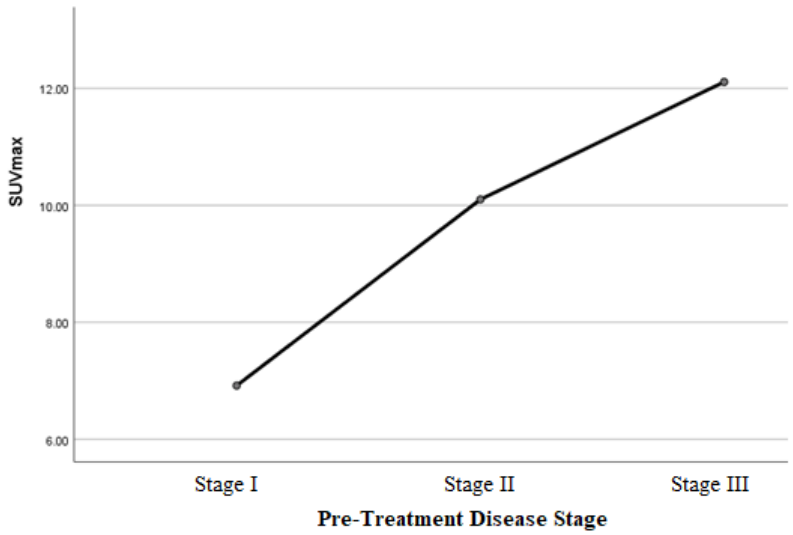


Figure 2. Correlation between SUVmax and initial pre-treatment disease stage

Comment: There was a trend of increasing SUVmax with more advanced pre-treatment disease stages, however, the difference was not statistically significant (p = 0.16).

Table 6. Correlation between SUVmax and lymph node metastasis initial pre-treatment

Patient characteristics		Have lymph nodes metastasis	No lymph node metastasis	Total
PET/CT positive	Number of patient (n)	17	11	28
	Mean SUVmax	11,7±1,3	7,7±1,2	-

Comment: Patients with pre-treatment lymph node metastasis had significantly higher SUVmax values than those without metastasis, the difference was statistically significant (p = 0.02).

Table 7. Correlation between SUVmax and immunohistochemical markers

Characteristics / Immunohistochemical Marker		PET/CT positive		PET/CT negative
		No of patients (n)	Mean SUVmax	
ER	Positive	16	7,7±0,9	4
	Negative	12	13,6±1,3	0
PR	Positive	12	7,6±1,2	3
	Negative	16	12,1±1,2	1
HER-2	Positive	12	11,9±1,6	0
	Negative	16	8,9±1,0	4

Comment: SUVmax was significantly higher in ER-negative and PR-negative groups, with p-values of 0.01 and 0.02, respectively. HER-2 positive patients had higher SUVmax than HER-2 negative patients, but the difference was not statistically significant (p = 0.12).

4. DISCUSSION

The study included 32 patients, with an average age of 53.7 ± 1.6 years. Before treatment, most patients were in stages II and III, with a high rate of lymph node metastasis. Regarding histopathological characteristics, invasive ductal carcinoma was the predominant subtype, which is also the most common histological type of breast cancer. The recurrence time in the study group ranged from 7 to 212 months, with a median of 25 months. The most frequent recurrence sites were local and regional (lymph nodes and chest wall, accounting for 79.1%), consistent with the typical recurrence pattern of breast cancer.

In this study, we compared the detection capability of 18F-FDG PET/CT for recurrent lesions with histopathological/cytological results. The findings demonstrated that the sensitivity of 18F-FDG PET/CT in diagnosing recurrent breast cancer was 87.5%, with an average SUVmax of 10.2 ± 0.9, facilitating the visualization of lesions on imaging. These results align with previous studies, such as Taalab et al. (2017), which evaluated 18F-FDG

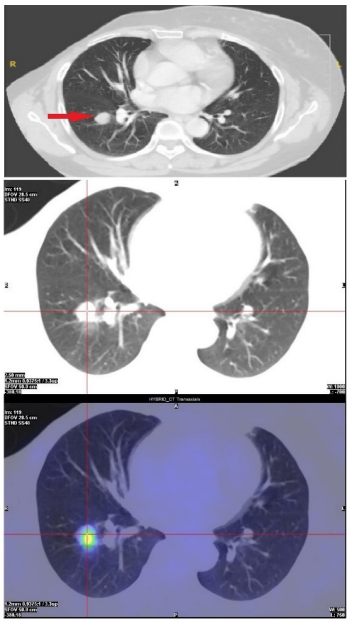
PET/CT in 37 patients with recurrent breast cancer, and Dong et al. (2015), which investigated the role of CA15-3 and 18F-FDG PET/CT in diagnosing recurrent breast cancer. These studies consistently highlight the high diagnostic accuracy of 18F-FDG PET/CT for detecting breast cancer recurrence [5, 6]. Additionally, in our study, 18F-FDG PET/CT identified additional suspicious recurrent lesions in 15 out of 28 patients with positive PET/CT findings. This represents a significant advantage of this imaging modality over conventional diagnostic techniques, which typically detect lesions at only a single site.

Our analysis of the relationship between 18F-FDG PET/CT characteristics and histopathological features in this study revealed no significant difference in SUVmax among different histopathological subtypes. However, a study conducted by Almir Galvão Vieira Bitencourt et al. (2014) reported a significant difference in SUVmax between invasive ductal carcinoma and other histological subtypes[10]. Since both studies had small sample sizes, further research is necessary to confirm these findings. Regarding disease stage, our study demonstrated that patients with more advanced disease stages or lymph node metastases exhibited higher SUVmax values compared to those in earlier stages or without lymph node involvement. This may be explained by the biological characteristics of cancer, as higher disease stages are associated with increased tumor burden and greater potential for metastasis. With respect to hormone receptor status, our results showed that patients with ER-negative or PR-negative tumors had significantly higher SUVmax values compared to those with positive hormone receptor expression. This finding is consistent with a 2023 study by Cornelis M. de Mooij et al., which also demonstrated a correlation between the immunohistochemical characteristics of breast cancer and 18F-FDG PET/CT findings. [11]. Regarding HER-2 status, our study found that SUVmax values were higher in HER-2-negative cases than in HER-2-positive cases, but this difference was not statistically significant ($p = 0.12$). In contrast, the study by Cornelis M. de Mooij et al. reported a similar trend, but their results were statistically significant ($p = 0.004$). This discrepancy may be attributed to the small sample size of our study, which may not have been sufficient to detect a significant difference.

Clinical case: A 53-year-old female patient was diagnosed with infiltrating duct carcinoma, NOS breast cancer, stage III, with lymph node metastasis in 2004. Her immunohistochemical profile was ER (-), PR (-), HER-2 (+), and she underwent surgical treatment followed by adjuvant chemotherapy. During a routine follow-up, a solitary pulmonary nodule in the right lung was detected on CT imaging. Histopathological examination of the lung lesion confirmed metastatic carcinoma originating from the breast. To further assess the extent of the disease, the patient underwent FDG-PET/CT imaging.

5. CONCLUSION

The 18F-FDG PET/CT imaging technique demonstrates high accuracy in diagnosing recurrent breast cancer. In our study, we observed that patients with a more advanced initial diagnosis stage, lymph node metastasis, ER-negative, PR-negative, and HER2-positive status exhibited higher SUVmax values. This suggests that 18F-FDG PET/CT may have greater diagnostic value in patients with these characteristics. However, further studies with larger patient cohorts and a broader range of clinical variables are necessary to fully establish the diagnostic utility of 18F-FDG PET/CT across different breast cancer subtypes.



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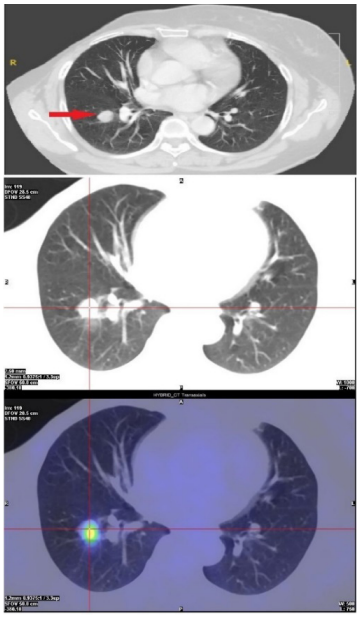

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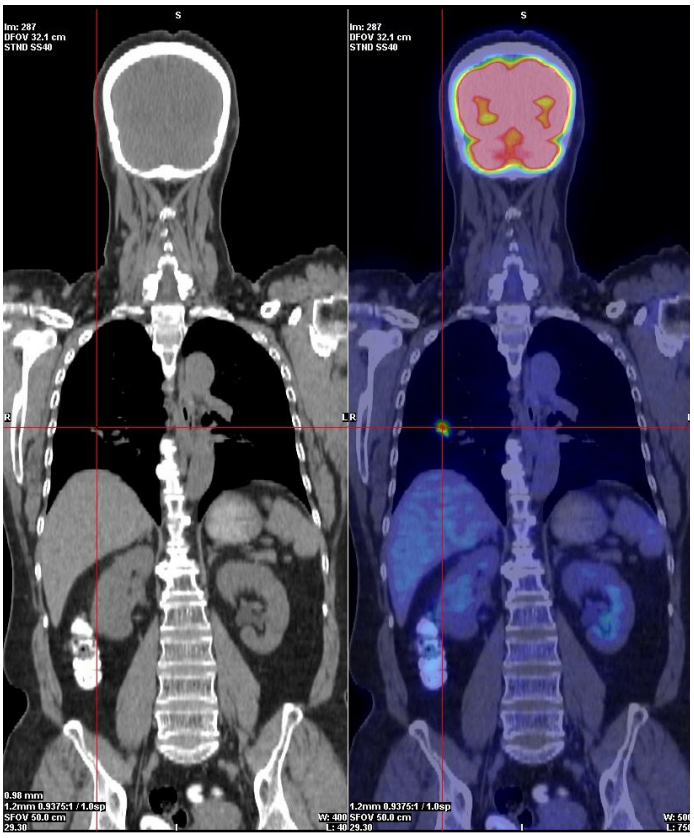

C

Figure 3. CT imaging revealed a solitary pulmonary nodule in the left lung (arrow) (Figure A). Figures B - C: FDG-PET/CT imaging demonstrated increased FDG uptake at the lesion site, with an SUVmax of 17.2, raising suspicion of metastatic disease

REFERENCES

[1]. Bray, F., et al., *Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries,* CA Cancer J Clin, 2024. 74(3): p. 229-263.

[2]. Courtney, D., et al., *Breast cancer recurrence: factors impacting occurrence and survival.* Ir J Med Sci, 2022, 191(6): p. 2501-2510.

[3]. Zhang-Yin, J., *State of the Art in 2022 PET/CT in Breast Cancer: A Review,* J Clin Med, 2023. 12(3).

[4]. Xiao, Y., et al., *Diagnostic efficacy of 18F-FDG-PET or PET/CT in breast cancer with suspected recurrence: a systematic review and meta-analysis,* Nucl Med Commun, 2016. 37(11): p. 1180-8.

[5]. Taalab, K., et al., *The diagnostic value of PET/CT in breast cancer recurrence and metastases.* Egyptian J. Nucl. Mel, 2017. 15.

[6]. Dong, Y., et al., *The diagnostic value of 18F-FDG PET/CT in association with serum tumor marker assays in breast cancer recurrence and metastasis.* Biomed Res Int, 2015. 2015: p. 489021.

[7]. Boellaard, R., et al., *Effects of noise, image resolution, and ROI definition on the accuracy of standard uptake values: a simulation study.* J Nucl Med, 2004. 45(9): p. 1519-27.

[8]. Sinn, H.P. and H. Kreipe, *A Brief Overview of the WHO Classification of Breast Tumors, 4th Edition, Focusing on Issues and Updates from the 3rd Edition.* Breast Care (Basel), 2013, 8(2): p. 149-54.

[9]. Giuliano, A.E., S.B. Edge, and G.N. Hortobagyi, *Eighth Edition of the AJCC Cancer Staging Manual: Breast Cancer.* Ann Surg Oncol, 2018, 25(7): p. 1783-1785.

[10]. Bitencourt, A.G., et al., *Correlation between PET/CT results and histological and immunohistochemical findings in breast carcinomas,* Radiol Bras, 2014. 47(2): p. 67-73.

[11]. De Mooij, C.M., et al., *The influence of receptor expression and clinical subtypes on baseline [18F]FDG uptake in breast cancer: systematic review and meta-analysis,* EJNMMI Res, 2023. 13(1): p. 5.

EVALUATION OF SET-UP ERRORS IN 4D-DIBH THORACIC RADIOTHERAPY USING WHOLE-BODY VACLOCK AT VINMEC TIMES CITY INTERNATIONAL GENERAL HOSPITAL

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ABSTRACT

Purpose: To determine the daily initial set-up errors and the patient position reproducibility pre-irradiation with 4D-DIBH breathing control radiotherapy technique the whole-body Vac-lock immobilisation device.

Materials and methods: A total of 53 patients were assigned to the Thoracic Radiotherapy (Esophageal cancer: 31 patients; lung cancer: 15 patients; thymic tumor: 5 patients; Rib metastasis: 1 patient) at Vinmec Times City International Hospital from June 2023 to September 2024. Patients were treated by VMAT technique with 4D – DIBH (Deep Inhale Breath-Hold) using Whole Body Vac-lock immobilization devices (QFIX, PA, USA) and (CIVCO, Orange City, IA, USA). Determined the set – up error and pre-treatment repoducibility by collecting daily kV and CBCT images before treatment. A total 1027 of 3D-CBCT image serries were collected and analyzed offline on the ARIA system (Varian Medical System, CA, USA). These data were used to determined the setup margin (SM), systematic margin, and random margin errors in three directions: anterior-posterior (AP); left-right (LR); Cranial-Caudal (CC) and stored on the ARIA system (Varian Medical System, CA, USA).

Results: Innitial set - up error of 4D-DIBH radiotherapy for the thoracic tumors were: 2.4 ± 0.9 mm (in the AP direction), 3.2 ± 1.3 mm (in the Cranial-Caudal direction), and 1.9 ± 1.1 mm (in the LR direction). Average set-up error for the 4D-DIBH radiotherapy group of patients with esophageal cancer: 2.4 ± 0.9 mm, 3.4 ± 1.2 mm, and 1.8 ± 1.1 mm in the AP, CC, and LR directions, respectively; average setting error for the 4D-DIBH radiotherapy group of patients with lung cancer: 2.7 ± 0.9 mm (AP direction), 2.9 ± 1.3mm (CC direction), and 1.8 ± 0.9 mm (LR direction). Average setting error for the 4D-DIBH radiotherapy group of patients with thymic cancer and ribs metastases: 1.8 ± 0.6 mm, 3.0 ± 2.3 mm, 3.1 ± 1.4 mm in the AP, CC, LR directions respectively; Set - up error (SM) for 4D-DIBH radiotherapy using Whole – Body Vac-lock is

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calculated according to the van Herk formula for the Thoracic region: 3.7 mm (AP) 4.8 mm (CC); 4.0 mm (LR); esophageal cancer: 3.9 mm (AP) 4.8 mm (CC); 3.6 mm (LR)); lung cancer: 3.5 mm (AP) 4.8 mm (CC); 4.1 mm (LR)); thymic cancer, bone metastasis: 2.9 mm (AP) 4.7 mm (CC); 4.9 mm (LR).

Conclusion: 4D-DIBH radiotherapy for the thoracic cancer using Body Vac-lock ensures well position repositioning, reduces initial set – up error to deliver accurate radiation dose to the tumors, and limits side effects on organ at risk (OAR). The results of the study and set – up error (SM) calculation is the base - evidence to help Radiation oncolosist determine the appropriate PTV - Margin for treatment in each location.

Keywords: Setup error; 2D-kV image verification; cone-beam computed tomography (CBCT); immobilization systems; esophageal cancer; lung cancer; thoracic tumours; Deep Inspirarion Breath Hold (DIBH).

1. INTRODUCTION

Thoracic malignancies such as breast cancer, esophageal cancer, lung cancer, thymoma, mediastinal tumors, or metastatic lesions of the spine and ribs are characterized by organ motion due to physiological respiratory activity and cardiac movement. Irregularities in respiratory cycles during inspiration and expiration, as well as stimuli such as coughing or swallowing due to esophageal secretion, can significantly affect the reproducibility and accuracy of treatment positioning throughout the entire course of radiotherapy. Without proper motion management strategies, these factors may result in treatment setup deviations, leading to displacement of the target volume, altered dose distribution, decreased treatment efficacy, and increased radiation exposure to surrounding organs at risk (OARs).

Respiratory-induced motion presents challenges to accurate target localization and complicates the delineation of the planning target volume (PTV) and patient immobilization. According to ICRU Report 62 [1], expansion from the clinical target volume (CTV) to PTV must consider both internal margin (IM), which accounts for physiological organ motion, and setup margin (SM), which compensates for patient positioning uncertainties: CTV–PTV margin = IM + SM. While the IM can be estimated based on prior published studies or 4D imaging data, the SM can be calculated more practically through statistical analysis of setup errors from daily image guidance data routinely collected at each center. Accurately quantifying the SM provides critical evidence for radiation oncologists to determine the optimal CTV-to-PTV expansion, thereby minimizing unnecessary radiation exposure to surrounding healthy tissues.

Given the significant motion of thoracic organs caused by respiration, the implementation of modern radiotherapy techniques such as Image-Guided Radiotherapy (IGRT), Volumetric Modulated Arc Therapy (VMAT), and 4D Deep Inspiration Breath Hold (4D-DIBH), in combination with full-body immobilization devices like Vac-Lok, has been widely adopted in clinical practice. These approaches aim to effectively control organ motion, ensure reproducible and precise patient positioning, enhance dose accuracy to the tumor, and minimize radiation-induced toxicity to critical adjacent structures.

At Vinmec Times City International Hospital, since 2017 we have systematically applied the 4D-DIBH technique for respiratory motion management, using immobilization systems such as Body Vac-Lok (QFIX, PA, USA), ProLock, and Wing Board (CIVCO, Orange City, IA, USA). Since 2022, full-body Vac-Lok systems (CIVCO, Orange

City, IA, USA) have also been introduced to further enhance control of respiratory-induced motion in thoracic radiotherapy. In this study, we aim to evaluate initial setup errors and the reproducibility of patient positioning using 4D-DIBH-controlled radiotherapy in combination with full-body Vac-Lok immobilization for thoracic malignancies.

2. SUBJECTS AND METHODS

2.1. Study subjects

A total of 53 patients diagnosed with thoracic malignancies and indicated for radiotherapy were included in this study. The cohort consisted of patients treated at Vinmec Times City International Hospital between June 2023 and September 2024. The patients were diagnosed with various thoracic cancers, including: esophageal cancer (31 patients), lung cancer (15 patients), thymic cancer (5 patients), and rib bone metastasis (1 patient). Patients were categorized into three groups based on their primary diagnosis: Group 1: 31 patients with esophageal cancer, Group 2: 15 patients with lung cancer, Group 3: 6 patients with thymic cancer or rib bone metastasis (Table 1).

Table 1. Patient characteristics and thoracic radiotherapy information

Patients		N (number)	Percentage (%)
Gender	Male	50	94.3%
	Female	3	5.7%
Pre-treatment image verification	2D-kV	-	-
	3D-CBCT	1027	100
Thoracic cancer type	Esophageal (Group 1)	31	58.4%
	Lung (Group 2)	15	28.3%
	Thymic or rib bone metastasis (Group 3)	6	13.3%
Immobilization device type	Wing board Whole - Body Vaclock	53	100
Breath-hold duration (DIBH)		15s - 30s	

2.1.1. Inclusion criteria

Patients were instructed on breath-hold training and assessed for their breath-holding capability. Inclusion criteria required patients to have good general condition, stable clinical indices, and vital signs, with no acute respiratory or airway conditions.

A breath-hold duration of ≥ 15 seconds was required to ensure comfort during treatment procedures, as well as reproducibility, amplitude stability and consistency throughout the entire radiotherapy course.

2.1.2. Exclusion criteria

Patients were excluded if they were unable to reproduce consistent breathing patterns or breath-hold amplitudes, or if their breath-hold duration was ≤ 15 seconds.

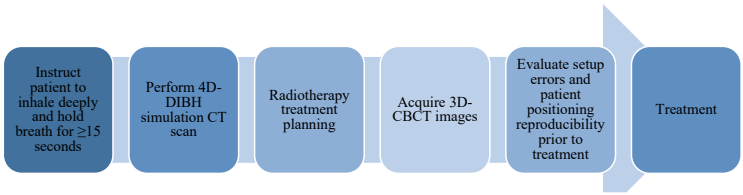
2.2. Study methodology

This was a retrospective study.

All daily 3D-CBCT (Cone-Beam Computed Tomography) verification image datasets were collected for analysis of initial setup errors and patient position reproducibility prior to treatment. A

total of 1,027 3D-CBCT image sets were collected and analyzed offline. These datasets were used to calculate: Setup margin (SM), Systematic error (Σ), Random error (σ). Measurements were analyzed along the anterior-posterior (AP), left-right (LR) and cranial-caudal (CC) directions, and stored in the treatment management system for further statistical evaluation.

2.2.1. Procedure for performing 4D-DIBH breath-hold-gated radiotherapy



2.2.2. Patient breathing training instructions

The patient lies in the supine position on the treatment couch or on the immobilization device, with both arms raised above the head. A cushion may be placed under the knees if needed. This position is identical to the treatment setup used during daily radiotherapy sessions (Figure 1).

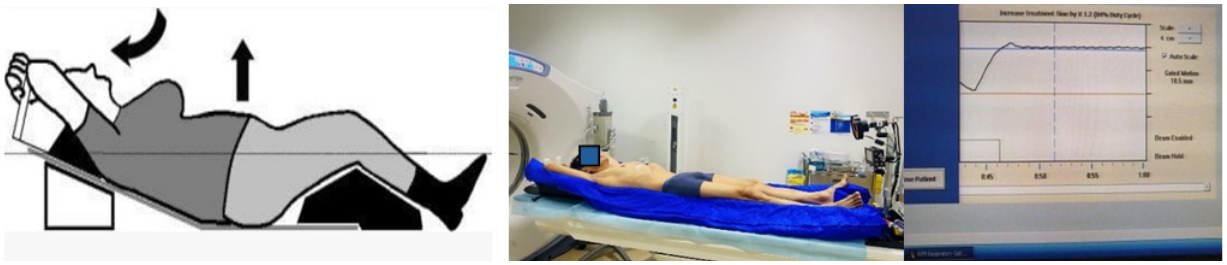


Figure 1. Patient setup position for treatment and breathing training guidance

The patient is instructed to perform several cycles of inhalation and exhalation. Inhale slowly and deeply through the nose, allowing the lungs and abdomen to fully expand, then exhale gently. Repeat this cycle 5-10 times while ensuring the body remains still, the treatment position is maintained correctly, and there is no straining or arching of the back off the treatment table or immobilization device (Figure 2).

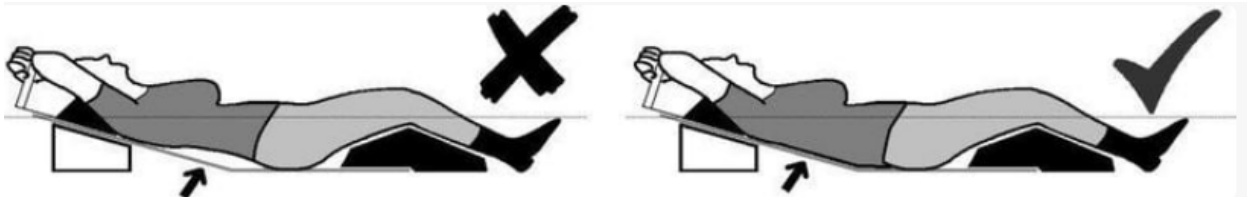


Figure 2. Standard posture for patient during DIBH breathing training

A minimum breath-hold duration of ≥ 15 seconds is required. The amplitude in the anterior-posterior (AP), cranial-caudal (CC) and lateral (LAT) directions during deep inspiration breath-hold must remain stable and consistent.

2.2.3. Patient Immobilization and positioning setup

Patients are positioned supine on a full-body Vaclock immobilization device, with both arms raised above the head using a Wing Board. The treatment origin is then marked and tattooed on the patient's skin in the CT simulation room. CT simulation is performed for the thoracic region using a 2.5 mm slice thickness protocol on a GE 16-slice CT Scanner (GE Healthcare System, USA). Following that, radiation oncologists contour the treatment volumes including GTV (Gross Tumor Volume), CTV (Clinical Target Volume), and PTV (Planning Target Volume) on the simulation CT images for treatment planning (Figure 3).

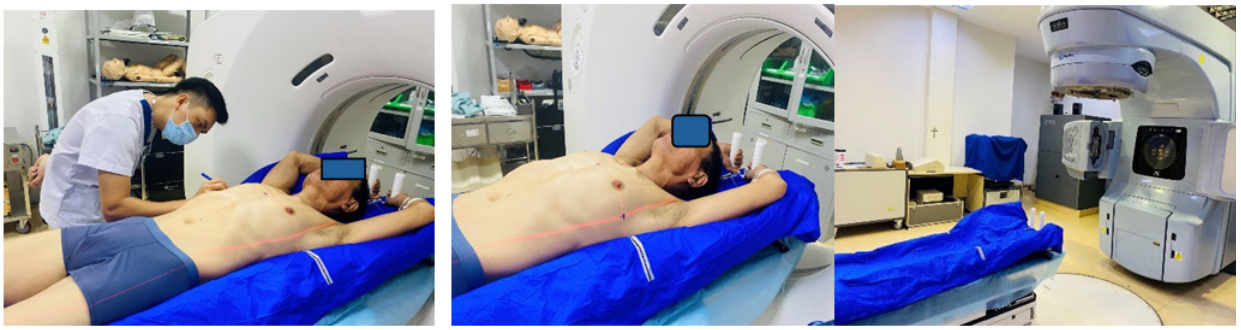


Figure 3. Patient positioning and origin marking

2.2.4. Pre-treatment 3D-CBCT image verification for setup error evaluation

All 53 patients underwent daily 3D-CBCT (Cone Beam CT) image verification prior to each radiotherapy session. A total of 1,027 3D-CBCT image sets were acquired using the OBI (On-Board Imager) system and analyzed both online and offline. The 3D-CBCT images were compared with the planning CT simulation (CT SIM) images to evaluate setup errors in three directions: anterior-posterior (AP), cranial-caudal (CC), and left-right (LR). The setup error data were recorded and managed using the ARIA software (Varian) (Figure 4).

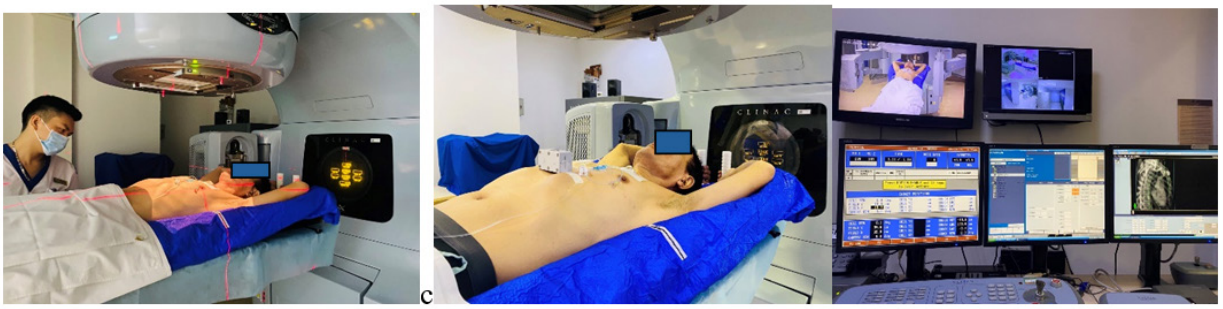


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Figure 4. Patient setup before treatment (A), breathing training (B) and pre-treatment 3D-CBCT image verification (C)

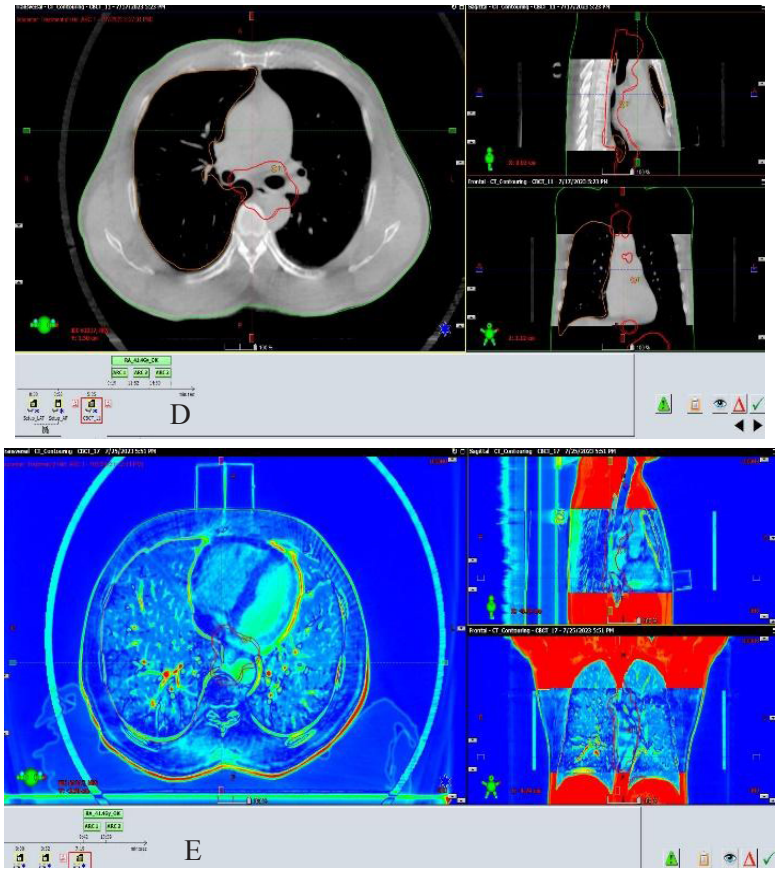

Figure 5. Evaluation of pre-treatment setup errors (D) and reproducibility of treatment position; DIBH breathing amplitude (E)

2.2.5. Analysis and evaluation of pre-treatment setup errors on 3D-CBCT images

A total of 1027 sets of 3D-CBCT images were collected to assess setup errors in three directions: anterior-posterior (AP), cranial-caudal (CC), and left-right (LR), using Bony Matching and PTV & Volume Matching methods on the ARIA Offline Review software. Initial setup errors and treatment position reproducibility were analyzed to determine the following objectives:

1. To evaluate initial setup errors in chest cancer patients undergoing 4D-DIBH radiotherapy using full-body Vaclock immobilization.

2. To assess initial setup errors in 4D-DIBH radiotherapy for esophageal cancer.

3. To assess initial setup errors in 4D-DIBH radiotherapy for lung cancer.

4. To assess initial setup errors in 4D-DIBH radiotherapy for thymic cancer and rib bone metastases.

5. To determine setup margins based on the Van Herk formula: $SM_{vanHerk} = 2,5\ \Sigma_{setup} + 0,7_{\sigma setup}$ for thoracic cancers including esophageal, lung, thymic cancers, and rib metastases [2,3], where: Setup margin ($SM_{vanHerk}$: Setup margin) represents the calculated expansion from CTV to PTV, Systematic

error (Σ) is defined as the standard deviation of the mean setup errors across all patients, Random error (σ) is defined as the average standard deviation of setup errors for each patient.

3. RESULTS AND DISCUSSION

3.1. Initial setup errors before treatment

The setup errors prior to 4D-DIBH radiotherapy for thoracic regions were: 2.5 mm ± 1.0 mm (AP), 3.2 mm ± 1.3 mm (CC), and 2.1 mm ± 1.5 mm (LR) (Table 2). In Group 1 (esophageal cancer patients receiving 4D-DIBH radiotherapy), the setup errors were: 2.4 mm ± 0.9 mm (AP), 3.4 mm ± 1.2 mm (CC), and 1.8 mm ± 1.1 mm (LR) (Table 3). For Group 2 (lung cancer patients), the corresponding errors were: 2.7 mm ± 0.9 mm (AP), 2.9 mm ± 1.3 mm (CC), and 2.3 mm ± 2.0 mm (LR) (Table 4). In Group 3 (patients with thymic cancer or rib bone metastasis), the setup errors were: 2.6 mm ± 1.6 mm (AP), 3.0 mm ± 1.3 mm (CC), and 3.1 mm ± 1.7 mm (LR) (Table 5). Setup margins (SM) calculated using the Van Herk formula for full-body Vac-lock–assisted 4D-DIBH radiotherapy were: Thoracic region overall: 3.7 mm (AP), 4.8 mm (CC), 4.0 mm (LR). Group 1 – Esophageal cancer: 3.9 mm (AP), 4.8 mm (CC), 3.6 mm (LR). Group 2 – Lung cancer: 3.5 mm (AP), 4.8 mm (CC), 6.8 mm (LR). Group 3 – Thymic cancer & rib metastases: 3.0 mm (AP), 4.7 mm (CC), 4.9 mm (LR) (Table 6).

3.2. Initial setup errors and reproducibility in 4D-DIBH thoracic radiotherapy

Table 2. Initial setup errors for 4D-DIBH radiotherapy using full-body vac-lok in thoracic cancer patients

Direction	Vrt (AP) mm	Lng (CC) mm	Lat (LR) mm
Mean Setup Error ± SD	2.4 ± 0.9	3.2 ± 1.3	1.9 ± 1.1
Systematic Error (∑SM)	2.2	3.2	2.7
Random Error (σSM)	1.5	1.6	2.0
Setup Margin (Van Herk formula)	3.7	4.8	4.0

Analysis and discussion: The results of this study indicate that the initial setup errors in thoracic radiotherapy using the 4D-DIBH technique with full-body Vac-Lok immobilization were effectively controlled, with pre-treatment setup deviations maintained at ≤ 3 mm in the anterior–posterior (AP) and lateral (LR) directions. Larger deviations (≥ 3 mm) were observed primarily in the cranial caudal (CC) direction. Both systematic and random setup errors were well-managed, ensuring accurate dose delivery to the tumor, minimizing respiratory-induced positional deviations, and optimizing radiation dose distribution to surrounding critical organs at risk (OARs). The calculated setup margins (SM) using Van Herk's formula for thoracic treatment were: 3.7 mm (AP), 4.8 mm (CC) and 4.0 mm (LR).

However, certain subjective and objective factors continue to affect positional accuracy and reproducibility, including patient fatigue, suboptimal breath-hold compliance, and insufficient breathing training. In some cases, setup deviations exceeded 3 mm in 4D-VMAT and SBRT treatments, necessitating repeat 3D-CBCT scans and extended treatment time to ensure alignment. Positional inconsistencies were most commonly observed in the diaphragm region, likely due to instability in abdominal and thoracic wall movement during deep inspiration and breath-hold. This highlights the need for improved pre-treatment respiratory coaching and patient compliance monitoring to enhance setup reproducibility and treatment efficiency.

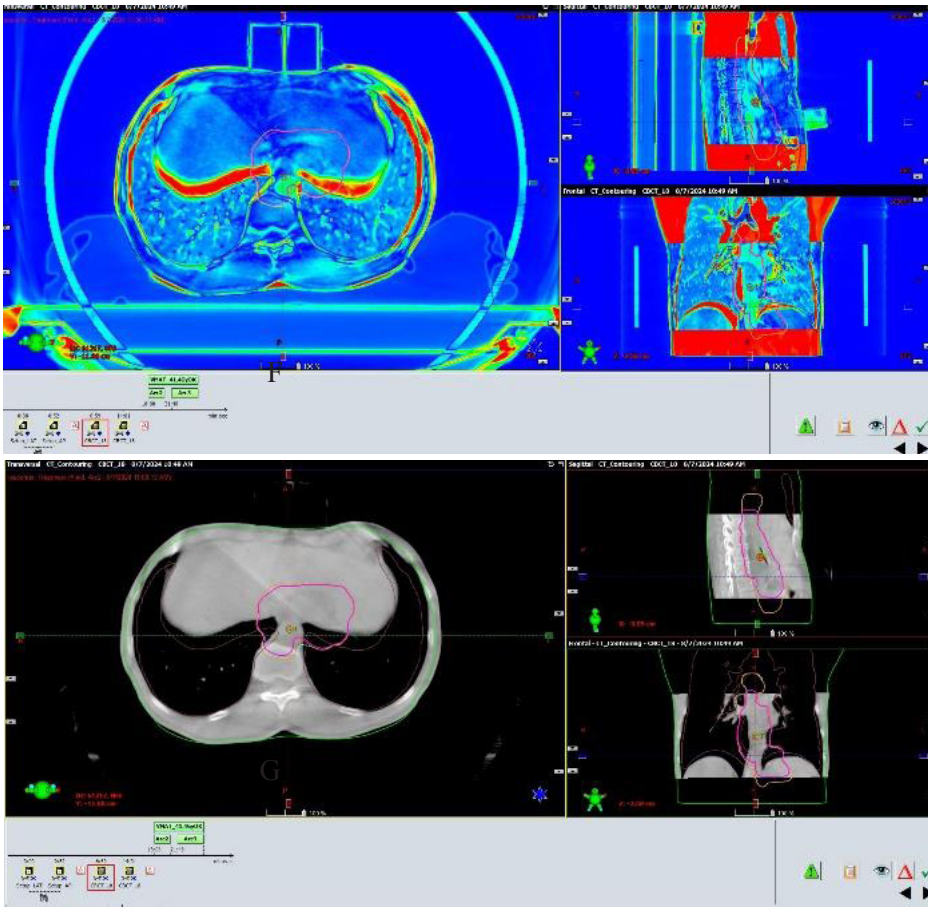

Figure 6. Positional variation due to suboptimal breath-hold reproducibility caused by excessive inhalation, resulting in non-reproducible organ volumes of the heart and lungs (F) and (G)

3.3. Initial setup error and positional reproducibility in 4D-DIBH radiotherapy for esophageal cancer

Table 3. Initial setup errors in 4D-DIBH radiotherapy using full-body vac-lok immobilization for esophageal cancer

Direction	Vrt (AP) mm	Lng (CC) mm	Lat (LR) mm
Mean setup error ± SD	2.4 ± 0.9	3.4 ± 1.2	1.8 ± 1.1
Systematic error (∑SM)	2.3	3.1	2.8
Random Error (σSM)	1.6	1.8	0.8
Setup margin (van Herk)	3.9	4.8	3.6

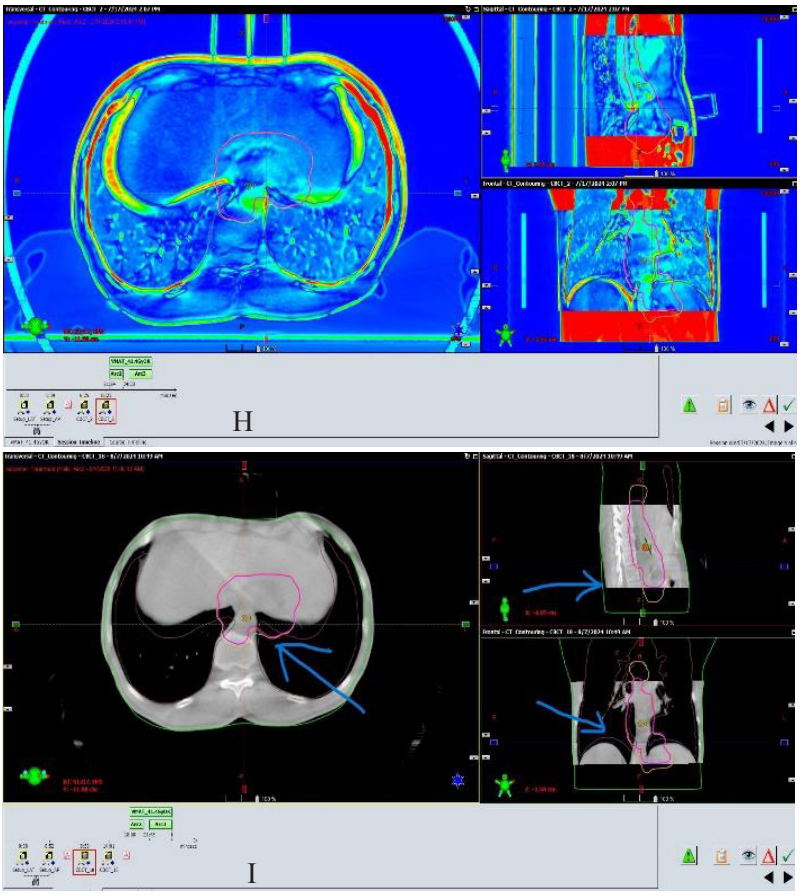

Figure 7. Positional variation due to suboptimal breath-hold reproducibility-excessive inhalation during deep inspiration breath-hold (DIBH) leads to lifting of the back off the Vac-Lok cushion, resulting in failure to reproduce the target organ volumes of the heart and lungs (H) and (I).

Analysis and discussion: The evaluation results for 4D-DIBH radiotherapy in esophageal cancer demonstrated setup errors of ≤ 3 mm in the AP and LR directions, while errors ≥ 3 mm tended to occur more frequently in the CC direction. For patients unable to reproduce the breath-hold pattern to adequately manage setup error and internal motion, breath-hold training and repeat 3D-CBCT image verification were performed to ensure accurate repositioning before irradiation. The calculated setup margins (SM) for esophageal cancer (Group 1) were: 3.9 mm (AP), 4.8 mm (CC) and 3.6 mm (LR).

Due to the anatomical characteristics of the esophagus-being a long digestive tube from the mouth to the stomach-tumor location may vary (upper, middle, or lower third), necessitating strict adherence to setup error management protocols and requiring good patient compliance during the radiotherapy process. The 4D-DIBH breath-hold technique combined with full-body Vac-Lok immobilization helps stabilize patients during treatment, minimizing positional changes caused by coughing or lifting of the back off the immobilization device during prolonged breath-hold periods.

3.4. Setup errors before treatment and position reproducibility in 4D-DIBH radiotherapy for Lung cancer

Analysis and discussion: The evaluation results for 4D-DIBH radiotherapy in lung cancer showed that the initial setup errors were ≤ 3 mm in the AP and LAT directions, while errors ≥ 3 mm tended to occur in the CC direction. The calculated setup margins (SM) for lung cancer (Group 2) were: 3.5 mm (AP), 4.8 mm (CC) and 4.1 mm (LR).

Motion management in 4D-DIBH lung radiotherapy presents significant challenges, particularly when treating small tumors located above the diaphragm-where respiratory-induced motion can be substantial if breathing is not well-controlled and patient breathing training is insufficient. Inadequate motion control during 4D-DIBH may lead to positional deviations in all three directions: AP, CC, and LAT, thereby compromising treatment accuracy and dose delivery.

Table 4. Initial setup errors in 4D-DIBH radiotherapy using whole-body vaclock for Lung cancer

Direction	Vrt (AP) mm	Lng (CC) mm	Lat (LR) mm
Mean setup error ± SD	2.7 ± 0.9	2.9 ± 1.3	1.8 ± 0.9
Systematic error (∑SM)	2.1	3.4	2.3
Random error (σSM)	1.4	1.4	1.9
Setup margin (van Herk)	3.5	4.8	4.1

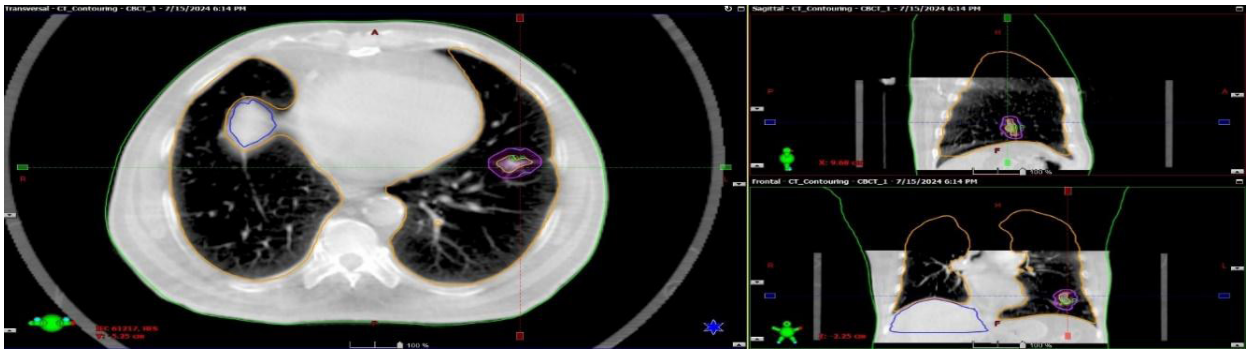

Figure 7. Accurate repositioning and reproducibility of the treatment volume for small tumors located above the diaphragm

3.5. Initial setup errors and reproducibility in 4D-DIBH radiotherapy for thymic and rib lesions

Table 5. Initial setup errors in 4D-DIBH radiotherapy using whole-body vaclock immobilization for thymic and rib metastatic tumors

Direction	Vrt (AP) mm	Lng (CC) mm	Lat (LR) mm
Mean setup error ± SD	1.8 ± 0.6	3.0 ± 1.3	2.3 ± 1.4

Direction	Vrt (AP) mm	Lng (CC) mm	Lat (LR) mm
Systematic error (∑SM)	1.5	3.3	3.4
Random error (σSM)	1.5	1.4	1.5
Setup margin (van Herk)	3.0	4.7	4.9

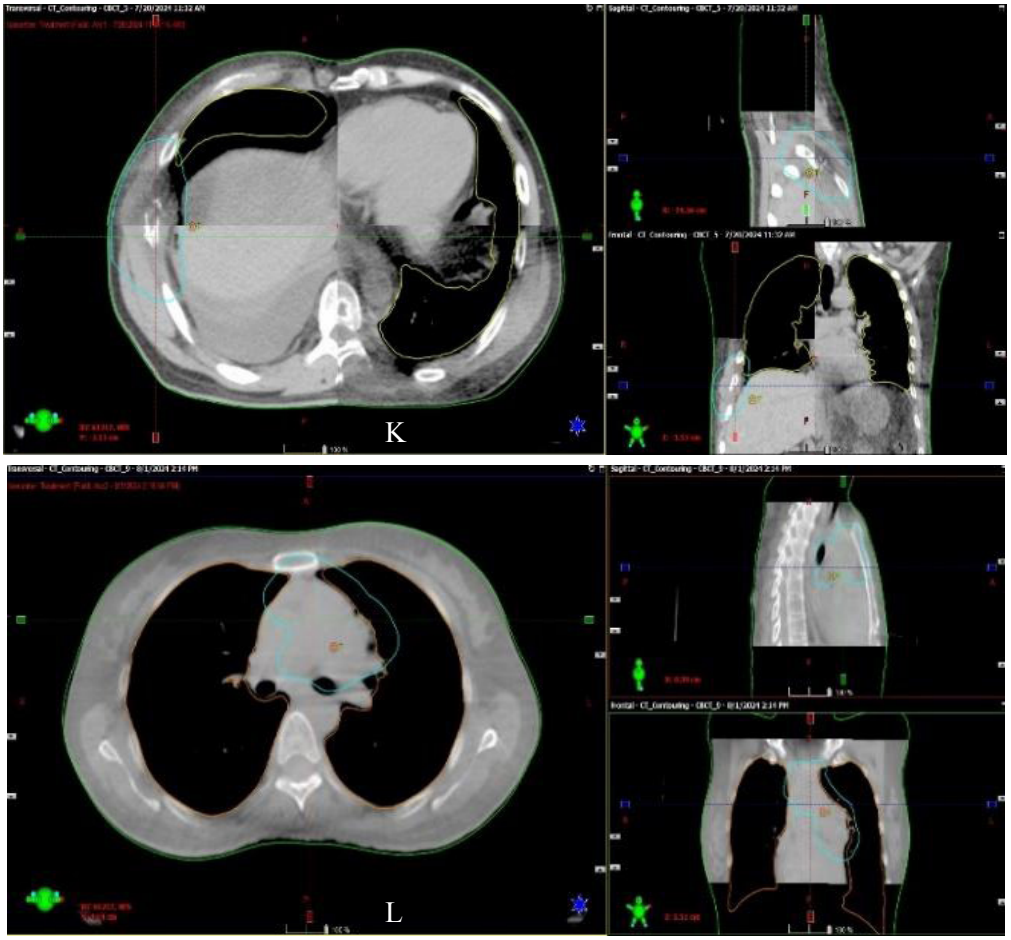

Figure 8. The accuracy of target volume repositioning for metastatic rib lesion (K) and thymic tumor (L)

Analysis and discussion: The evaluation results for 4D-DIBH radiotherapy in thymic tumors or rib metastases demonstrated initial setup errors ≤ 3 mm in the AP and LR directions, with a tendency for larger errors ≥ 3 mm in the CC direction. The calculated setup margins (SM) for Group 3 (thymic tumors and rib metastases) were 3.0 mm (AP), 4.7 mm (CC) and 4.9 mm (LR).

Based on our observations in setup error control and repositioning reproducibility, the thymus is a centrally located mediastinal organ, where the

respiratory motion-induced volume and positional variations are typically minimal, allowing effective control of setup errors within ≤ 3 mm. However, for certain cases involving rib or chest wall metastases, achieving accurate target positioning and consistent patient posture, along with stable breath-hold amplitude, poses considerable challenges. These difficulties underscore the importance of tailored respiratory training protocols and strict patient compliance requirements, particularly for this patient subgroup. As a result of these findings, we have implemented enhanced breath-hold training and stricter procedural adherence for patients receiving radiotherapy for rib metastases or chest wall involvement.

3.6. Setup margins calculated using the van herk formula

Table 6. Setup margins (SM) calculated by the van herk formula in 4D-DIBH radiotherapy using Full-body vaclock immobilization

Patient Group	Vrt (AP) mm	Lng (CC) mm	Lat (LR) mm
Thoracic Region (General)	3.7	4.8	4.0
Esophageal Cancer (Mean)	3.9	4.8	3.6
Lung Cancer (Mean)	3.5	4.8	4.1
Thymic/Rib Mets	2.7	4.7	4.9
Setup Margin (Van Herk)	7.0	9.0	5.0

Analysis and discussion: The results of this study on setup errors prior to treatment and the evaluation of reproducibility of patient positioning in 4D-DIBH radiotherapy using full-body Vac-Lok immobilization demonstrated favorable outcomes. These findings meet the clinical standards for high-precision radiotherapy as practiced at Vinmec Times City International General Hospital, ensuring accurate dose distribution to the target tumor volume, high treatment efficacy, and patient safety. The setup margins (SM) calculated at the center align well with those reported in the published work by van Herk and colleagues, further validating the accuracy and consistency of our clinical workflow and positioning protocols.

4. CONCLUSION

4D-DIBH radiotherapy utilizing full-body Vac-Lok immobilization ensures daily reproducibility and positional stability during treatment. It allows for precise radiation dose delivery to the tumor target while minimizing exposure to surrounding healthy tissues. This study provides an important clinical basis for radiation oncologists to define appropriate PTV margins tailored to tumor location and pathology within the thoracic region.

REFERENCES

[1]. ICRU 62: International CommisCCon on Radiation Units and Measurements report 62.

[2]. van Herk M, Remeijer P, Rasch C, Lebesque JV (2000), *The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy*, Int J Radiat Oncol Biol Phys. 2000; 47(4):1121–35.

[3]. Van Herk M (2004), *Errors and margins in radiotherapy*, Semin Radiat Oncol 2004; 14:52-64.

[4]. Hawkins M.A., Aitken A., Hansen V.N., McNair H.A., Tait D.M. (2011), *Set-up errors in radiotherapy for oesophageal cancers – is electronic portal imaging or conebeam more accurate?* Radiother Oncol J Eur Soc Ther Radiol Oncol. 2011; 98:249–254.

[5]. Yamashita H., Haga A., Hayakawa Y. (2010), *Patient setup error and day-to-day esophageal motion error analyzed by cone-beam computed tomography in radiation therapy*, Acta Oncol. 2010; 49:485–490.

[6]. Hashimoto T, Shirato H, Kato M, Yamazaki K, Kurauchi N, Morikawa T (2005), *Real-time monitoring of a digestive tract marker to reduce adverse effects of moving organs at risk (OAR) in radiotherapy for thoracic and abdominal tumors*, Int J Radiat Oncol Biol Phys 2005; 61:1559–64.

[7]. Cohen R.J., Paskalev K., Litwin S., Price R., Feigenberg S.J., Konski A. (2010), *Esophageal motion during radiotherapy: quantification and margin implications: esophageal motion during radiotherapy*, Dis Esophagus. 2010; 23:473–479.

[8]. SaCCdharan S., Allison R., Jenkins T., Wolfe M., Mota H., CCbata C. (2005), *Interfraction esophagus motion study in Image Guided Radiation Therapy (IGRT) Int J Radiat Oncol Biol Phys*, 2005;63: S91–S92.

[9]. Gao X.-S., Qiao X., Wu F. (2007), *Pathological analyCCs of clinical target volume margin for radiotherapy in patients with esophageal and gastroesophageal junction carcinoma*, Int J Radiat Oncol Biol Phys. 2007;67: 389–396.

[10]. Dieleman E.M.T., Senan S., Vincent A., Lagerwaard F.J., Slotman B.J., van Sörnsen de Koste J.R. (2007), *Four-dimenCConal computed tomographic analyCCs of esophageal mobility during normal respiration*, Int J Radiat Oncol Biol Phys. 2007; 67:775–780.

[11]. Welch RW, Gray JE. (1982), *Influence of respiration on recordings of lower esophageal sphincter pressure in humans*, Gastroenterology. 1982; 83:590–594.

[12]. Good E, Oral H, Lemola K, et al. (2005), *Movement of the esophagus during left atrial catheter ablation for atrial fibrillation*, J Am Coll Cardiol. 2005; 46:2107–2110. [PubMed].

[13]. Liliana Martins, Jose Guilherme Couto, Barbara Barbosa (2016), *Use of planar kV vs. CBCT in evaluation of setup errors in oesophagus carcinoma radiotherapy*, Oncol Radiother. 2016; 21(1): 57-62.

EVALUATION OF INITIAL SETUP ERRORS AND DETERMINATION OF SETUP MARGIN IN VMAT RADIOTHERAPY FOR PELVIC TREATMENT PATIENTS AT VINMEC TIMESCITY HOSPITAL

Pham Tuan Anh*, Doan Trung Hiep, Tran Ba Bach, Nguyen Dinh Long, Ha Ngoc Son, Nguyen Trung Hieu, Nguyen Van Nam, Phung Thi Thu Huong, Bo Thi Minh Cham

ABSTRACT

Introduction and purpose: In radiation therapy, accurate dose distribution to the target volume requires precision in treatment setup. Patient setup errors are unavoidable and always present during the treatment process. By identifying these errors, it is possible to determine the setup margin from the Clinical Target Volume (CTV) to the Planning Target Volume (PTV) to cover the target volume while minimizing the dose to adjacent healthy tissues. This study aims to evaluate the random and systematic errors occurring during the setup of pelvic radiation therapy using the On-Board Imaging (OBI) system, and subsequently propose an optimal setup margin distance from CTV to PTV for patients with pelvic cancer.

Materials and methods: A total of 40 patients evenly divided between rectal and cervical cancer for VMAT treatment were given radiation therapy at Vinmec Times City International Hospital from 01/2023 to 8/2024. The patients were scanned by CT simulation on CT Optimal 580 (GE Medical System, Milwaukee, Wisconsin USA), planning on the Eclipse software (ver 13.0) of varian firm (USA), The patients were taken photo verification 2D-KV images (daily) and 3D-CBCT (Monday and Thursday) are analyzed online on OBI software and compared with DRR images from the plan, thereby evaluating and recording errors in 3 directions front after (AP Anterior-Posterior); above and below (SI Superior-Inferior); left right (LR Lateral). Random and systematic errors are identified based on the collected error data, The set-up margin for CTV to PTV was calculated by published margin formulae of Van Herk et al.

Results: A total of 534 pairs of 2D-KV cervical images and 448 pairs of 2D-KV rectal images were performed and evaluated. For cervical cancer, the systematic error and random error in the AP, SI, and LR directions were (1.28 ± 1.92 mm), (2 ± 3.5 mm) and (1.41 ± 1.78 mm), respectively. For rectal cancer, the systematic error and random error in the AP, SI, and LR directions were (1.18 ± 1.57 mm), (2.01 ± 3.06 mm), and (0.89 ± 1.89 mm), respectively. The setup margin required to cover the target volume retrospectively was calculated based on Van Herk et al were: 5 mm (AP), 7 mm (SI), 5 mm (LR) for the cervix uteri and 5 mm (AP), 7.5 mm (SI), 5 mm (LR) for the rectum.

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Conclusion: The assessment and verification of images before treatment with OBI system helps reduce setting errors, increase dose in tumors, reduce unwanted side effects and allows estimating the setup of the planning target volume (PTV) expansion according to our configuration. Based on the results of the study, we propose that setup margin with radiotherapy for the pelvis at our hospital are: 5mm (AP), 7mm (SI), 5mm (LR) for the cervix uteri and 5mm (AP), 7.5mm (SI), 5mm (LR) for the rectum.

Keywords: Setup errors; setup margin; VMAT radiotherapy; cervical cancer; rectal cancer…

I. INTRODUCTION

Over the past decade, there have been significant advancements in cancer treatment, particularly for pelvic tumors such as rectal cancer and cervical cancer. External treatment modalities like radiotherapy demand a very high level of precision. However, numerous errors can occur from the simulation and planning stages to daily treatment delivery, potentially affecting treatment quality. Therefore, accurate daily patient repositioning in radiotherapy is critically important and represents a significant potential source of error that must be carefully addressed. These daily setup deviations also known as setup errors can be classified as either systematic or random errors.

Such errors arise from discrepancies between the treatment planning process and the actual treatment setup and may lead to variations in radiation dose distribution [1]. Random errors may vary from day to day, reflecting the uncertainty of reproducibility and positional stability during treatment. To account for these uncertainties, the International Commission on Radiation Units and Measurements (ICRU) introduced the concept of the Planning Target Volume (PTV), which includes these setup uncertainties [2]. Van Herk et al. identified approximately ten potential sources of error and developed a formula to estimate the required margin from a homogeneous patient group to ensure a 90% probability that the Clinical Target Volume (CTV) is within the 95% isodose region [3]. The PTV is defined as the safety margin necessary to ensure that the CTV receives the prescribed dose. This concept is indispensable in treatment planning and evaluation and encompasses the CTV, an internal target volume (ITV) margin, and a setup margin accounting for positioning and reproducibility errors. Defining the setup margin helps to minimize the influence of mechanical and technical factors from the machine (systematic errors) and residual uncertainties (random errors) [4].

One of the most critical factors in ensuring radiotherapy accuracy is determining the setup margin (SM) the safety distance around the treatment volume to compensate for setup errors. This margin must be determined accurately and appropriately to ensure that the tumor receives the necessary dose without causing excessive harm to surrounding healthy tissues. However, determining the optimal SM is not always straightforward and requires a careful balance between protecting healthy tissues and ensuring effective tumor control.

At our center, patients are prioritized for radiotherapy using VMAT (Volumetric Modulated Arc Therapy) with the modern Clinac iX linear accelerator (Varian Medical Systems, Palo Alto, CA). Errors are assessed and corrected daily prior to treatment using the Portal Vision and OBI systems, which enable 2D-KV imaging and 3D-CBCT for error detection and repositioning based on the treatment plan [5-6].

Although many previous studies have examined setup errors in radiotherapy and methods for determining SM, there is still a lack of detailed and updated analysis regarding the application of these methods in VMAT treatment for the pelvic region. This article aims to evaluate setup errors in VMAT pelvic radiotherapy at our center, analyze factors affecting treatment setup accuracy, and determine

the optimal SM to improve treatment efficacy and minimize side effects. Conducting this study will provide deeper insight into managing setup errors and developing more appropriate treatment strategies, ultimately enhancing the quality of care for patients.

2. SUBJECTS AND METHODS

2.1. Subjects

This retrospective study randomly selected 40 patients with pelvic cancers, equally divided between cervical cancer and rectal cancer cases, who were treated with VMAT (Volumetric Modulated Arc Therapy) at the Department of Radiation Oncology, Vinmec Times City International Hospital from January 2023 to August 2024. A total of 982 pairs of daily 2D-KV images (from Monday to Friday) were collected, including 534 image pairs for cervical cancer patients and 448 image pairs for rectal cancer patients.

2.2. Patient preparation and Immobilization devices prior to simulation

All patients undergoing pelvic radiotherapy were carefully prepared with attention to bladder and rectal conditions to ensure reproducibility and stability throughout the treatment process. Typically, at our center, patients are instructed to completely empty their bowels. The bladder and rectum are then checked by the radiation technologist using a CT scanner (Computed Tomography) to confirm an empty bladder and clean rectum (free of gas and stool; if not, enemas may be prescribed by the physician). Following that, patients are instructed to drink approximately 400-500 ml of water, including a diluted contrast mixture in a water-to-contrast ratio of about 10:1 (to aid physicians in contouring the bowel structures during treatment planning) and wait for 45-60 minutes before the simulation scan.

The immobilization devices used for pelvic radiotherapy in patients with cervical or rectal cancer include: a hipfix system with or without a vac-lock, an appropriate headrest, feetfix leg support, and a pelvic mask for immobilization.

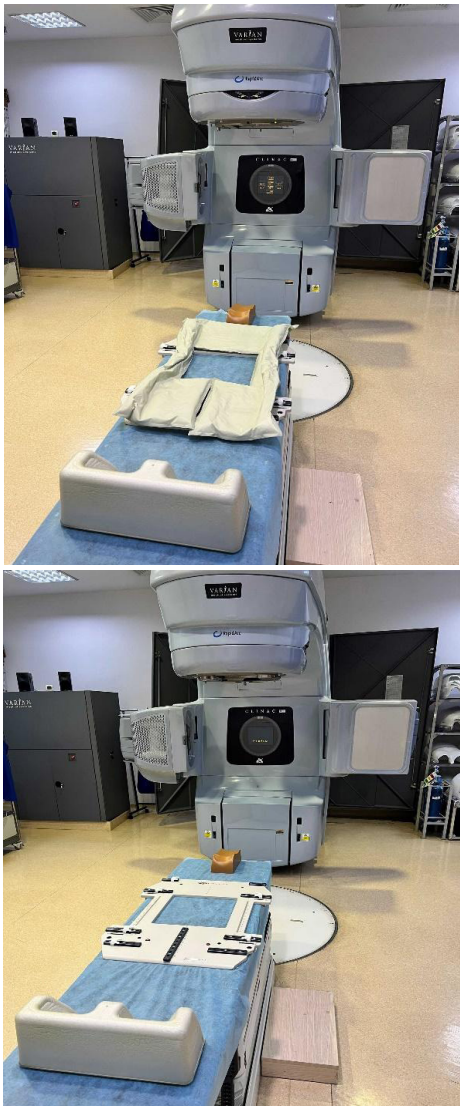


Figure 1. Pelvic radiotherapy Immobilization device set

2.3. Simulation imaging

All patients lay in the supine position on a hipfix system, in a comfortable posture. The glabella philtrum xiphoid process pubic symphysis points were aligned along the laser axis. Arms were placed over the chest and legs were immobilized

using a feetfix system. A tight-fitting thermoplastic mask was molded to cover the pelvic-abdominal region. Patients underwent simulation CT scans using a 16-slice CT scanner (CT 580-Optima, GE Healthcare), with a slice thickness of 2.5 mm. Intravenous contrast was administered, and the scan range extended from vertebral level L1 to the upper third of the femur.

2.4. 2D-KV image verification before treatment

Prior to radiation delivery, all 40 patients underwent daily 2D-KV imaging and 3D-CBCT imaging on Mondays and Thursdays as part of the VMAT protocol. The 2D-KV images were X-ray images showing bone anatomical structures. A total of 534 2D-KV image pairs for cervical cancer and 448 pairs for rectal cancer were acquired in three directions: anteroposterior (AP), superoinferior (SI), and left-right (LR). These images were recorded using the OBI system and directly compared with digitally reconstructed radiographs (DRRs) to determine setup errors in all three directions.

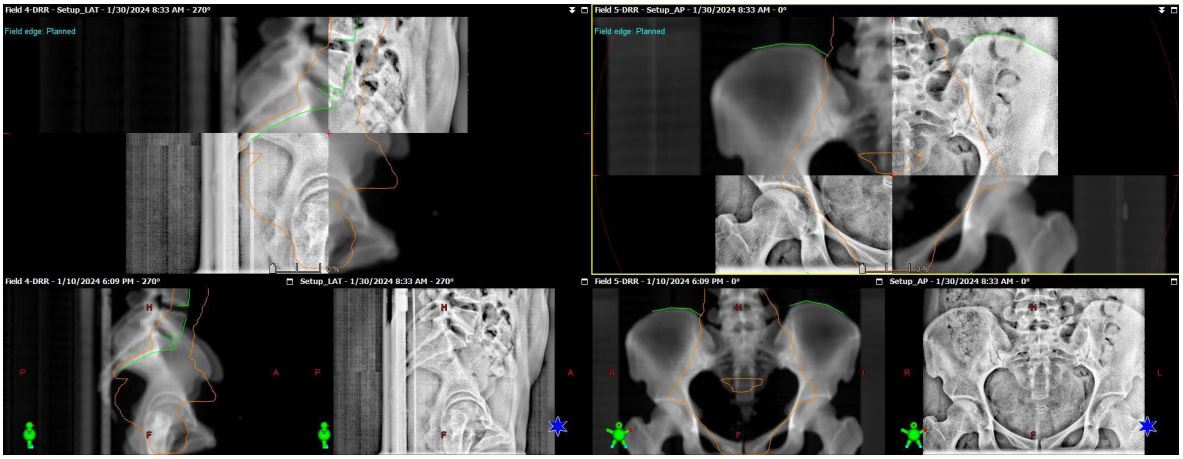


Figure 2. Comparison of 2D-KV image with DRR image before treatment

2.5. Retrospective study design and error calculation method

In each patient group, all setup errors in the three directions-anterior-posterior (AP), superior-inferior (SI) and left-right (LR)-were recorded after each treatment session by comparing the 2D-KV images with the DRR images based on bony landmarks. A total of 534 sets of cervical cancer setup errors and 448 sets for rectal cancer were collected across all three directions to determine:

- The average setup error in each direction for each patient in both groups.

- The mean (M) of the average setup errors in each direction for each patient.

- The standard deviation (SD) of the setup errors in each direction per patient.

- The standard deviation of the mean setup errors (M) for each patient.

- The average of the standard deviations across all patients.

The setup margin (CTV–PTV) for each group (cervical and rectal cancer) was calculated using the Van Herk et al. formula[7]:

$$SM = 2{,}5\Sigma + 0{,}7\sigma$$

Where:

Σ represents the systematic error, determined as the standard deviation of the mean setup errors across the three directions;

σ represents the random error, calculated as the average of the standard deviations for each individual patient.

3. RESULTS AND DISCUSSION

A total of 40 patients were included in the study, comprising 20 patients (50%) with cervical cancer and 20 patients (50%) with rectal cancer. All patients were treated with the VMAT technique using the immobilization devices as previously described.

A total of 982 pairs of 2D-KV images were acquired during treatment to assess setup deviations in all three directions for all 40 patients. From these, we calculated the overall mean setup error (M) and the overall standard deviation (SD) for each direction per patient. The average values for each direction were: Anterior-posterior (AP): 0.62 ± 1.75 mm, Superior-inferior (SI): 1.88 ± 2.75 mm, Left-right (LR): 1.02 ± 1.83 mm. Among the 534 initial setups for cervical cancer treatments and 448 for rectal cancer treatments, we observed that the proportion of initial setup errors exceeding 3 mm in the AP, SI, and LR directions were: For cervical cancer: 14.04% (AP), 32.58% (SI), 14.04% (LR), for rectal cancer: 8.93% (AP), 30.36% (SI), 19.20% (LR).

Table 1. Setup errors (Mean) and standard deviation of patients receiving pelvic radiotherapy

Direction	M ± SD	SD (range)
AP	0.62 ± 1.23	1.75 ± 0.61
SI	1.88 ± 1.96	2.75 ± 2.25
LR	1.02 ± 1.28	1.83 ± 0.54

At the treatment position, the setup error (M) and standard deviation (SD) of patient positioning errors in the AP, SI, and LR directions were as follows: For cervical cancer patients: 0.58 ± 1.92 mm (AP), 1.96 ± 2.45 mm (SI), and 0.52 ± 1.77 mm (LR). For rectal cancer patients: 0.67 ± 1.57 mm (AP), 1.79 ± 3.06 mm (SI), and 1.53 ± 1.89 mm (LR).

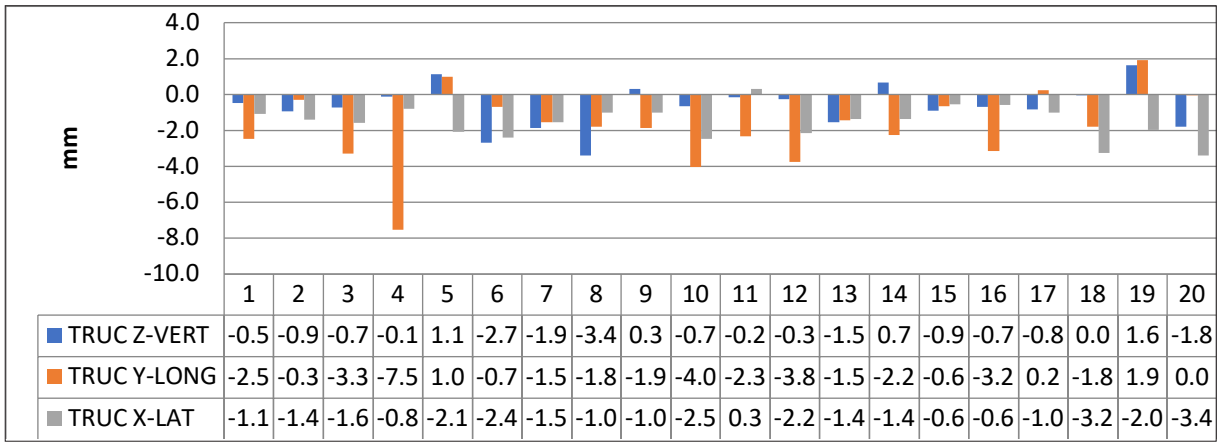
Table 2. Mean setup errors (M) and mean standard deviations (SD) by cancer type (mm)

Site	AP		SI		LR	
	M ± SD	Range	M ± SD	Range	M ± SD	Range
Cervical	0.58 ± 1.92	0.1 – 2.2	1.96 ± 2.45	0.09 – 6.5	0.52 ± 1.77	0.04 – 3.7
Rectal	0.67 ± 1.57	0.04 – 3.4	1.79 ± 3.06	0.04 – 7.54	1.53 ± 1.89	0.32 – 3.4

The systematic error (Σ) and random error (σ) were calculated based on the standard deviations of the mean setup errors and the average of individual standard deviations. From these values, the setup margin (SM, CTV–PTV) was determined using the Van Herk et al. formula. For cervical cancer patients, the calculated SM values in the AP, SI, and LR directions were 4.54 mm, 6.75 mm, and 4.75 mm, respectively. For rectal cancer patients, the corresponding SM values were 4.05 mm, 7.16 mm and 3.55 mm.

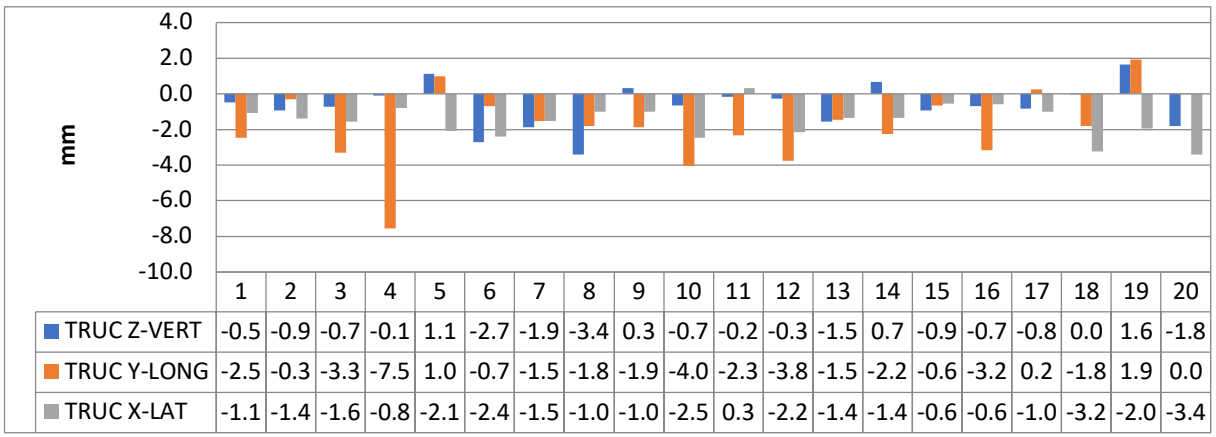
Table 3. Comparison of systematic error (Σ), random error (σ) and setup margin (SM) by cancer type (mm)

Site	AP			SI			LR		
	Σ	σ	$SM_{vanHerk}$	Σ	σ	$SM_{vanHerk}$	Σ	σ	SMv_{anHerk}
Cervical	1.28	1.92	4.54	2	3.5	6.75	1.41	1.78	4.75
Rectal	1.18	1.57	4.05	2.01	3.06	7.16	0.89	1.89	3.55



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
TRUC Z-VERT	-0.5	-0.9	-0.7	-0.1	1.1	-2.7	-1.9	-3.4	0.3	-0.7	-0.2	-0.3	-1.5	0.7	-0.9	-0.7	-0.8	0.0	1.6	-1.8
TRUC Y-LONG	-2.5	-0.3	-3.3	-7.5	1.0	-0.7	-1.5	-1.8	-1.9	-4.0	-2.3	-3.8	-1.5	-2.2	-0.6	-3.2	0.2	-1.8	1.9	0.0
TRUC X-LAT	-1.1	-1.4	-1.6	-0.8	-2.1	-2.4	-1.5	-1.0	-1.0	-2.5	0.3	-2.2	-1.4	-1.4	-0.6	-0.6	-1.0	-3.2	-2.0	-3.4

Figure 3. Distribution chart of setup errors for each cervical cancer radiotherapy patient



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
TRUC Z-VERT	-0.5	-0.9	-0.7	-0.1	1.1	-2.7	-1.9	-3.4	0.3	-0.7	-0.2	-0.3	-1.5	0.7	-0.9	-0.7	-0.8	0.0	1.6	-1.8
TRUC Y-LONG	-2.5	-0.3	-3.3	-7.5	1.0	-0.7	-1.5	-1.8	-1.9	-4.0	-2.3	-3.8	-1.5	-2.2	-0.6	-3.2	0.2	-1.8	1.9	0.0
TRUC X-LAT	-1.1	-1.4	-1.6	-0.8	-2.1	-2.4	-1.5	-1.0	-1.0	-2.5	0.3	-2.2	-1.4	-1.4	-0.6	-0.6	-1.0	-3.2	-2.0	-3.4

Figure 4. Distribution chart of setup errors for each rectal cancer radiotherapy patient

This study presents our center's clinical experience in using VMAT (Volumetric Modulated Arc Therapy) technique for the treatment of cervical and rectal cancers. The primary goal was to assess the overall accuracy of the radiotherapy process and calculate the appropriate margin from the Clinical Target Volume (CTV) to the Planning Target Volume (PTV), thereby providing useful guidance for physicians during treatment planning.

Evaluating errors and patient setup deviations

is crucial, as treatment effectiveness relies heavily on the consistency and reproducibility of organ positioning, fixation devices and the clinical experience of radiation therapists [8]. Furthermore, insufficient definition of the Planning Target Volume (PTV) can lead to inaccurate targeting of the tumor or unnecessarily high radiation doses to surrounding healthy tissues adjacent to the CTV.

Systematic and random errors have been discussed in numerous previous studies. Errors occurring from the simulation to daily treatment sessions are a major contributor to systematic errors. One significant cause is inaccurate tattoo marking on the skin, especially when patient setup relies on these marks. Other contributing factors may include machine-related errors such as laser misalignment, collimator angle deviations, or treatment couch inaccuracies [9].

Organs within the pelvic region especially the cervix and rectum are subject to anatomical variability and can shift or change position, which is a major cause of random errors. Contributing factors include bladder filling, gas or fecal matter in the rectum, patient movement, and differences in body composition (e.g., obesity or thinness). These factors directly impact patient positioning, treatment time, and setup errors, ultimately affecting the precision and efficacy of radiotherapy. They may result in underdosing the tumor or overdosing nearby healthy tissue. To minimize such errors and enhance setup consistency and reproducibility, our center has emphasized meticulous patient preparation, particularly concerning bladder and rectal status during pelvic simulation. Achieving this requires cooperation and adherence from patients, as well as close coordination among physicians, physicists, therapists, and nurses during the simulation and treatment process, combined with the experience of radiation technologists.

From the error data analyzed at our center, we observed that the setup margin (CTV-PTV) for rectal cancer was slightly larger than that for cervical cancer, though the difference was not significant. This similarity can be attributed to the fact that both organs are located within the pelvis and share comparable anatomical and mobility characteristics, largely influenced by the filling status of the bladder and rectum. The datasets used in our study to calculate setup margins for each group were derived from initial patient positioning. Re-verification using 2D-KV imaging was performed if the setup error exceeded 3 mm, and patient repositioning was done if needed. The SM was calculated based on daily setup errors using the Van Herk formula, which accounts for positional uncertainties in pelvic radiotherapy [7]. Our estimated CTV-PTV margins for pelvic cancers are: 5 mm (AP), 7 mm (SI), 5 mm (LR) for cervical cancer and 5 mm (AP), 7.5 mm (SI), 5 mm (LR) for rectal cancer. These values align closely with the margins typically applied by physicians at our center.

Evaluating initial setup errors in treatment sessions, along with identifying systematic and random errors and standard deviations, provides us with a deeper and more comprehensive understanding of setup reproducibility and patient stability throughout the treatment course. Moreover, the statistical data obtained allow for the establishment of specific setup margins for each cancer type, which is extremely important in guiding physicians to expand margins from CTV to PTV appropriately ensuring that the prescribed radiation dose is delivered accurately and effectively to the intended target volume.

4. CONCLUSION

Each radiotherapy center has its own unique characteristics and conditions; therefore, these differences need to be assessed and used to calculate an appropriate and specific margin expansion for each center. The daily use of 2D-KV imaging in VMAT technique helps to detect and correct setup errors in accordance with the treatment plan,

allowing the expansion of the PTV margin based on our center's setup error data. Through this study, we identified the average setup errors for each anatomical location, enabling us to calculate a setup margin (SM) for each group. This provides valuable guidance for physicians when expanding from CTV to PTV, in addition to considering the internal margin (IM). At our center, the recommended SM for pelvic radiotherapy is: 5 mm (AP), 7 mm (SI) and 5 mm (LR) for cervical cancer; and 5 mm (AP), 7.5 mm (SI), and 5 mm (LR) for rectal cancer.

REFERENCES

[1]. International Atomic Energy Agency (2016), *IAEA Human Health Report No.31. Accuracy requirements and uncertainties in radiotherapy*, Vienna: IAEA; 2016.

[2]. Chavaudra J, Bridier A, *Definition of volumes in external radiotherapy: ICRU Reports 50 and 62*, Cancer/Radiother. 2001;5(5):472-478. https:// doi.org/10.1016/s1278- 3218(01)00117-2.

[3]. Kron T, *Reduction of margins in external beam radiotherapy*, J Med Phys. 2008;33(2): 41-42. https://doi.org/10.4103/0971-6203.41190.

[4]. ICRU, *ICRU Report No. 50. Prescribing, recording and reporting photon beam therapy*, Bethesda: ICRU; 1993.

[5]. Amaoui B, Mohssine D, Bouih N, et al, *VMAT dosimetric study in rectal cancer patients*, Int Res J Med Biomed. 2020;5(1):1-6. https://doi. org/10.15739/ irjmbs.20.001.

[6]. Amaoui B, Mohssine D, Bourhim MM, et al, *Dosimetric comparison of conformal radiotherapy and arc-therapy of ineligible cervical cancers for intracavitary brachytherapy*, J Cancer Sci Clin Ther. 2019;3(4):221-228. https://doi.org/ 10.26502/ jcsct.5079036.

[7]. Van Herk M, Remeijer P, Rasch C, et al, *The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy*, Int J Radiat Oncol Biol Phys. 2000;47(4):1121-1135. https://doi. org/10.1016/s0360- 3016(00)00518-6.

[8]. Cacicedo J, Perez J, Ortiz de Zarate R, et al, *A Prospective analysis of inter- and intrafractional errors to calculate CTV to PTV margins in head and neck Patients*, Clin Transl Oncol. 2015;17(2):113-120. https://doi. org/10.1007/s12094-014-1200-z.

[9]. Hurkmans CW, Remeijer P, Lebesque JV, et al, *Set-up verification using portal imaging: review of current clinical practice*, Radiother Oncol. 2001;58(2):105-120. https://doi.org/10.1016/ s0167-8140(00)00260-7.

EFFECTS OF ANXIETY, DEPRESSION AND FATIGUE ON QUALITY OF LIFE IN EARLY ESOPHAGEAL CANCER PATIENTS FOLLOWING ENDOSCOPIC SUBMUCOSAL DISSECTION

Nguyen Duc Thanh*, Nguyen Phuong Minh, Tran Bao Ngoc, Vu Bich Huyen, Trinh Thi Ngan

ABSTRACT

Background: Emotional problems such as anxiety, depression, and fatigue may affect the quality of life (QoL) of cancer patients. However, there are no related studies investigating the effects of emotional problems on the QoL of early esophageal cancer (EC) patients receiving endoscopic submucosal dissection (ESD).

Methods: This is a prospective observational study enrolling 75 early EC patients. Demographic and clinical characteristics of enrolled patients were recorded. QoL was assessed according to the European Organization for Research and Treatment of Cancer QoL (EORTC QLQ-C30). The Beck Anxiety Scale and the Beck Depression Scale were used to measure the severity of anxiety symptoms and depression intensity, respectively. Fatigue was assessed according to the symptom subscale of the EORTC QLQ-C30. Multivariable logistic regression models were constructed to determine the causes of emotional problems.

Results: Of the enrolled early EC patients, 21, 15 and seven had symptoms of mild, moderate and anxiety, respectively. Also, 15, 19 and two patients had symptoms of mild, moderate, and severe, respectively. In total, 27 patients frequently felt fatigue. The multivariable logistic regression model revealed that the financial capacity to pay for treatment had an important effect on the prevalence of anxiety and depression symptoms in enrolled patients (both P values < 0.001). Age, gender, education status, and tumor size also played a role in emotional problems. Mean while, fatigue was found to be related only to age and gender. The mean score for QoL was (76,9 ± 15,2). After adjusting for confounding factors using the multivariable linear regression model, moderate or severe symptoms of anxiety, depression and fatigue, older age, and insufficient capacity to pay were identified as independent risk factors for reduced QoL.

Conclusions: Emotional distress is a significant problem for early EC patients receiving ESD treatment as it may affect their QoL.

Keywords: Anxiety; depression; fatigue; quality of life (QoL); endoscopic submucosal dissection (ESD); early esophageal cancer (early EC), Quality of life, eosophageal cancer, Thai Nguyen Oncology.

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1. INTRODUCTION

Esophageal cancer (EC) is one of the most common malignancies of the upper gastrointestinal tract and is reported to be the sixth leading cause of cancer-related death worldwide [1]. It was estimated that approximately 455,800 new cases of EC and 400,200 deaths occurred globally in 2012. The incidence of esophageal cancer varies among countries, with the highest rates observed in East Asia and Eastern and Southern Africa, and the lowest rates in Western Africa [1]. In China, esophageal cancer ranks sixth among all cancer types, with an estimated incidence of 17.87 per 100,000 people and a mortality rate of 13.6 per 100,000. According to statistics from the World Cancer Association, the early diagnosis rate of esophageal cancer in Vietnam is only about 2%. In contrast, early detection rates for other cancers can reach 20% or even nearly 50%, such as breast and cervical cancers. Consequently, the 5-year survival rate for patients with EC in Vietnam is only around 5%. With the advancement of gastrointestinal cancer screening through endoscopy particularly the development of endoscopic submucosal dissection (ESD) there is now an effective treatment option for early-stage EC. ESD offers several advantages over esophagectomy, including preservation of esophageal function, minimal invasiveness, fewer complications, lower costs and shorter hospital stays. Additionally, quality of life (QOL) after ESD is considered a significant outcome for patients with early-stage EC. Previous studies have mainly focused on the impact of physical issues on the QOL of EC patients, with minimal attention paid to the emotional factors affecting their well-being. Baudry et al. revealed that alleviating emotional distress in EC patients could improve their QOL in both the pre- and post-ESD periods.

Based on this context, we conducted this study with the following objective:

To evaluate the impact of emotional factors on the quality of life of patients with early-stage esophageal cancer after endoscopic submucosal dissection (ESD).

2. SUBJECTS AND RESEARCH METHODS

2.1. Study subjects

All patients newly diagnosed with esophageal cancer (EC) and treated for various purposes at Thai Nguyen Oncology Center from January 2020 to April 2024 who met the inclusion and exclusion criteria.

2.1.1. Inclusion criteria

- Patients aged over 18 years.

- Diagnosed with early-stage EC (cT1aN0M0 or cT1bN0M0) by biopsy or imaging, with no contraindications to endoscopic submucosal dissection (ESD), no prior esophagectomy, and willing to participate in the study. Patients who declined or withdrew their consent could exit the study at any time.

2.1.2. Exclusion criteria

- Patients diagnosed with two concurrent primary cancers.

- Patients with EC who had undergone surgical resection.

- Patients in poor general condition, unable to complete the interview questionnaire.

- Non-cooperative patients or those who refused to answer.

2.2. Study design

Retrospective medical record review.

Sample size:

Purposive sampling method-selecting all patients who met the criteria during the study period.

2.3. Data collection method

Direct interviews with inpatients using administrative information forms and standardized questionnaires on pain levels and quality of life at two time points: prior to hospital admission and before discharge.

2.3.1. Instruments

A demographic questionnaire including age and gender. Patient clinical characteristics were extracted from medical records.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), version 3, was used. This standardized questionnaire includes 30 items covering: Physical functioning (items 1-5); Role functioning (items 6-7); Emotional functioning (items 21-24); Cognitive functioning (items 20, 25); Social functioning (items 26, 27); Global health status (items 29, 30) and 13 symptom items. A total score of 75 is considered the cut-off: scores <75 indicate poor quality of life (QOL), while scores >75 indicate satisfactory QOL. The Beck Anxiety Scale (BAS) was used to assess anxiety severity. BAS includes 21 self-report items, each scored from 0 to 3, with a total score ranging from 0 to 63: 0-8: Minimal anxiety; 9-15: Mild anxiety; 16-25: Moderate anxiety; 26-63: Severe anxiety. The Beck Depression Scale (BDS) was used to assess the intensity of depression. It also includes 21 items scored from 0 to 3, with total scores ranging from 0 to 63: 0-9: Minimal depression; 10-18: Mild depression; 19-29: Moderate depression; 30-35: Severe depression.

2.3.2. Research ethics

The study protocol was approved by the Ethics Committee of Thai Nguyen Central General Hospital.

Participants were clearly informed and only enrolled with full consent. Data were used strictly for research purposes.

2.4. Data processing

Data were entered and analyzed using SPSS version 22.0. Categorical variables were presented as frequencies and percentages; continuous variables were reported as means and standard deviations.

3. RESEARCH RESULTS

Table 1. Demographic and clinical characteristics of enrolled patients (n = 75)

Characteristics		Number of patients	Percentage %
Male		41	54,7
Female		34	45,3
Age range (years)			
	40 - 50	3	4,0
	50 - 60	17	22,7
	60 - 70	36	48
	70 - 80	13	17,3
	> 80	6	8
Education level			
	Primary school	33	44
	Secondary school	30	40
	High school	12	16
Marital status			
	Married	57	76

Characteristics		Number of patients	Percentage %
	Single/Widowed	18	24
Financial capacity			
	Able to pay	49	65,3
	Unable to pay	26	34,7
Number of comorbidities	0	21	28
	1	17	22,7
	2	37	49,3
Tumor stage			
	T1aNoMo	53	70,7
	T1bNoMo	22	29,3
Tumor location			
	Upper esophagus	7	9,3
	Middle esophagus	55	73,3
	Lower esophagus	13	17,3
Tumor size			
	< 20	49	65,3
	> 20	26	34,7
Tumor circumference involvement			
	<1/2	63	84
	>1/2	12	16
Complete resection rate			
	Complete resection	74	98,7
	Incomplete resection	1	1,3

A total of 92 early-stage esophageal cancer (EC) patients were admitted between January 2020 and April 2024. Thirteen patients declined to participate in this study. The ESD procedure could not be completed in two patients one due to severe bleeding and the other due to fibrosis. Ultimately, 75 early-stage patients were enrolled in this study. The majority of the patients were elderly, with those aged 60-70 years accounting for 48% of the total. There were 41 male patients and 34 female patients. Twelve patients (16%) had completed high school. Fifty-seven patients (76%) were married. As many as one-third of the patients (26 patients, 34.7%) were unable to afford the treatment costs. Thirty-seven patients (49.3%) had at least two comorbidities.

All patients enrolled were diagnosed with early-stage EC, with 53 patients (70.7%) classified as T1aN0M0 and 22 patients (29.3%) as T1bN0M0. The tumor was located in the middle esophagus in 55 patients (73.3%). Tumor size exceeded 20 mm in 26 patients (34.7%). Tumor invasion involving more than half of the esophageal circumference was observed in 12 patients (16%). The complete resection rate was 74 patients (98.7%).

Table 2. Assessment of Emotional Issues in EC Patients (N = 75)

Psychological Factors		N	%
Anxiety			
	Mild	32	42,7
	Moderate	21	28
	Severe	15	20
	Very Severe	7	9,3
Depression			
	Mild	39	52
	Moderate	15	20
	Severe	19	25,3
	Very Severe	2	2,7
Fatigue			
	Present	27	36
	Absent	48	64

Emotional issues including anxiety, depression, and fatigue were assessed in all participating patients. Overall, 32 patients (42.7%) exhibited minimal anxiety symptoms, 21 patients (28%) had mild anxiety symptoms, 15 patients (20%) experienced moderate anxiety and 7 patients (9.3%) reported severe anxiety. Regarding depression, 39 patients (52%) had mild depressive symptoms, 15 patients (20%) had moderate symptoms, 19 patients (25.3%) experienced moderately severe symptoms and 2 patients (2.7%) showed severe depression. As for fatigue, 27 patients (36%) reported feeling fatigued, while 48 patients (64%) did not experience fatigue.

Table 3. Demographic and clinical characteristics associated with emotional issues in early-stage EC patients based on logistic regression model

Characteristic	Anxiety			Depression			Fatigue		
	Minimal or mild	Moderate or severe	P	Minimal or mild	Moderate or severe	P	Absent	Present	P
	53	22		54	21		48	27	
< 60	18 (34,0)	2 (9,1%)	0,045	1 (4,8%)	17 (35,4)				
> 60	35 (66%)	20 (90,9%)		35 (64,8%)	20 (95,2%)		31 (64,65)	24 (88,9%)	0,03
Gender									
Male	33 (62,3%)	8 (36,4%)	0,044	35 (64,8%)	6 (28,6%)	0,006	32 (66,7%)	9 (33,3%)	0,007
Female	20 (27,7%)	14 (63,6%)		19 (35,2%)	15 (71,4%)		16 (33,3%)	18 (66,7%)	

Characteristic	Anxiety			Depression			Fatigue		
	Minimal or mild	Moderate or severe	P	Minimal or mild	Moderate or severe	P	Absent	Present	P
Education									
Primary school	18 (34%)	15 (68,2%)		17 (31,5%)	16 (76,2%)		21 (43,8%)	12 (44,4%)	
Secondary school	24 (45,3%)	6 (27,3%)	0,044	26 (48,1%)	4 (19,0%)	0,034	21 (43,8%)	9 (33,3%)	0,593
High school	11 (20,8%)	1 (4,5%)	0,375	11 (20,4%)	1 (4,8%)	0,654	6 (12,5%)	6 (22,2%)	0,411
Financial status									
Able to pay	43 (81,1%)	6 (27,3%)	< 0,01	45 (83,3%)	4 (19%)	< 0,01	28 (58,3%)	21 (77,8%)	0,094
Unable to pay	10 (18,9%)	16 (72,7%)		9 (16,7%)	17 (81%)		20 (41,7%)	6 (22,2%)	
Comorbidities									
0	16 (30,2%)	5 (22,7%)		14 (25,9%)	7 (33,3%)		13 (27,1%)	8 (29,6%)	
1	10 (18,9%)	7 (31,8%)	0,788	12 (22,2%)	5 (23,8%)	0,462	9 (18,8%)	8 (29,6%)	0,578
>2	27 (50,9%)	10 (45,3%)	0,302	28 (51,9%)	9 (42,9%)	0,692	26 (54,2%)	11 (40,7%)	0,515

Emotional fatigue was analyzed using both univariate and multivariate logistic regression models, as shown in Table 3. The multivariate logistic regression model revealed that older patients (> 60 years) and female patients were more likely to experience moderate to severe anxiety compared to younger or male patients (P = 0.045 and P = 0.048, respectively). Financial capacity to cover treatment expenses had a significant impact on the occurrence of anxiety symptoms in the studied population (P < 0.001). Similarly, age, gender, and financial status also played important roles in the manifestation of depressive symptoms. Additionally, a higher level of education and smaller tumor size appeared to be associated with reduced depressive symptoms to a certain extent (P = 0.048 and P = 0.018, respectively). Fatigue was found to be associated only with age and gender, without significant links to other factors in the model.

Table 4. Quality of life among patients with early-stage EC

Quality of Life Domain	Mean Score ± SD
Physical functioning	88,1 ± 12.9
Role functioning	85,5 ± 16.8
Emotional functioning	77.9 ± 12.5
Cognitive functioning	93.4 ± 14.7
Social functioning	91.0 ± 17.2
Global health status	76.9 ± 15.2

Comment: As shown in Table 4, the mean scores for the enrolled patients were as follows: physical functioning (88.1 ± 12.9), role functioning (85.5 ± 16.8), emotional functioning (77.9 ± 12.5), cognitive functioning (93.4 ± 14.7) and social functioning (91.0 ± 17.2). The mean score for global health status was 76.9 ± 15.2.

4. DISCUSSION

It can be understood that the inability to afford treatment costs is a primary cause of emotional fatigue in patients. Several studies have also emphasized the critical role of financial difficulties in the development of emotional issues among cancer patients. The most important finding of our study is that independent risk factors negatively impact the quality of life (QoL) in patients with early-stage esophageal cancer (EC). Among these, depression was identified as the principal factor influencing QoL, particularly functional status. Previous studies have demonstrated that patients with depression generally have poorer QoL compared to those without. Our findings are consistent with this, showing that depression significantly decreased QoL scores in early EC patients. Moreover, anxiety was also found to contribute similarly to decreased QoL, highlighting the impact of psychological distress on patients with early-stage EC. Bellali et al. suggested that early screening for anxiety and depression could provide valuable insights into vulnerable patients and help inform targeted interventions. Fatigue, a common symptom among cancer patients, was present in 36.0% of our study population. It is noteworthy that fatigue itself is part of the QoL assessment tools. Previous research has demonstrated that fatigue is associated with inflammation, as well as poor sleep quality, particularly in patients with advanced-stage cancer [5]. While multiple factors can contribute to cancer-related fatigue, our study showed that fatigue was associated only with age and gender, likely due to the relatively low cancer burden in early EC patients. Interestingly, tumor characteristics such as tumor location and size were not significantly associated with emotional problems or QoL in early-stage EC. In practice, most early EC patients do not require additional chemotherapy after ESD, and thus ESD does not add a substantial treatment burden. Consequently, reduced QoL was primarily associated with financial difficulties rather than the procedure itself. Several limitations of this study should be considered. First, only 75 early-stage EC patients were enrolled, and the small sample size, combined with the short study duration and single-center design, limited the scope of further analysis. Second, the majority of patients had low educational attainment, which posed challenges in analyzing the impact of education level on emotional issues and QoL. Third, esophageal stricture after ESD is a major factor that can affect recovery and QoL, yet we did not assess the degree of stricture during follow-up in our cohort. In conclusion, ESD is considered an acceptable treatment for early-stage EC and is associated with better QoL outcomes compared to other treatment modalities. Our prospective study identified the prevalence of anxiety, depression, and fatigue among early EC patients following ESD treatment, which may contribute to decreased QoL. These findings emphasize the importance of psychosocial health in patients undergoing ESD and highlight the need to strengthen psychological counseling and support provided by nurses in clinical practice.

REFERENCES

[1]. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.

[2]. A Cancer J Clin 2018; 68: 394-424.

[3]. Li H, Fang W, Yu Z, et al. Chinese expert consensus on mediastinal lymph node dissection in esophagectomy for esophageal cancer (2017 edition). J Thorac Dis 2018; 10: 2481-9.

[4]. Zhang H, Yang Y, Shang Q, et al. Predictive value of preoperative weight loss on survival of elderly patients undergoing surgery for esophageal squamous cell carcinoma. Transl Cancer Res 2019;8:2752-8.

[5]. Darling GE. Quality of life in patients with esophageal cancer. Thorac Surg Clin 2013; 23: 569-75.

[6]. Kim SG, Ji SM, Lee NR, et al. Quality of Life after Endoscopic Submucosal Dissection for Early Gastric Cancer: A Prospective Multicenter Cohort Study. Gut Liver 2017; 11: 87-92.

ASSESSMENT OF SATISFACTION, QUALITY OF LIFE AND SAFETY IN SUBCUTANEOUS PORTS FOR CHEMOTHERAPY ADMINISTRATION AT HUE CENTRAL HOSPITAL

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ABSTRACT

Objective: To survey complications related to subcutaneous ports, evaluate satisfaction and quality of life in cancer patients undergoing chemotherapy via subcutaneous ports at Hue Central Hospital.

Subjects and methods: Cross-sectional descriptive study conducted on 30 chemotherapy-treated patients using subcutaneous ports at Hue Central Hospital from October 2023 to April 2024.

Results: Median age 52.1±14.4, male, female ratio are 20% and 80% respectively. Breast cancer patients accounted for the highest proportion at 43.3%. Only 4 (13.3%) patients experienced complications during the use of subcutaneous ports, with no patients experiencing dislodgement or port removal due to complications. 96.7% of patients were satisfied with subcutaneous port placement. 93.3% of patients would agree to have subcutaneous ports placed again if given the choice. 86.7% of patients were satisfied with the cosmetic aspect after subcutaneous port placement. Physical Component Summary (PCS) and Mental Component Summary (MCS) scores according to the SF-12 tool were 44.9 and 40.8, respectively. The cosmetic result of implantation procedure and the patient's fear of needles entering the injection chamber affect quality of life in terms of mental component summary.

Conclusion: Subcutaneous port placement is beneficial for patients, both reducing events during the process of multiple injections, creating a comfortable feeling for the patient when administering medication as well as in daily living activities, bringing high satisfaction contributing to improve the quality of life.

Keywords: Subcutaneous port; chemotherapy; cancer; satisfaction; quality of life.

1. INTRODUCTION

Cancer is one of the leading causes of mortality worldwide, with the number of new cases increasing annually. According to GLOBOCAN 2020, there are nearly 20 million new cancer cases and over 9.7 million cancer-related deaths globally each year [2]. Advances in early detection, diagnosis, and treatment have contributed to the rising incidence. Among cancer patients, more than 70% require intravenous chemotherapy. Patients frequently experience both psychological and physical distress due to the disease itself and the associated treatments [2]. Conventional treatment approaches-including surgery, radiotherapy, and systemic therapy via peripheral intravenous access-are associated with multiple complications and significantly reduce quality of life. Therefore, the use of central venous

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access devices has become essential to facilitate drug administration, particularly for patients undergoing long-term or frequent treatment within a short period.

In recent years, the widespread use of totally implantable venous access ports (TIVAPs) has provided substantial comfort to patients, particularly in terms of aesthetics and ease of use. In the initial phase, this technique reduces the risk of extravasation, ensures the safe administration of vesicant and irritant drugs, and maintains continuous treatment, especially compared to peripheral venous access. However, in Vietnam, there remains a lack of specific research evaluating patient satisfaction and quality of life following TIVAP implantation. Therefore, we conducted this study with the following objectives:

- To describe the clinical characteristics and assess complications related to totally implantable venous access ports in cancer patients undergoing chemotherapy at Hue Central Hospital.

- To evaluate patient satisfaction and quality of life related to intravenous chemotherapy administration via TIVAPs.

2. SUBJECTS AND METHODS

2.1. Study population

The study included 30 cancer patients undergoing chemotherapy via totally implantable venous access ports (TIVAPs) at Hue Central Hospital from October 2023 to April 2024.

2.1.1. Inclusion criteria

Cancer patients receiving chemotherapy and indicated for TIVAP placement.

2.1.2. Exclusion criteria

Patients who declined participation.

Patients with unstable mental health or those under treatment with antipsychotic medications.

2.2. Study design

A descriptive cross-sectional study.

2.2.1. Study variables and evaluation metrics

Patient characteristics: Age, gender, educational level, occupation, site of primary cancer, and cancer stage.

TIVAP characteristics: Port implantation site, complications during TIVAP use, and reasons for port removal (if any).

Patient satisfaction survey: A standardized questionnaire using a 5-point Likert scale (1 = very satisfied, 2 = satisfied, 3 = moderately satisfied, 4 = slightly satisfied, 5 = not satisfied). Satisfaction rate = scores 1 + 2 + 3; Dissatisfaction rate = scores 4 + 5.

Quality of life assessment: Based on the SF-12 Health Survey, including the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores.

2.2.2. Data Analysis

Data were analyzed using SPSS version 26.0. Multivariate regression analysis was applied to calculate quality of life scores according to the SF-12 instrument.

2.3. Ethical considerations

The indication for TIVAP placement in chemotherapy is approved by the Ministry of Health. All participants provided informed consent after a full explanation of the study objectives and procedures. Collected data were used solely for research purposes, and participants' personal information was kept confidential.

3. RESULTS

3.1. General characteristics of study participants

Table 1. General characteristics of study participants

General Characteristics		Number (n)	Percentage (%)
Mean Age		52,1 ± 14,4 (20-78)	
Gender	Male	6	20,0
	Female	24	80,0
Educational Level	Illiterate	0	0
	Primary school	4	13,3
	Secondary school	11	36,7
	High school or higher	15	50,0
Occupation	Office worker/Retired	7	23,3
	Manual laborer	0	0
	Business/Trade	1	3,3
	Housework/Farming	13	43,3
	Other	9	30,0

Among the 30 patients included in the study, the majority were female (80%). The mean age was 52.1 years. Half of the participants had attained at least a high school education, and none were illiterate. Regarding occupation, the most common group was those engaged in housework or farming (43.3%).

Table 2. Characteristics related to subcutaneous port (Port-a-Cath)

Characteristics		Number (n)	Percentage (%)
Primary Cancer Site	Breast	13	43,3
	Colorectal	2	6,7
	Esophagus/Stomach	3	10,0
	Malignant Lymphoma	4	13,3
	Other	8	26,7
Disease Stage	I	7	23,3
	II	5	16,7
	III	6	20
	IV	12	40
Port Insertion Site	Left internal jugular vein	2	6,7
	Right internal jugular vein	28	93,3

Characteristics		Number (n)	Percentage (%)
Reason for Port Removal	Completion of treatment	6	20
	Not removed	22	73,3
	Due to port-related complications	2	6,7

In our study, breast cancer was the most common indication for subcutaneous port placement, accounting for 43.3% of cases, followed by malignant lymphoma at 13.3%. A majority of patients (60%) were in advanced stages (Stage III–IV) at the time of port placement. The right internal jugular vein was the predominant site for port insertion, used in 93.3% of cases. By the end of the study, 8 patients (26.7%) had their ports removed, of which 2 cases (6.7%) were due to port-related complications, specifically port occlusion.

Table 3. Complications during the use of subcutaneous port

Complication	Number (n)	Percentage (%)
Port-related infection	0	0
Skin erythema/ulceration	0	0
Catheter occlusion	3	10
Pneumothorax	0	0
Subcutaneous hemorrhage	0	0
Catheter displacement/malposition	0	0
Catheter fracture/breakage	0	0
Pain at port site	1	3,3
No complications	26	86,7

No serious complications were observed during the use of the subcutaneous port (Port-a-Cath). At the end of the study, complications were recorded in only 4 patients (13.3%). Among them, 3 patients (10%) experienced catheter occlusion and 1 patient (3.3%) reported pain at the port insertion site.

3.2. Patient satisfaction and quality of life with subcutaneous port implantation

Table 4. Patient satisfaction with the use of subcutaneous port (Port-a-Cath)

Assessment questions	Patient satisfaction summary				
	Very satisfied n (%)	Satisfied n (%)	Moderate n (%)	Dissatisfied n (%)	Not at all n (%)
Overall, are you satisfied with the subcutaneous port (Port-a-Cath)?	18 (60)	8 (26,7)	3 (10,0)	1 (3,3)	0

Assessment questions	Patient satisfaction summary				
	Very satisfied n (%)	Satisfied n (%)	Moderate n (%)	Dissatisfied n (%)	Not at all n (%)
If given the choice again, would you opt to have a port inserted?	13 (43,3)	15 (50,0)	0	2 (6,7)	0
Are you afraid of possible port complications?	0	1 (3,3)	4 (13,3)	5 (16,7)	20 (66,7)
Do you frequently worry about the port?	0	1 (3,3)	3 (10,0)	10 (33,3)	16 (53,4)
Do you feel the port is a foreign object that causes discomfort?	0	1 (3,3)	2 (6,7)	8 (26,7)	19 (63,3)
Are you satisfied with the cosmetic appearance after port placement?	9 (30,0)	14 (46,7)	3 (10,0)	1 (3,3)	3 (10,0)
Were you thoroughly informed about the port procedure?	20 (66,7)	8 (26,7)	2 (6,6)	0	0
Did you experience pain during the procedure?	1 (3,3)	0	5 (16,7)	6 (20,0)	18 (60,0)
Do you currently experience any pain at the port site?	0	1 (3,3)	0	10 (33,3)	19 (63,4)
Are you afraid of needle insertion into the port?	0	0	4 (13,3)	6 (20,0)	20 (66,7)
Do you think the port makes chemotherapy infusion easier?	15 (50,0)	14 (46,7)	1 (3,3)	0	0
Do you feel more comfortable during chemotherapy when using the port?	20 (66,7)	8 (26,7)	2 (6,7)	0	0
Does the port interfere with your daily activities?	0	1 (3,3)	0	9 (30,0)	20 (66,7)
Are you able to rest well with the port in place?	12 (40,0)	11 (36,7)	3 (10,0)	1 (3,3)	3 (10,0)
Would you recommend port insertion to other patients undergoing chemotherapy?	16 (53,3)	12 (40)	2 (6,7)	0	0

The study showed that 96.7% of patients were satisfied with subcutaneous port (Port-a-Cath) placement. All participants (100%) were well-informed about the procedure prior to implantation. A total of 93.3% felt more comfortable receiving chemotherapy through the port, and daily activities were not hindered for the majority of patients (66.7%). In terms of cosmetic concerns, 86.7% expressed satis-

faction with the aesthetic outcome. Notably, only 2 patients (6.7%) had minor reservations about opting for the port again, and the vast majority showed little to no anxiety regarding potential complications. However, 10% of patients perceived the port as a foreign object. Overall, patient perception of the subcutaneous port was highly favorable in terms of comfort, ease of chemotherapy administration, and impact on quality of life.

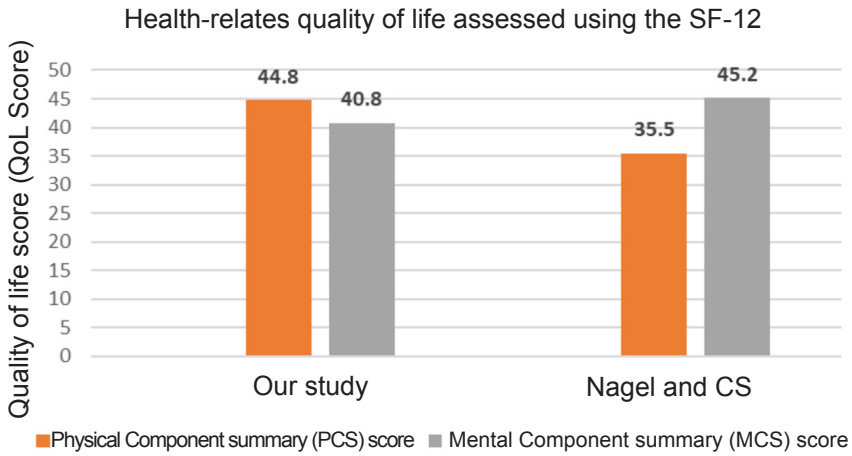

Figure. Quality of life scores among cancer patients with subcutaneous port use assessed by SF-12

In our study, quality of life among cancer patients using a subcutaneous port (Port-a-Cath) was assessed using the 12-Item Short Form Survey (SF-12). The results showed a median Physical Component Summary (PCS) score of 44.8 and a median Mental Component Summary (MCS) score of 35.5.

Table 5. Multivariate regression analysis based on mental health scores

	Mental component score (SF-12 MCS)		
	Beta (SE)	**T**	**P**
Satisfaction with subcutaneous port	0,149	0,845	0,406
Complications of the port	0,043	0,246	0,163
Fear of port-related complications	0,232	1,156	0,258
Frequent worries about the port	-0,149	-1.112	0,276
Fear of needle insertion into the port	-0,443	-2,826	0,009
Perception of the port as a foreign object	-0,169	-1,064	0,297
Satisfaction with the aesthetics of the port	0,332	2,118	0,044
Pain from the port	0,149	0,845	0,406
Impact on daily activities	0,149	0,845	0,406

The multivariate regression analysis showed that the aesthetic aspect of the subcutaneous port and the patient's fear of needle insertion significantly affected mental health-related quality of life, with statistically significant p-values of 0.044 and 0.009, respectively.

4. DISCUSSION

4.1. General characteristics of study participants

The mean age in our study was 52.1 ± 14.4 years (ranging from 20 to 78), which is lower than some previous studies. For instance, Le Van Long (2023) reported a mean age of 59[5], while Nagel et al. reported a mean age of 60.6 years for port placements[3]. In our study, females accounted for 80% of participants. This gender distribution differs from several other reports. Kumar et al[4], found that male patients predominated in port placements, whereas Nagel et al. reported 60.2% of patients were female[3]. The gender disparity in our study may be attributed to a high proportion of breast cancer cases. Notably, no illiterate patients were recorded in our sample. The majority of patients were female, likely due to concerns about aesthetics and the desire to avoid skin damage caused by repeated peripheral vein infusions during chemotherapy.

4.2. Characteristics and complications related to subcutaneous ports

Among the 30 patients included in our study, those with breast cancer comprised the largest proportion of port placements at 43.3%, followed by lymphoma at 13.3%. This aligns with several other studies-for instance, Irappa Madabhavi et al. reported breast cancer cases made up 38.4% of their cohort[5]. According to Nagel et al., breast and gastrointestinal cancers each accounted for 23.5% of cases[3]. The right internal jugular vein was the preferred site for port placement in 93.3% of patients, consistent with many international reports. Two cases involved placement in the left internal jugular vein due to difficulty accessing the right side (e.g., right-sided mastectomy in prior surgeries). In our study, 12 out of 30 patients (40%) were in stage IV, comparable to the 47% reported by David et al[6].

During port usage, 4 patients (13.3%) experienced complications: 3 with port occlusion (10%) and 1 with pain at the insertion site. These rates differ from some published data. Irappa Madabhavi et al. reported a 12% infection rate, 2% catheter migration, 2% port fracture, and 1% with recurrent pleural effusion due to catheter tip placement in the pleural space. They also observed 1% with thrombosis[5]. Le Van Long (2023) recorded 4.8% infections, 3.2% catheter occlusions, and 1.6% venous thrombosis [5]. Among 483 patients in a study by Eric Voog et al., there were 7.6% infections, 3.6% thrombosis, and 1.9% extravasation, with 71.3% of complications occurring within the first year of use [7]. Another study by Nilgün Yıldırım reported complications in 54 out of 260 patients, with port occlusion being the most common at 8.4% [8]. The lower complication rate in our study may be due to the limited sample size. Nonetheless, our findings suggest that subcutaneous ports are safe for intravenous chemotherapy administration.

4.3. Patient satisfaction and quality of life with subcutaneous ports

Overall, 96.7% of patients expressed satisfaction with port placement, with 60% selecting "very much" 26.7% "much" and 10% "moderate". Additionally, 93.3% of patients indicated they would choose to have a port again. All patients were informed about the procedure beforehand, and all felt comfortable receiving chemotherapy through the port. Daily activities were not hindered, with 66.7% choosing "very much" when asked about comfort with the port. Regarding pain, 20% experienced "a little", while 60% reported "none". Only 2 patients expressed hesitation about having the port again. The majority did not worry about potential complications, and only 3 patients (10%)

perceived the port as a foreign object. Aesthetic satisfaction was high, with 86.7% satisfied with the appearance post-placement.

These findings are consistent with both domestic and international studies. Le Van Long (2023) reported that 98.4% of patients were satisfied or very satisfied with their port use [5]. In Nagel et al.'s (2012) study, 85.7% of patients reported being "very" or "quite" satisfied, and 90.5% would opt to have a port again. Moreover, 88.1% reported little or no pain from the port, and 71.4% said they could enjoy leisure time during treatment [3]. Nilgün Yıldırım et al. reported that 59.6% of patients experienced "little" or "no" pain, and only 6 patients reported significant pain. Meanwhile, 87.1% did not feel discomfort or pain during treatment, and just 3.8% said the port affected daily life [8]. While subcutaneous ports provide high satisfaction, a small number of patients remain dissatisfied, highlighting the need for better patient education before port placement and improvements in port aesthetics post-placement.

Using the SF-12 quality of life tool (12 questions), the median physical and mental health scores in our study were 44.8 and 35.5, respectively lower than the general population, but similar to results from Nagel et al[3]. Our multivariate regression analysis showed that port aesthetics and fear of needle insertion significantly influenced mental health scores, with statistically significant p-values of 0.044 and 0.009. These findings emphasize that improving port aesthetics and patient education, along with reducing psychological distress, can enhance the quality of life for patients using subcutaneous ports.

5. CONCLUSION

Subcutaneous port implantation ensures safety with a low rate of complications during infusion procedures. It provides comfort for patients both during chemotherapy administration and in daily life activities. Most patients expressed satisfaction with the use of subcutaneous ports, which contributed positively to their overall quality of life during chemotherapy treatment. The results highlight the importance of considering the aesthetic aspect of the port, as it is significantly associated with patients' quality of life.

REFERENCES

[1]. Le Van Long, Hoang Cong Tung, Nguyen Thanh Hung (2023), *Evaluation of the use of infusion ports in cancer patients at Bach Mai Hospital*, Nuclear Medicine and Oncology Center, Bach Mai Hospital. 2023;134.07:54–60.

[2]. Kontodimopoulos N (2015), *The potential for a generally applicable mapping model between QLQ-C30 and SF-6D in patients with different cancers: a comparison of regression-based methods*, Qual Life Res. 2015;24(6):1535-1544.

[3]. Nagel SN, Teichgräber UK, Kausche S, Lehmann A (2012), *Satisfaction and quality of life: a survey-based assessment in patients with a totally implantable venous port system*, Eur J Cancer Care (Engl). 2012 Mar;21(2):197-204.

[4]. Kumar AH, Srinivasan NM, Thakkar JM, Mathew S (2013), *A prospective observational study of the outcome of central venous catheterization in 100 patients*, Anesth Essays Res. 2013;7:71–75.

[5]. Madabhavi I, Patel A, Sarkar M, Anand A, Panchal H, Parikh S (2017), *A Study of Use of "PORT" Catheter in Patients with Cancer: A Single-Center Experience. Clin Med Insights Oncol*, 2017 Feb 23; 11: 1179554917691031.

[6]. Lebeaux, David MD; Larroque, Béatrice MD; Gellen-Dautremer, Justine MD; Leflon-Guibout, Véronique MD; Dreyer, Chantal MD; Bialek, Suzanne MD et al (2012), *Clinical Outcome After a Totally Implantable Venous Access Port-Related Infection in Cancer Patients: A Prospective Study and Review of the Literature. Medicine*, 2012 November, 91(6):p 309-318.

[7]. Eric Voog, Loic Campion, Pauline du Rusquec, Hugues Bourgeois, Julien Domont, Fabrice Denis et al (2018), *Totally implantable venous access ports: a prospective long-term study of early and late complications in adult patients with cancer*, Support Care Cancer. 2018 Jan;26(1):81-89.

[8]. Nagel S.N., Teichgräber U.K.M., Kausche S. & Lehmann A (2020), *Questionnaire-based evaluation of satisfaction levels in patients receiving chemotherapy through implanted venous access ports*, Medical Science and Discovery. 2020, 7(6), 509-514.

DELAYED RADIATION THERAPY IN THE TREATMENT OF EMBRYONAL RHABDOMYOSARCOMA: A CASE REPORT AND LITERATURE REVIEW

Dang Nguyen Van[1,2*], Phan Nguyen Huy[1], Luc Tieu Van[1], Duc Nguyen Dinh[1]

ABSTRACT

Background: Rhabdomyosarcoma (RMS) is a rare malignancy, accounting for 3% of all cancers in children, as the most common primary site for RMS is in the head and neck region. The most common histology in children is the embryonal subtype. The diagnosis of embryonal rhabdomyosarcoma in the head and neck region is primarily based on histopathology, following biopsy of the tumor. Despite the improved outcome based on the EFS and OS using the three different treatment modalities-chemotherapy, radiotherapy and surgical treatment, the survival of patients depends on their IRS groups pathological and surgical.

Case presentation: We present a clinical case of a nine-year-old male with initial complaints of painful mass in the region near the left parotid gland**.** Clinical and paraclinical investigations were conducted for diagnostic purposes. The postoperative histopathology report given at the centre of primary wide excision and cervical neck dissection was embryonal rhabdomyosarcoma. The patient then was treated with adjuvant chemotherapy. The strategy of concurrent chemo-radiotherapy was not implemented, and radiotherapy was delayed for 4 months due to the patient's refusal of the treatment.

Results: The combination of surgery, chemotherapy and local control with radiotherapy achieved a good result in our patient.

Conclusions: Rhabdomyosarcoma (RMS) is a predominantly pediatric malignancy which can present throughout the body including the head and neck region. The use of radiation therapy is an important part of multimodality treatment for rhabdomyosarcoma.

Keywords: Embryonal rhabdomyosarcoma; pediatric cancer; chemoradiotherapy; head and neck cancer; delay treatment.

1. INTRODUCTION

Rhabdomyosarcoma (RMS) is a highly malignant soft tissue tumor derived from primitive embryonal mesenchymal tissue that differentiates into striated skeletal muscle. It is the most common soft tissue sarcoma

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in children, accounting 3-4% of all childhood malignancies with an annual incidence of 4.4 per million people under 20[1,2]. There are two main subtypes of RMS, distinguished by histopathology: embryonal subtype, alveolar subtype with difference clinical characteristics and prognosis. The most common in children (70-80%) is the embryonal subtype which predominates in head and neck regions and has better prognosis compared with alveolar ones. A multimodality approach involving surgical treatment, chemotherapy and radiotherapy is necessary in the treatment of pediatrics with RMS. According to the patient's individual risk group assignment, the optimal timing and intensity of these three treatment modalities must be evaluated with taking into consideration prognostic factors but also the late effects of treatment. Generally, the multimodal approach seemed to be the ideal management of RMS with good outcome in localised stage but poor prognosis in extensive, metastatic disease.

We report a case of rhabdomyosarcoma with an advanced stage located near the left parotid gland. The standard treatment plan was not implemented due to several factors. This report reflects our clinical experience and contributes to the understanding of this disease.

2. CASE PRESENTATION

A 9-year-old male patient with no remarkable medical history was admitted to our hospital because of painful mass in the region near the left parotid gland over the past few weeks. Clinical examination revealed no abnormalities except for a tumor near the left parotid gland, measuring 5 cm, which was tender to palpation. The head and neck MRI was performed, which showed a mass measuring about 54 mm located mainly near the left parotid gland that displaced the medial pterygoid muscle anteriorly. It showed hypointensity in the T1-weighted (T1W) image, hyperintensity in the both T2W and T2FS, heterogeneous enhancement postcontrast (Figure 1). The addition CT confirmed that the tumour invaded the apex of the ipsilateral petrous bone but no intracranial invasion was seen. The chest and abdominal computed tomography (CT), whole body scan, showed no evidence of metastasis was seen.

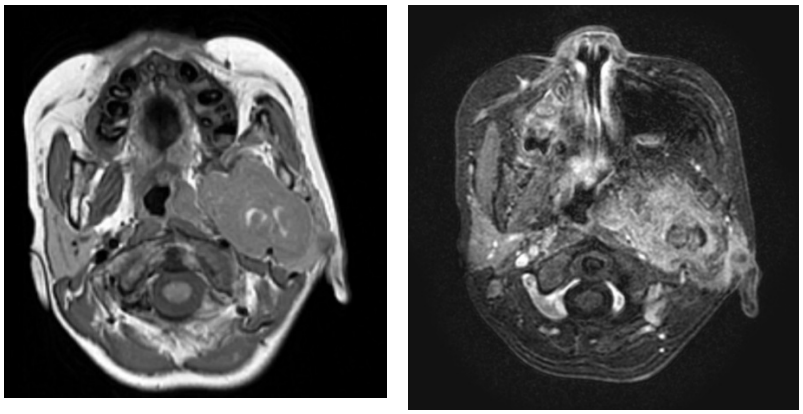
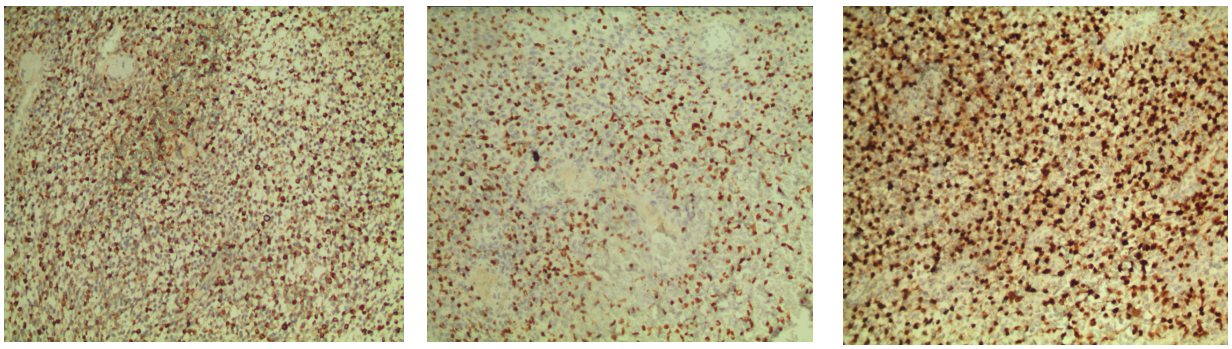


Figure 1. The MRI imaging in axial T1 (left) and axial postcontrast (right) at time of diagnosis

The patient underwent the wide excision of the primary site of tumor and the ipsilateral neck dissection. Incomplete resection with gross residual disease was performed. In addition, the entire left parotid gland and the level II cervical lymph nodes were dissected. Postoperative pathology and immunohistochemistry (IHC) were consistent with embryonal rhabdomyosarcoma with 16/16 negative lymph nodes (Figure 2). The genetic mutation testing showed no evidence of FOXO1 gene rearrangements.



Desmin 2 (+) MyoD1 (+) Myogenin (+)

Figure 2. The immunohistochemistry results

The final diagnosis was embryonal rhabdomyosarcoma, group F – High risk group (according to Cooperative Weichteilsarkom Study-CWS). Based on the CWS protocol, our patient was planned to receive 9 cycles of chemotherapy with I2VA (Ifosfamide, Vincristine, Actinomycin-D) for every 3 weeks, combined with concurrent chemoradiotherapy starting from week 13. After 4 cycles of chemotherapy, the disease showed a complete response (Figure 2). However, due to economic constraints and difficulties in patient transportation, the patient refused to receive the planned radiotherapy and continued with the additional 9 cycles of chemotherapy at a local hospital near his house. The patient refused radiotherapy and was discharged with no evidence of disease after 13 cycles of chemotherapy.

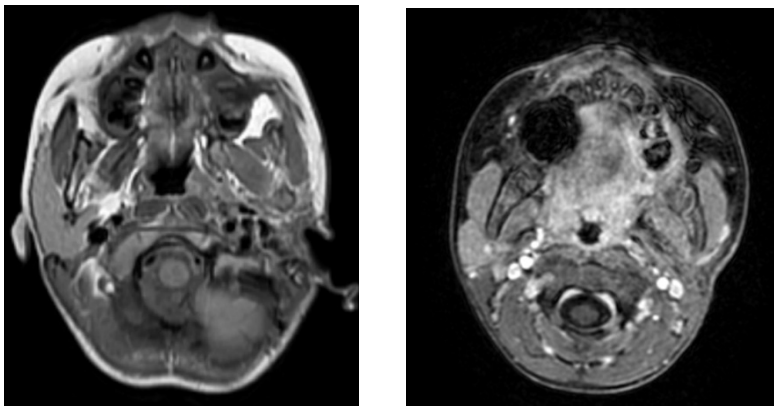


Figure 3. The MRI imaging after 13 cycles of chemotherapy

The patient returned to our hospital after 4 months with progressive lesions at the surgical site. After a multidisciplinary consultation, we decided to proceed with radiotherapy for this patient. The patient then received the adjuvant radiotherapy in 28 fractions with a total dose of 50.4 Gy for tumor bed (Five fractions per week) using VMAT technique. No significant toxicity was recorded during and at the end of treatment. The patient recovered well and achieved complete response (CR) after two months in the both clinical and paraclinical examination (Figure 5).

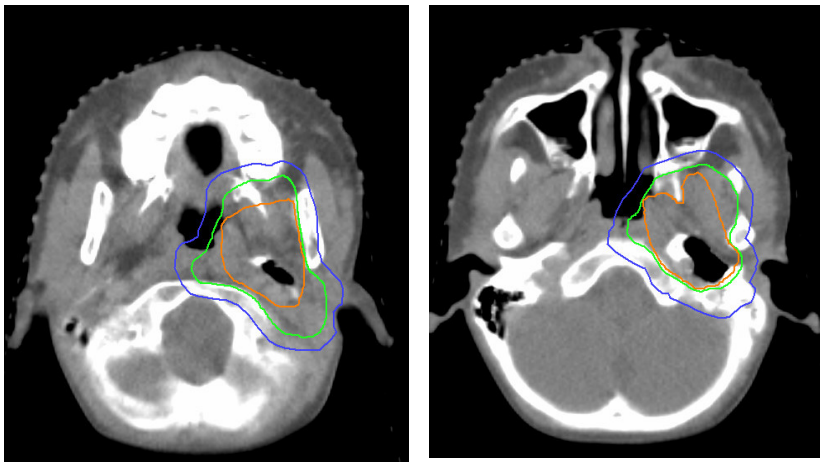


Figure 4. The patient's target volumes (Orange contour: Tumor bed; green contour: CTV 50.4; blue contour: PTV 50.4)

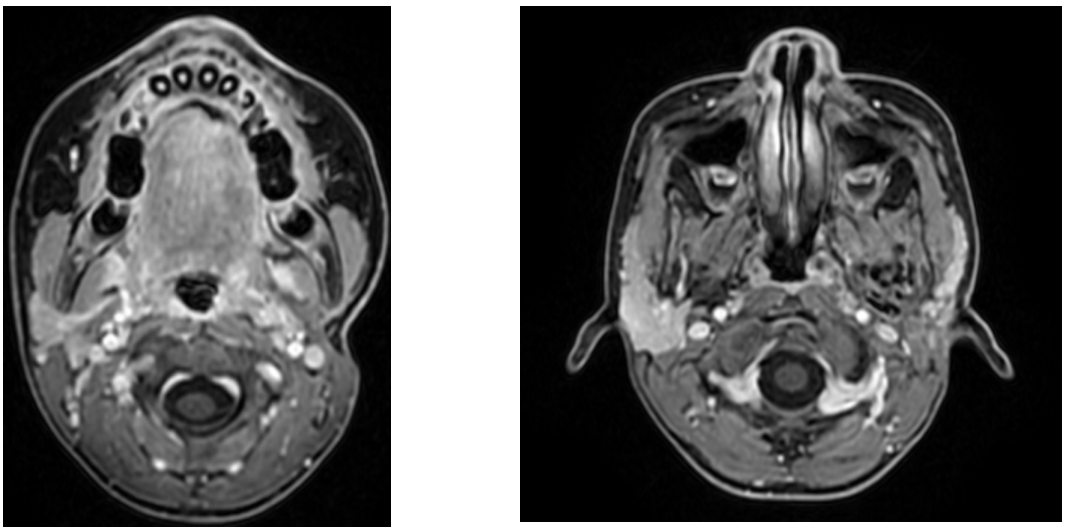


Figure 5. The MRI imaging after two months of radiotherapy

3. DISCUSSION

Rhabdomyosarcoma is the most common pediatric soft tissue sarcoma but relatively rare in adults. Although these tumors can occur anywhere in the body, the most common sites are the head and neck (accounting for nearly 40%), the urinary tract (20%), the extremities (20%), and other locations (20%).[3,4] Rhabdomyosarcoma in children is commonly found in the head and neck region, whereas in adults, it is more frequently located in the extremities. Head and neck RMS (HNRMS) is divided into three anatomic subsites based on prognosis and location: parameningeal (50%), orbital (25%), and other head and neck (25%). Parameningeal RMS comprise 16% of all of cases and include those tumors specifically arising from the nasal cavity/nasopharynx, paranasal sinuses, parapharyngeal space, pterygopalatine/ infratemporal fossa, and mastoid/middle ear[4].

Histopathology and immunohistochemistry plays the critical role for diagnosing rhabdomyosarcoma. It is expressed in immunohistochemistry with markers including Desmin, Myogenin, CD 56, muscle-specific actin, Myoglobin, Vimentin, and VioD1. Differential diagnoses include Ewing's sarcoma, lymphoma, neuroblastoma, nasopharyngeal carcinoma, among others. Regarding histopathology, the WHO classification from 2013, as well as the update version in 2020, divides rhabdomyosarcoma into four main subtypes: Embryonal rhabdomyosarcoma (ERMS), Alveolar rhabdomyosarcoma (ARMS), Pleomorphic rhabdomyosarcoma (PRMS) and Spindle Cell/Sclerosing rhabdomyosarcoma (SRMS). Embryonal and alveolar rhabdomyosarcoma are the most common types in children. Embryonal rhabdomyosarcoma is more frequently seen in younger children and has a good prognosis, whereas alveolar rhabdomyosarcoma can occur in both children and adults, with a poor prognosis with hight propensity of recurrent or metastasises. Among all the subtypes of rhabdomyosarcoma, alveolar rhabdomyosarcoma is the only one associated with translocation mutations. Approximately 80% of cases of alveolar rhabdomyosarcoma carry mutations in the FOXO1 and PAX3 (or PAX7) genes. Skapek et al.'s study showed that PAX3-FOXO1 or PAX7-FOXO1 mutations significantly reduce both overall survival (OS) and event-free survival (EFS)[5].

The decision about the appropriate therapeutic protocol for RMS is preceded by a complex classification process that includes clinical staging and evaluation of the completeness of the primary surgical procedure. The staging of embryonal rhabdomyosarcoma is commonly assessed using the IRSG (The Intergroup Rhabdomyosarcoma Study Group) classification. Stage is based on the anatomic site (favorable versus unfavorable), tumor size, nodal involvement, and presence or absence of distant metastases. While the post-surgical 'Group' is based on whether the tumor was completely resected before chemotherapy, it helps guide the radiotherapy strategy (Table 1 and 2)[6]. For all available information, our patient was classified into Group 3. The EpSSG (European Paediatric Soft Tissue Sarcoma Study Group) risk classification for non-metastatic rhabdomyosarcoma is divided into 4 risk groups, based on histopathology, post-surgical staging, location, lymph node involvement, tumor size, and the patient's age (Table 3). Our patient herein belongs to high-risk group E due to the tumor's location near the meninges (in the infratemporal fossa) and the tumor size >5cm. Risk stratification not only helps in disease prognosis but also in determining the intensity of treatment. Patients with low risk, where the tumor was completely resected, are treated with 8 cycles of VA chemotherapy at a lower dose, while other groups are treated with 9 cycles. The intermediate-risk group is treated with 4 cycles of IVA (ifosfamide, vincristine, actinomycin D), followed by 5 cycles of VA, whereas the high-risk group is recommended to receive 9 cycles of IVA [7, 8].

The multimodal approach seemed to be the ideal management of RMS including surgery, chemotherapy and radiotherapy. For head and neck regions, considering functional preservation, cosmetics and the complex structures, the role of surgery was limited to biopsy. Radiotherapy is indicated for all patients who do not achieve R0 resection, thus, almost all rhabdomyosarcomas in the head and neck region are indicated for radiotherapy. Radiotherapy may begin earlier if the patient has symptoms from the tumor or intracranial invasion, but rhabdomyosarcoma is chemosensitive, so radiotherapy is typically delayed until the 13th week[9]. The available guideline suggest the dose for primary tumor is 50.4Gy, 36Gy for micrometastasis. Primary positive lymph nodes should receive 50.4Gy and 41.4Gy is enough for post neck dissection. The prophylactic neck irradiation should not be recommended. CTV was created by expanding 0.5-1cm in all directions from GTV[1,9]. Previously, patients with tumors near the meninges received concurrent chemoradiotherapy,

with whole-brain radiotherapy starting on day 0. In recent decades, due to a better understanding of the risk factors for meningeal invasion, whole-brain radiotherapy is no longer used[10].

Our patient belongs to the IRS III group. The patient did not receive concurrent chemoradiotherapy starting from week 13 according to the CWS guidelines due to several factors. Although the disease showed a complete response after 13 weeks of chemotherapy, the recurrence rate remains very high if radiotherapy is not included in the initial treatment. For head and neck rhabdomyosarcoma, when the primary tumor is not completely resected, radiotherapy and chemotherapy were the mainstay treatment. In this condition, although the disease responded well to chemotherapy, it showed a tendency to progress when radiotherapy was delayed. We decided to administer radiotherapy after chemotherapy with a dose of 50.4 Gy in 28 fractions to the tumor bed, which is higher than the CWS guidelines (Table 4) due to the the delay of treatment and lack of concurrent chemotherapy. Regarding radiotherapy techniques, in Vietnam, 3D radiotherapy, IMRT, and VMAT are commonly used. With more advanced techniques, IMRT and VMAT minimize the impact on surrounding organs, thereby reducing side effects compared to the 3D technique. Our patient received radiotherapy using the VMAT technique, and after 28 fractions, there were virtually no significant side effects from radiotherapy. After evaluating the treatment results two months later, the disease showed a complete response.

Table 1. The stage of rhabdomyosarcoma according to IRSG

Stage	Site	Tumor size	Nodal Involvement	Metastatic Spread
I	Favorable	Any	Any	No
II	Unfavorable	< 5cm	No	No
III	Unfavorable	< 5cm	Yes	No
		> 5cm	Any	No
IV	Any	Any	Any	Yes

Table 2. IRS clinical grouping classification

IRSG grouping	Description
Group I	**Localized disease with microscopic margin-negative (RO) resection** A-Confined to muscle/organ of presentation B-Extension beyond muscle/organ of presentation
Group II	**Gross total resection** A-Margin-positive resection (R1) B-Regional lymph node involvement with RO resection of nodal disease C-Regional lymph node involvement with R1 resection of nodal disease
Group III	**Gross residual disease following resection** A-Biopsy only B->50% resection completed
Group IV	**Distant metastatic disease at presentation**

Table 3. Risk Stratification for RMS according to EpSSG

Risk group	Subgroups	Pathology	Post surgical stagc	Site	Node stage	Size & age
Low-risk	A	Favourable	I	Any	NO	Favourable
Standard-risk	B	Favourable	I	Any	NO	Unfavourable
	C	Favourable	II, III	Favourable	NO	Any
	D	Favourable	II, III	Unfavourable	NO	Favourable
High-risk	E	Favourable	II, III	Unfavourable	NO	Unfavourable
	F	Favourable	II, III	Any	NI	Any
	G	Unfavourable	I, II, III	Any	NO	Any
Very High-risk	H	Unfavourable	I, II, III	Any	NI	Any

Pathology: Favourable = All embryonal, spindle cells, botryoid RMS, Uníavourablc = Alí alveolar RMS (including the solid-alveolar variant); **Post surgical stage:** Group I = Primary complete resection (RO), Group II = Microscopic residual (RI) or primary complete resection but NI, Group III = Macroscopic residual (R2); **Site:** Favourable = Orbit, genitourinary non-bladder prostate (i.e., paratesticular and vagina/uterus) and non-parameningeal head and neck, Unfavourable = all other sites (parameningeal, extremities, genitourinary bladder-prostate and "othersites"; **Node stage:** NO = No clinical or pathological node involvement, N1 = Clinical or pathological nodal involvement; **Size & Age:** Favourable = Tumor size (maximum dimension) < 5 cm and age < 10 y, Unfavourable = All others (/>., size >5 cm or age > 10 y).

Table 4. Radiation doses used in CWS

IRS group	Resection and response	Embryonal RMS (RME)	Alveolar RMS (RMA)
1		No RTX	41.4 Gy; 23 F
II		41.4 Gy; 23 F	41.4 Gy; 23 F
III	Secondary complete resection (RO) prior to (or atter) RTX	36 Gy; 20 F (good response) 41.4 Gy; 23 F (poor response) Subgroup C: omittance of RTX only in case of íavourable size and age.	41.4 Gy; 23 F
III	Incomplete secondary resection (R1 or R2)	50.4 Gy; 28 F	50.4 Gy; 28 F
III	Clinical complete remission, no secondary resection	41.4 Gy; 23 F	50.4 Gy; 28 F
III	Partial remission, no secondary resection or no RO expected	50.4 Gy; 28 F Orbit and PR (>2/3): 45 Gy; 25 F	50.4 Gy; 28 F
III	Poor response, Progressive disease, no secondary resection	50.4 Gy; 28 F	50.4 Gy; 28 F (+ optional boost: 5.4 Gy; 3 F)

4. CONCLUSIONS

Head and neck rhabdomyosarcoma is a uncommon, complex condition with a variable prognosis based upon the subsite of presentation and the histologic and molecular subtype. The diagnosis should be based on based on the precise physical investigation, past medical history, radiological imaging, histology, laboratory and molecular tests. The treatment strategy for rhabdomyosarcomas of the head and neck involves strict multidisciplinary cooperation. Radiotherapy plays a crucial role in the group of diseases manifesting in the head and neck region difficulty to achieve R0 resection and it's radiosensitive.

REFERENCES

[1]. Casey DL, Wolden SL. Rhabdomyosarcoma of the Head and Neck: A Multimodal Approach. *Journal of neurological surgery Part B, Skull base*. 2018;79(1):58-64.

[2]. Amer KM, Thomson JE, Congiusta D, et al. Epidemiology, Incidence, and Survival of Rhabdomyosarcoma Subtypes: SEER and ICES Database Analysis. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society*. 2019;37(10):2226-2230.

[3]. Radzikowska J, Kukwa W, Kukwa A, Czarnecka A, Krzeski A. Rhabdomyosarcoma of the head and neck in children. *Contemporary oncology (Poznan, Poland)*. 2015;19(2):98-107.

[4]. Kern L, Henssen A, Eggert A, Scheer M. The Other Site of Rhabdomyosarcoma. *Cancer medicine*. 2024;13(20):e70348.

[5]. Kendall GC, Watson S, Xu L, et al. PAX3-FOXO1 transgenic zebrafish models identify HES3 as a mediator of rhabdomyosarcoma tumorigenesis. *eLife*. 2018;7.

[6]. Beverly Raney R, Walterhouse DO, Meza JL, et al. Results of the Intergroup Rhabdomyosarcoma Study Group D9602 Protocol, Using Vincristine and Dactinomycin With or Without Cyclophosphamide and Radiation Therapy, for Newly Diagnosed Patients With Low-Risk Embryonal Rhabdomyosarcoma: A Report From the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *Journal of Clinical Oncology*. 2011;29(10):1312-1318.

[7]. Ferrari A, De Salvo GL, Brennan B, et al. Synovial sarcoma in children and adolescents: the European Pediatric Soft Tissue Sarcoma Study Group prospective trial (EpSSG NRSTS 2005). *Annals of Oncology*. 2015;26(3):567-572.

[8]. Totadri S, Bansal D, Donaldson SS, et al. Common queries in managing rhabdomyosarcoma in low- and middle-income countries: An Indo-North American collaboration. *Pediatric blood & cancer*. 2023;70(11):e30616.

[9]. Frankart AJ, Breneman JC, Pater LE. Radiation Therapy in the Treatment of Head and Neck Rhabdomyosarcoma. *Cancers*. 2021;13(14).

[10]. De B, Kinnaman MD, Wexler LH, Kramer K, Wolden SL. Central nervous system relapse of rhabdomyosarcoma. *Pediatric blood & cancer*. 2018;65(1).

MALT LYMPHOMA PRESENTING IN THE THYROID GLAND: A REPORT OF THREE CASES AT VIETNAM NATIONAL CANCER HOSPITAL

Ngo Quoc Duy[1,2], Bui Xuan Thang[1], Ngo Xuan Quy[1*], Le Van Quang[1,2]

Abtract:

Primary lymphoma presenting in the thyroid gland is rare, accounting for 2-8% of thyroid malignancies and 1-2% of extranodal malignancies. Mucosal lymphoid tissue-associated lymphoma (MALT) is one of the rare variants, first described by Isaacson and Wright in 1984. Primary MALT lymphoma of the thyroid gland accounts for 6-28% of tumors, closely related to chronic inflammatory or local autoimmune processes because thyroid tissue has no lymphatic organs. The coexistence between local inflammation and tumor formation causes many difficulties in disease diagnosis. Clinically, most patients are diagnosed at the age of over 60, with about 30% of patients having symptoms of local compression related to the tumor such as difficulty swallowing, shortness of breath, hoarseness. The standard treatment in MALT lymphoma is radiotherapy combined with chemotherapy; Surgery is valuable in diagnosis and symptom resolution. For asymptomatic patients regardless of stage who can be closely monitored, no treatment is required. In general, MALT lymphoma has a good prognosis, different from other histopathological types such as diffuse large B-cell lymphoma. Currently, there are not many reports on this clinical form, so we report 3 clinical cases, thereby drawing experience in the diagnosis and treatment of MALT lymphoma in the thyroid gland.

Key words: Primary thyroid lymphoma; MALT.

1. INTRODUCTION

Primary thyroid lymphoma (PTL) is a rare malignant disease, accounting for approximately 2–8% of all thyroid malignancies and less than 1–2% of all extranodal lymphomas. PTL primarily belongs to the group of non-Hodgkin B-cell lymphomas. Among these, diffuse large B-cell lymphoma (DLBCL) is the most common subtype, comprising 60–80% of cases, followed by mucosa-associated lymphoid tissue (MALT) lymphoma also known as extranodal marginal zone B-cell lymphoma accounting for 6–28% of cases. Several studies have demonstrated a strong association between thyroid MALT lymphoma and chronic lymphocytic thyroiditis (Hashimoto's thyroiditis). This correlation presents diagnostic challenges in both cytological and histopathological evaluations, as MALT lymphoma must be differentiated from other primary thyroid neoplasms with similar presentations. Treatment options for thyroid MALT lymphoma include surgery, radiotherapy and chemotherapy, with a generally more favorable prognosis compared to other histological subtypes of thyroid lymphomas. However, due to the rarity of this disease, there are limited reports in the medical literature. Therefore, we present three clinical cases of thyroid MALT lymphoma to review its pathological characteristics and treatment outcomes.

1.1. Clinical case descriptions

Three cases of thyroid MALT lymphoma treated at Vietnam National Cancer Hospital between March 2016 and May 2019 were included in this study. The clinical presentation, diagnostic workup, and treatment details are summarized in Table 1.

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	Patient 1	Patient 2	Patient 3
Age	56	69	42
Sex	Female	Female	Female
Medical history	Healthy	Healthy	Healthy
Thyroid tumor size	4 cm	8 cm	4 cm
Tumor location	Bilateral lobes	Bilateral lobes	One lobe
Cervical lymphadenopathy	Bilateral, max 17 mm	Bilateral, max 17 mm	None
Other lymphadenopathy	Bone marrow, abdominal lymph nodes	None	None
B symptoms	Absent	Absent	Absent
TSH	Normal	Normal	Normal
FT4	Normal	Normal	Normal
Diagnosis	After total thyroidectomy	After total thyroidectomy	After hemithyroidectomy
Histopathology	MALT lymphoma	MALT lymphoma	MALT lymphoma
Ann Arbor Stage	IVAE (thyroid, cervical and abdominal lymph nodes, bone marrow)	IIE (thyroid, cervical lymph nodes)	IE (thyroid only)
Treatment	Observation	Surgery + R-CVP	Surgery + R-CVP
Survival status	Alive	Alive	Alive
Follow-up duration	24 months	49 months	81 months

The mean age of the three patients was 54 years (range: 42–69 years), and all were female. All patients presented with a palpable neck mass, and one reported dysphagia due to compressive effects of a large thyroid tumor. Other clinical signs were stable.

On physical examination, all three patients had large thyroid masses with bilateral cervical lymphadenopathy. The mean tumor size was 5.3 cm (range: 4–8 cm). None of the patients exhibited B symptoms.

Neck ultrasound was the initial imaging modality employed, revealing multifocal lesions involving both thyroid lobes. The lesions appeared as heterogeneous hypoechoic or hyperechoic masses. All three patients underwent fine-needle aspiration cytology (FNAC), which failed to suggest a diagnosis of non-Hodgkin lymphoma in any case. Consequently, thyroidectomy (total or lobectomy) was performed for diagnostic purposes. Intraoperative frozen section analysis was suggestive of lymphoma, which was subsequently confirmed by routine histopathological examination. Immunohistochemistry supported the diagnosis of MALT lymphoma, with tumor cells positive for CD20, CD22, and CD79a, and negative for CD5 and CD10.

Regarding disease staging, two patients were classified as stage IIAE according to the Lugano classification and received chemotherapy with the R-CVP regimen. The number of cycles ranged from 3 to 9, with complete response observed in both cases. The remaining patient was staged as IVAE; however, due to the absence of clinical symptoms and not meeting GELF criteria for treatment initiation, the patient was managed with active surveillance. During a mean follow-up period of 17 months (range: 5–24 months), all patients remained alive with no evidence of disease progression.

2. DISCUSSION

Primary MALT lymphoma of the thyroid is an indolent subtype with a typically slow progression and minimal clinical symptoms. While B symptoms are commonly seen in 40–50% of non-Hodgkin lymphomas (NHL), they are rare in MALT lymphoma, making early clinical diagnosis challenging for physicians. Although the exact pathogenesis of thyroid MALT lymphoma remains unclear, Kuper-Hommel et al. suggested that the disease arises as a result of chronic autoimmune stimulation, particularly associated with Hashimoto's thyroiditis. This mechanism is similar to that observed in gastric MALT lymphoma, which is commonly linked to Helicobacter pylori infection. In 2009, Munemasa and colleagues studied B-cell reactivity to thyroglobulin, demonstrating that immunohistochemical analysis of MALT lesions revealed thyroglobulin presence in follicular dendritic cells within the germinal centers.

Fine-needle aspiration (FNA) is often the first-line diagnostic tool for thyroid nodules. However, in the case of thyroid lymphomas, especially MALT subtype, cytological features can closely resemble reactive lymphoid infiltrates seen in Hashimoto's thyroiditis, thereby reducing diagnostic accuracy. Sangalli et al. analyzed 17 cases of thyroid lymphoma and found that only 4 out of 10 MALT lymphoma cases were correctly diagnosed via cytology. In our three reported cases, cytological evaluation failed to indicate lymphoma. Histopathology and immunohistochemistry remain essential for definitive diagnosis, with MALT lymphoma showing positivity for CD20, CD22, and CD79a, and negativity for CD5 and CD10.

MALT lymphoma is a low-grade malignancy with slow progression; however, complete cure is rare, and relapse may occur, particularly in advanced stages. Treatment strategies are not standardized due to the rarity of the disease and vary depending on stage and histological subtype. Chemotherapy and radiotherapy are the mainstays of treatment. Radiotherapy is considered the treatment of choice for localized disease and can potentially result in cure. Surgery plays a limited therapeutic role and is primarily used for diagnosis via biopsy or in symptomatic cases to relieve airway obstruction. It may be considered in selected cases with localized, resectable lesions such as those in the breast, lung, colon, or thyroid. In a study by Nam YJ, Kim BH, and Lee SK et al., patients with localized disease who underwent thyroidectomy showed a 100% 5-year survival rate. Similarly, Saito et al. demonstrated that for stage IE MALT lymphoma, surgical management was associated with fewer treatment-related complications such as xerostomia from radiotherapy and reduced local recurrence. For patients with longstanding, asymptomatic lesions, active surveillance can be considered across all stages, and treatment may be deferred unless clinical criteria for intervention such as those defined by the Groupe d'Etude des Lymphomes Folliculaires (GELF) are met. Chemotherapy remains an important option for advanced-stage disease. Common regimens include R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and R-CVP (rituximab, cyclophosphamide, vincristine, prednisolone).

In our report, all three patients underwent thyroidectomy (total or lobectomy) primarily for diagnostic confirmation and to alleviate

compressive symptoms. In the first case, although the disease was staged as IV, the patient remained asymptomatic and did not meet GELF treatment criteria; therefore, active surveillance was adopted. After a 3-year follow-up, the disease showed signs of progression but did not yet warrant treatment. The other two patients received R-CVP chemotherapy according to GELF criteria and achieved good treatment responses. They remained disease-free at follow-ups of 49 and 81 months, respectively.

Prognosis is largely dependent on disease stage. In general, MALT lymphoma has a favorable prognosis, with median overall survival exceeding 10 years. The MALT-IPI prognostic index (age >70 years, stage III/IV disease, elevated LDH) can help stratify patients by risk. Five-year overall survival (OS) rates in low, intermediate and high-risk groups are approximately 99%, 93% and 64%, respectively. In our study, the median follow-up duration was 51 months (range: 24–81 months). All patients were alive at the time of last follow-up, with no evidence of relapse or disease progression.

These findings underscore that although complete cure is uncommon, MALT lymphoma particularly when presenting in the thyroid has an indolent course with favorable prognosis. Patients may remain asymptomatic and live for many years with the disease without requiring immediate treatment.

3. CONCLUSION

Primary MALT lymphoma of the thyroid is a rare entity, and its diagnosis often poses significant challenges. Chemotherapy and radiotherapy remain the mainstays of treatment, while surgery is typically reserved for diagnostic purposes or to alleviate compressive symptoms. Active surveillance is an appropriate management strategy in asymptomatic cases. The prognosis is generally favorable, with a median overall survival exceeding 10 years.

REFERENCES

[1]. Shrestha P, Aderhold K, Swierczynski S, Lin C, Herb R. Primary thyroid MALToma– a rare diagnosis of an unassuming thyroid nodule. *J Community Hosp Intern Med Perspect*. 2018;8(1):42-45. doi:10.1080/20009666.2018.1424487

[2]. Isaacson P, Wright DH. Malignant lymphoma of mucosa-associated lymphoid tissue. A distinctive type of B-cell lymphoma. *Cancer*. 1983;52(8):1410-1416. doi:10.1002/1097-0142(19831015)52:8<1410::aid-cncr2820520813>3.0.co;2-3.

[3]. Lee SC, Hong SW, Lee YS, et al. Primary thyroid mucosa-associated lymphoid tissue lymphoma; a clinicopathological study of seven cases. *J Korean Surg Soc*. 2011;81(6):374-379. doi:10.4174/jkss.2011.81.6.374

[4]. Van Heertum RL, Scarimbolo R, Wolodzko JG, et al. Lugano 2014 criteria for assessing FDG-PET/CT in lymphoma: an operational approach for clinical trials. *Drug Des Devel Ther*. 2017;11:1719-1728. doi:10.2147/DDDT.S136988.

[5]. Kuper-Hommel MJJ, Snijder S, Jansen-Heijnen MLG, et al. Treatment and survival of patients with thyroid lymphoma: a population-based study with clinical and pathologic reviews. *Clin Lymphoma Myeloma*. 2005;6(3):240-247. doi:10.3816/clm.2005.n.05.

[6]. Munemasa M, Yoshino T, Kobayashi K, et al. Expression of thyroglobulin on follicular dendritic cells of thyroid mucosa-associated lymphoid tissue (MALT) lymphoma. *Acta Med Okayama*. 2009;63(2):71-78. doi:10.18926/AMO/31834.

[7]. Sangalli G, Serio G, Zampatti C, Lomuscio G, Colombo L. Fine needle aspiration cytology of primary lymphoma of the thyroid: a report of 17 cases. *Cytopathology*. 2001;12(4):257-263. doi:10.1046/j.1365-2303.2001.00338.x

[8]. Nam YJ, Kim BH, Lee SK, et al. Co-Occurrence of Papillary Thyroid Carcinoma and Mucosa-Associated Lymphoid Tissue Lymphoma in a Patient with Long-Standing Hashimoto Thyroiditis. *Endocrinol Metab (Seoul)*. 2013;28(4):341-345. doi:10.3803/EnM.2013.28.4.341.

[9]. Saito Y, Watanabe N, Suzuki N, et al. Role of Surgery in Patients with Stage IE Primary Thyroid MALT Lymphoma Staged by a Modified Classification System: The Tokyo Classification. *Cancers (Basel)*. 2023;15(5):1451. doi:10.3390/cancers15051451.

[10]. Chen Q, Ayer T, Nastoupil LJ, et al. Initial management strategies for follicular lymphoma. *Int J Hematol Oncol*. 2012;1(1):35-45. doi:10.2217/ijh.12.7.

[11]. Thieblemont C, Cascione L, Conconi A, et al. A MALT lymphoma prognostic index. *Blood*. 2017;130(12):1409-1417. doi:10.1182/blood-2017-03-771915.

REAL-WORLD DATA ON THE EFFICACY AND SAFETY OF PAZOPANIB AS FIRST-LINE TREATMENT FOR ADVANCED RENAL CELL CARCINOMA AT VIETNAM NATIONAL CANCER HOSPITAL

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Nguyen Thu Phuong[1,2], Can Thi Anh Hong[1]

ABSTRACT

Background: Pazopanib is an effective first-line treatment for advanced renal cell carcinoma (RCC), but its efficacy and safety in the Vietnamese population are not well-documented. This study evaluates the outcomes and adverse effects of pazopanib at Vietnam National Cancer Hospital, with a focus on the impact of initial dosing.

Methods: A retrospective and prospective study of 60 patients with advanced RCC treated with pazopanib between January 2018 and July 2024. The initial doses were 200 mg, 400 mg, 600 mg or 800 mg. Primary endpoints were overall response rate (ORR) and disease control rate (DCR), with secondary endpoints including progression-free survival (PFS), overall survival (OS), and adverse events.

Results: The ORR was 45%, with 3.3% achieving complete response and 41.7% partial response. Median PFS was 13.1 months, and median OS was 21.5 months. The initial dose of pazopanib did not significantly affect OS (25.5 months for 800 mg vs. 20.5 months for lower doses, p=0.945). Common adverse effects included elevated liver enzymes and fatigue.

Conclusions: Pazopanib is effective and well-tolerated in the Vietnamese population, with no significant impact of initial dosing on overall survival. Dose adjustments based on tolerability may be beneficial. Further research with larger samples and longer follow-up is needed to confirm these findings.

Keywords: Renal cell carcinoma; pazopanib; advanced stage.

1. INTRODUCTION

Renal cell carcinoma (RCC) is the most common malignancy originating from the kidneys, accounting for approximately 85% of all kidney cancers. It is a significant global health burden, with incidence rising partly due to improvements in imaging technologies. In Vietnam, RCC accounts for an estimated 2,246 new cases and 1,112 deaths annually[1]. Early-stage RCC is typically treated with surgery; however, 20-30% of patients will experience recurrence or metastasis[2].

While international guidelines now recommend first-line combination therapies, such as immune-oncology (IO) agents with tyrosine kinase inhibitors (TKIs) or dual IO combinations for advanced RCC[3], the high cost of these regimens makes them inaccessible to many patients in Vietnam. As a result, pazopanib, a TKI, remains the most widely used and affordable option in routine clinical practice. Although its efficacy has been established in clinical trials, real-world data in Vietnamese

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patients are limited. This study aims to evaluate the effectiveness and safety of pazopanib in advanced RCC in Vietnam, with particular attention to the impact of initial dosing.

2. SUBJECTS AND METHODS

2.1. Subjects

This retrospective and prospective observational study was conducted at Vietnam National Cancer Hospital from January 2018 to July 2024. Sixty patients with histologically confirmed advanced RCC receiving pazopanib as first-line systemic therapy were included.

2.2. Inclusion Criteria

- Patients aged 18 years or older with histologically confirmed RCC.

- Locally advanced disease that is not amenable to surgery OR recurrent or metastatic disease.

- ECOG performance status 0-2.

- Receipt of at least two cycles of pazopanib.

2.3. Exclusion Criteria

- Patients with prior systemic therapy for RCC.

- Uncontrolled comorbidities or significant medical conditions that could interfere with treatment.

2.4. Methods

This is retrospective and prospective observational study. Clinical data were collected from medical records and patient interviews, including demographic characteristics, pathological subtype, initial pazopanib dose, and treatment response. The initial pazopanib dose was determined by the treating physician based on patient performance status and comorbidities, with options including 200mg, 400mg, 600mg, or 800mg daily. Efficacy was assessed via overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). Tumor response was evaluated using RECIST 1.1. Adverse events were recorded and graded using CTCAE v5.0.

2.5. Data Analysis

Survival data were analyzed using Kaplan-Meier methods and comparisons were made using the log-rank test.

3. RESULTS

The cohort had a median age of 57.2 ± 11.9 years, with 80% male patients. The most common comorbidities were hypertension (21.7%) and diabetes mellitus (16.7%). Of the 60 patients, 55% were diagnosed with advanced RCC, while 45% had recurrent disease. Clear cell RCC (ccRCC) was the predominant histological subtype, accounting for 85% of cases.

Table 1: Patient characteristic

Patient	N = 60 (100%)
Age	
Average	57.2 ± 11.9 (Years)
Gender	
Male	48 (80%)
Female	12 (20%)
Performance status	
PS 0	40 (66.7%)
PS 1	11 (18.3%)

PS 2	9 (15%)
Denovo/Recurrence	
De novo metastatic	33 (55%)
Recurrence	27 (45%)
Histopathology	
Clear cell carcinoma	51 (85%)
Non-clear cell carcinoma	9 (15%)
IMDC risk group	
Low risk	3 (5%)
Intermediate risk	27 (45%)
High risk	9 (15%)
Indeterminate	21 (35%)
Initial dose of Pazopanib	
200 mg	5 (8.3%)
400 mg	26 43.3%)
600 mg	17 (28.3%)
800 mg	12 (20%)

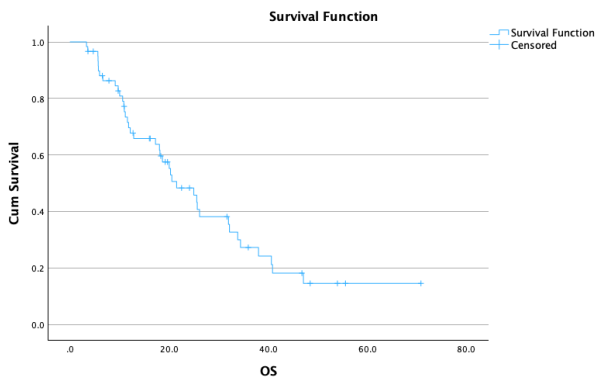

Figure 1: Overall survival

Pazopanib was administered as first-line treatment at an initial dose of 400 mg in 43.3% of patients, with the remainder receiving lower or higher doses based on tolerability. The median treatment duration was 46.8 months. The ORR was 45%, with 3.3% of patients achieving a complete response and 41.7% achieving a partial response. Disease stabilization was observed in 40% of patients, while 15% experienced disease progression during the initial assessment.

After a median follow-up time of 46.8 months, the median PFS was 13.1 months (95% CI: 10.6-15.5), and the median OS was 21.5 months (95% CI: 15.0-28.0). The estimated one-year and two-year OS rates were 67.8% and 48.3%, respectively.

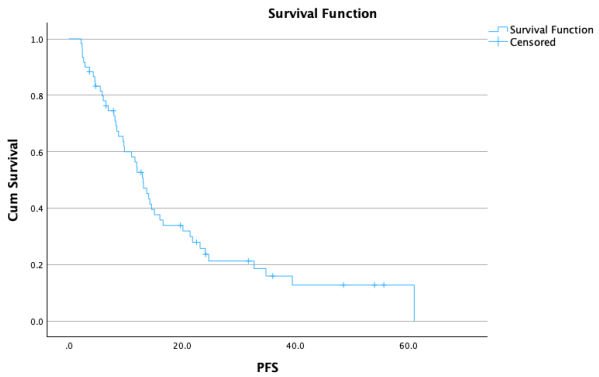

Figure 2: Progression free survival

The analysis of the initial dose of pazopanib indicated that the dose had no significant impact on overall survival. Patients on higher initial doses (800 mg) showed similar survival outcomes as those

on lower doses. The median OS for patients on the 800 mg dose was 25.5 months, while those on lower doses had a median OS of 20.5 months (p=0.945).

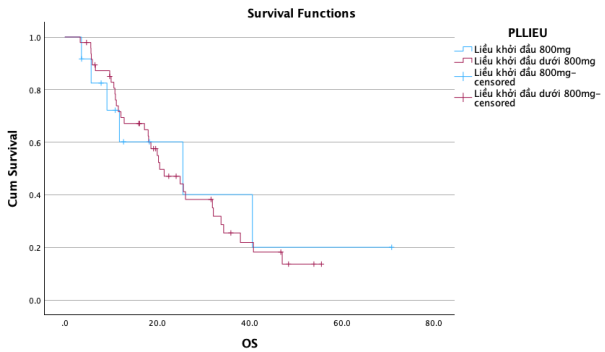

Figure 3: OS according to initial dose of Pazopanib

Regarding adverse effects, 71.7% of patients experienced some form of toxicity, with the most common being increased liver enzymes (43.3%) and fatigue (38.3%). Severe adverse events (CTCAE grade 3-4) occurred in 10% of patients, with the most notable being elevated liver enzymes and hypertension. No patient discontinued treatment due to adverse effects.

Table 2: Adverse events

Adverse event	All grade N (%)	Grade 3-4 N (%)
Fatigue	23 (38.3%)	0
Nausea/vomiting	7 (11.7%)	0
Diarrhea	6 (10%)	0
Hypertension	11 (18.3%)	2 (3.3%)
Rash	3 (5%)	0
Hair color change	12 (20%)	0
Anemia	10 (16.7%)	1 (1.7%)
Neutropenia	6 (10%)	2 (3.3%)
Thrombocytopenia	7 (11.7%)	0
Elevated liver enzyme	26 (43.3%)	3 (5%)
Elevated bilirubin	3 (5%)	0
Elevated creatinine	15 (25%)	0
All	**43 (71.7%)**	**6 (10%)**

4. DISCUSSION

The findings of this study confirm that pazopanib is an effective and tolerable first-line treatment option for advanced RCC in Vietnamese patients, aligning well with global clinical trial data. Notably, the overall response rate of 45% observed in this cohort exceeds that reported in the pivotal COMPARZ (31%) and PISCES (32%) trials, suggesting encouraging tumor control even in a real-world setting[4,5]particularly between approved targeted therapies with similar efficacy. This double-blind cross-over study evaluated patient preference

for pazopanib or sunitinib and the influence of health-related quality of life (HRQoL. The median progression-free survival of 13.1 months also compares favorably with the 8.4–9.2 months reported in those studies, indicating sustained disease control. Although the median overall survival of 21.5 months is slightly lower than the COMPARZ trial's 28.4 months, it remains clinically meaningful, particularly in the context of limited access to subsequent lines of therapy in Vietnam[4]. By contrast, modern IO+TKI regimens, such as pembrolizumab plus axitinib, have demonstrated ORR around 60% and median OS exceeding 45 months[6], while IO+IO combinations like nivolumab plus ipilimumab report ORR around 42% and median OS of 47 months[7], highlighting the efficacy gap where access to these regimens is limited.

Pazopanib was well-tolerated overall, though adverse effects were prevalent, particularly liver enzyme elevation and hypertension, which are commonly associated with VEGF inhibitors. The overall AE rate (71.7%) and grade 3-4 event rate (10%) were comparable to the COMPARZ trial, where any-grade AEs were reported in over 80% of patients and grade 3-4 events in approximately 33%[4]. Notably, no patients discontinued treatment due to toxicity in this study, suggesting manageable side effects with appropriate dose modification and monitoring.

Importantly, the initial dose of pazopanib did not have a significant impact on overall survival. This suggests that dose adjustments based on tolerability may be appropriate without compromising efficacy. Patients receiving 800mg as the initial dose had a comparable median OS to those on lower doses, which supports the flexibility in dosing to reduce side effects while maintaining treatment effectiveness.

5. CONCLUSION

Pazopanib is an effective and generally well-tolerated option for the first-line treatment of advanced RCC in the Vietnamese population. This study contributes valuable data to the body of evidence regarding pazopanib's role in RCC treatment within a resource-limited setting. The initial dose of pazopanib did not significantly affect overall survival, suggesting that dose adjustments based on tolerability may be appropriate without compromising efficacy. Further studies, particularly with larger sample sizes and longer follow-up, are needed to confirm these findings and explore potential improvements in patient management strategies. Given the promising results, pazopanib remains a cornerstone in the treatment of advanced RCC, though individual treatment plans should consider patient-specific factors, including comorbidities and treatment tolerability.

REFERENCES

[1]. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2024). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.who.int/today, accessed.

[2]. Gupta K, Miller JD, Li JZ, Russell MW, Charbonneau C. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): A literature review. *Cancer Treat Rev*. 2008;34(3):193-205. doi:10.1016/j.ctrv.2007.12.001

[3]. NCCN guidelines, Kidney cancer, version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf.

[4]. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med*. 2013;369(8):722-731. doi:10.1056/NEJMoa1303989

[5]. Escudier B, Porta C, Bono P, et al. Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES Study. *J Clin Oncol Off J Am Soc Clin Oncol*. 2014;32(14):1412-1418. doi:10.1200/JCO.2013.50.8267

[6]. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2019;380(12):1116-1127.doi:10.1056/NEJMoa1816714

[7]. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2018;378(14):1277-1290. doi:10.1056/NEJMoa1712126

SURGICAL OUTCOMES OF TRANSDUODENAL AMPULLECTOMY FOR EARLY CANCER OF THE AMPULLA OF VATER: A SINGLE-CENTER STUDY

Pham The Anh*, Truong Manh Cuong, Trinh Huy Phuong

ABSTRACT

Background: Transduodenal ampullectomy (TDA) is performed for early cancer of the ampulla of Vater (AoV). This study aimed to analyze the short- and long-term outcomes of TDA.

Methods: Patients who underwent TDA performed for AoV malignancy with carcinoma in-situ (Tis) and T1 stage from August 2017 to February 2025 were reviewed.

Results: Twenty-eight patients with malignant tumors underwent TDA. The mean operation time was 118.6 ± 36.8 min. The median estimated blood loss was 60 (0-700)ml. The median length of hospital stays was 9 (6-22) days. The mean overall complication rate was 14.3 % with postoperative pancreatic fistula was 17.9%. Lymph node metastasis rates were 20%. The overall survival (OS) and disease-free survival (DFS) rate were 52.4 and 51.2 months, respectively.

Conclusion: TDA accompanied with lymph node dissection was advisable in Tis and T1 AoV cancers in view of superior perioperative outcomes and similar long-term survival rates.

Keywords: Transduodenal ampullectomy; ampulla of vater.

1. INTRODUCTION

Carcinoma of the ampulla of Vater (AoV) is the second most common periampullary malignancy after pancreatic cancer, yet it remains a rare disease, representing less than 1% of all gastrointestinal cancers [1]. The scarcity of this condition means that current clinical practices rely on retrospective data and lack standardized guidelines. For ampullary carcinoma, conventional pancreaticoduodenectomy (PD) or pylorus-preserving pancreaticoduodenectomy (PPPD) are the most frequently performed procedures, involving complete removal of the primary tumor and radical lymph node dissection (LND). However, PD is associated with significant complications, including postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE), postoperative hemorrhage, and post-pancreatectomy diabetes mellitus [2]. As a result, a less invasive procedure, transduodenal ampullectomy (TDA), has been attempted for early-stage cancers confined to the AoV or sphincter of Oddi (carcinoma in situ or pT1).

The debate over TDA as an alternative to PD in early AoV cancer centers on the radicality of the procedure, which is influenced by the resection margin status and lymph node (LN) metastasis-key prognostic factors for recurrence and long-term survival [2], [3], [4]. Previous studies have

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examined histopathological factors related to LN metastasis [5] as well as patterns of lymphatic spread [4] and recurrence [3] to propose suitable indications for TDA. However, the role of TDA in early AoV cancers remains inconclusive. Despite this, the role of TDA in early AoV cancers remains uncertain. Some centers have performed TDA with LND and achieved oncologic outcomes comparable to PD in early AoV cancer [6]. These findings suggest that TDA with LND could be a viable surgical option for patients who are not candidates for PD. However, the appropriate extent of regional LND is still unclear. Studies on TDA in early AoV cancer have been limited by small sample sizes or short follow-up periods. This study aimed to review and summarize the experience of TDA in a single large-volume center, focusing on its viability as a surgical treatment for early AoV cancer with acceptable clinical and oncologic outcomes.

2. METHODS

2.1. Patient and data collection

In this retrospective study, we reviewed and analyzed a prospectively maintained database of patients with AoV cancer who underwent TDA at our hospital, between August 2017 and February 2025.

Clinical and pathological characteristics such as age, sex, tumor size, pathologic T stage, LN metastasis, and differentiation were retrieved, along with data on perioperative and long-term patient outcomes. The pathologic stage was defined according to the seventh edition of the American Joint Committee on Cancer (AJCC) staging system. Low-grade dysplasia was considered benign and high-grade dysplasia was regarded as Tis according to the current World Health Organization classification. Complications were graded using Clavien-Dindo (CD) classification [7]. CD grade C III was considered severe. Clinically relevant POPF (CR-POPF) and DGE were defined and graded according to the International Study Group of Pancreatic Surgery [8]. This retrospective study was approved by the Ethical Review board of our hospital.

2.2. Indication and procedure

Inclusion Criteria:

- Endoscopic papillectomy (EP) was contraindicated (e.g., bile duct and/ or pancreatic duct involvement).

- Failure of EP (incomplete tumor removal or recurrence).

- Patients unwilling to undergo PD for various reasons such as advanced age, uncontrolled hypertension, diabetes mellitus, bronchial asthma, cardiovascular conditions, etc.

- Preoperative diagnosis of adenocarcinoma of the Vater ampulla (cTis-1N0M0) according to the AJCC TNM staging system (2017), based on preoperative imaging modalities like computed tomography (CT), magnetic resonance imaging (MRI), or endoscopic ultrasonography.

Operative technique: (Figure 1).

- The patient was positioned supine under general anesthesia. Make a 20 cm midline incision. Observe the peritoneum to assess tumor invasion, suspected lymph nodes, and metastases.

- Cholecystectomy and Kocher maneuver to mobilize the duodenum and head of the pancreas from the retroperitoneum.

- Making an incision at the second part of duodenum (D2). Total excision of the ampulla of Vater included part of the pancreatic head, duodenum, and distal common biliary duct with electrocauterization. Frozen resection to determine resection border.

- Suture to anastomose the duct to the duodenum and close the duodenal excision with continuous absorbable 4/0 suture. Care was made when suturing far from the pancreatic duct to avoid belated stenosis.

- Lymph node dissection could be applied in case of suspected malignancy, including lymph nodes at stations 7, 8, 12, 13.

- A gastric tube was used to dilate and ensure no stenosis in the common bile duct. Another gastric tube was pushed down from the mouth to the duodenum for decompressive drainage to prevent post-operative duodenal fistula. Close the duodenal incision.

- Two subhepatic drains were placed. Hemostasis. Close the abdomen.

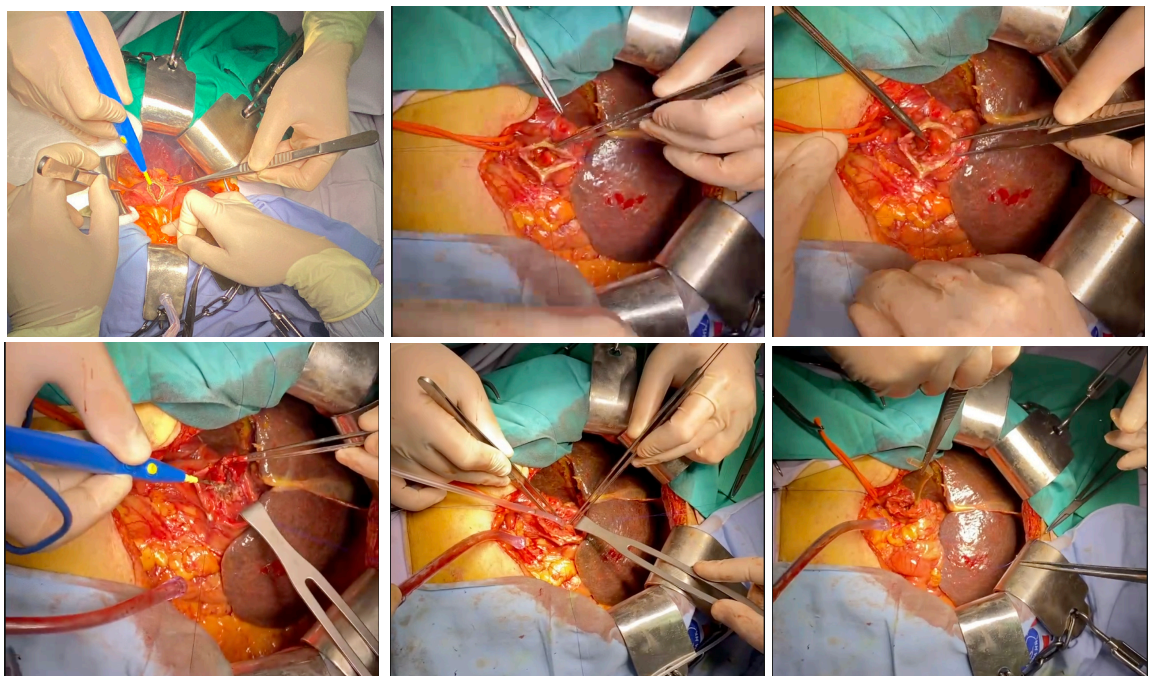

Fig. 1. *(1) After Kocher maneuver, make a transverse incision at D2 over the lesion. (2) Hang the duodenal wall for better exposure. (3) Suture to hang the ampullary lesion. (4) Cut the lesion, including part of the duodenum, distal common bile duct and pancreatic head. (5) Gastric tube for bile duct dilation to ensure no stenosis. (6) Decompressive nasal gastric tube to D2 duodenum. (7) Lymph node dissection.*

2.3. Statistical analyses

The Cox proportional hazards model was used to determine independent predictors of recurrence. Univariate analysis was performed for age, sex, tumor size, type of operation, intraoperative transfusion, T-stage, LN metastasis, lymphovascular invasion, perineural invasion, and adjuvant therapy. Variables with $p < 0.05$ were included for multivariate analysis. Disease-free survival (DFS) was defined as the time between the date of surgery and date of local or distal recurrence and censored at last follow-up or death irrelevant to cancer recurrence. Overall survival (OS) was calculated from the date of operation to the date of death. Patients not experiencing the relevant endpoint were censored at the last follow-up. Five-year OS was calculated using the Kaplan-Meier method, and differences were examined using the log-rank test. Data analyses were performed using SPSS 25.0

software (SPSS, Chicago, IL). A p-value of < 0.05 was considered statistically significant.

3. RESULTS

From August 2017 to February 2025, 28 patients at our hospital underwent TDA for ampullary cancer, excluding cases with other organ malignancies, history of TDA, M1 disease, preoperative chemotherapy, combined pancreatic malignancy, adenoma/low-grade dysplasia histology, T2-T4 stage, other pathology classifications.

Patient and tumor characteristics of the TDA cases for malignant AoV tumors

Table 1 shows the clinicopathological findings after TDA for malignant ampullary tumors (pTis, T1). LND was performed in 53.6% (15 of 28) of patients with 20% (3 cases) showing positive LN involvement. The rate of lymphovascular and perineural invasion were 17.9% and 7.1%, respectively.

Perioperative outcomes after TDA for malignant AoV tumors

According to Table 2, the TDA patients had significantly short surgery durations and hospital stays. Additionally, the TDA group experienced considerably less blood loss. Only one patient needed a blood transfusion during surgery. The overall complication rate was 14.3% while severe complications were 7.1%. There was no deaths within 90 days post-surgery.

Long-term outcomes after TDA for malignant AoV tumors

Over a median follow-up period of 23 months (ranging from 1 to 73 months), the recurrence rates was 17.9 %. The overall survival (OS) and disease-free survival (DFS) rate were 52.4 and 51.2 months, respectively (Fig. 2a,b). Based on the presence or absence of LND, showed that LND did not impact the 5-year DFS or OS (Fig. 2c, d).

Table 1. Clinicopathologic findings of the transduodenal ampullectomy (TDA) for malignant ampullary tumors (Tis/T1)

Characteristic	TDA (n = 28)	
Age (years), mean ± SD	62.8 ± 9.1	
Sex, n (%)		
Male	21	(75.0%)
Female	7	(25.0%)
ASA score, n (%)		
1	16	(57.1%)
2	12	(42.9%)
Preoperative endoscopic papillectomy, n (%)		
Yes	7	(25.0%)
No	21	(75.0%)
Preoperative tumor marker, median (range)		
CA 19-9 (U/ml)	173.8	(0.6-1200.0)
CEA (ng/ml)	4.8	(1.6-14.3)

Characteristic	TDA (n = 28)	
Tumor size (mm), mean ± SD	17.3 ± 4.6	
T stage (Seventh edition of AJCC)		
pTis	10	(35.7%)
pT1	18	(54.3%)
N stage (Seventh edition of AJCC)		
pN0	25	(89.3%)
pN1	3	(10.7%)
Stage (Seventh edition of AJCC)		
0	9	(32.1%)
I	10	(35.8%)
IB	9	(32.1%)
Differentiation		
Well	6	(21.4%)
Moderate	15	(53.6%)
Poor	3	(10.7%)
NA	4	(14.3%)
Lymphovascular invasion		
Yes	5	(17.9%)
No	13	(46.4%)
NA	10	(35.7%)
Perineural invasion		
Yes	2	(7.1%)
No	17	(60.7%)
NA	9	(32.1%)

SD, standard deviation; ASA, American Society of Anesthesiologists; Tis, carcinoma in situ; NA, not available.

Table 2. Surgical and oncologic outcomes after transduodenal ampullectomy (TDA) (pTis/T1)

Outcomes	TDA (n = 28)	
Operation time (min), mean ± SD	118.6 ± 36.8	
Estimated blood loss (ml), median (range)	60	(0-700)
Intraoperative transfusion, n (%)		

Outcomes	TDA (n = 28)	
Yes	1	(3.6%)
No	27	(96.4%)
Hospital stays (days), median (range)	9	(6-22)
Complications, n (%)		
Yes	4	(14.3%)
No	24	(85.7%)
Severe complications (CD grade ≥ IIIa), n (%)		
Yes	2	(7.1%)
No	26	(92.9%)
Clinically relevant POPF, n (%)	5	(17.9%)
Grade A	5	(17.9%)
Grade B	0	(0.0%)
DGE (grade ≥ B), n (%)	1	(3.6%)
Duodenal stricture, n (%)	0	(0.0%)
Complicated fluid collection, n (%)	2	(7.1%)
Bleeding, n (%)	2	(7.1%)
Readmission related with complications (<90 days)		
Yes	1	(3.6%)
No	27	(96.4%)
Surgical mortality, n (%)	0	(0.0%)
Recurrence, n (%)		
No	17	(60.7%)
Yes	5	(17.9%)
NA	6	(21.4%)
Local	1	(20.0%)
Systemic	4	(80.0%)
Both	0	(0.0%)
Adjuvant therapy		
No	1	(3.6%)
Yes	27	(96.4%)

SD, standard deviation; CD, Clavien-Dindo classification; POPF, postoperative pancreatic fistula; DGE, delayed gastric emptying.

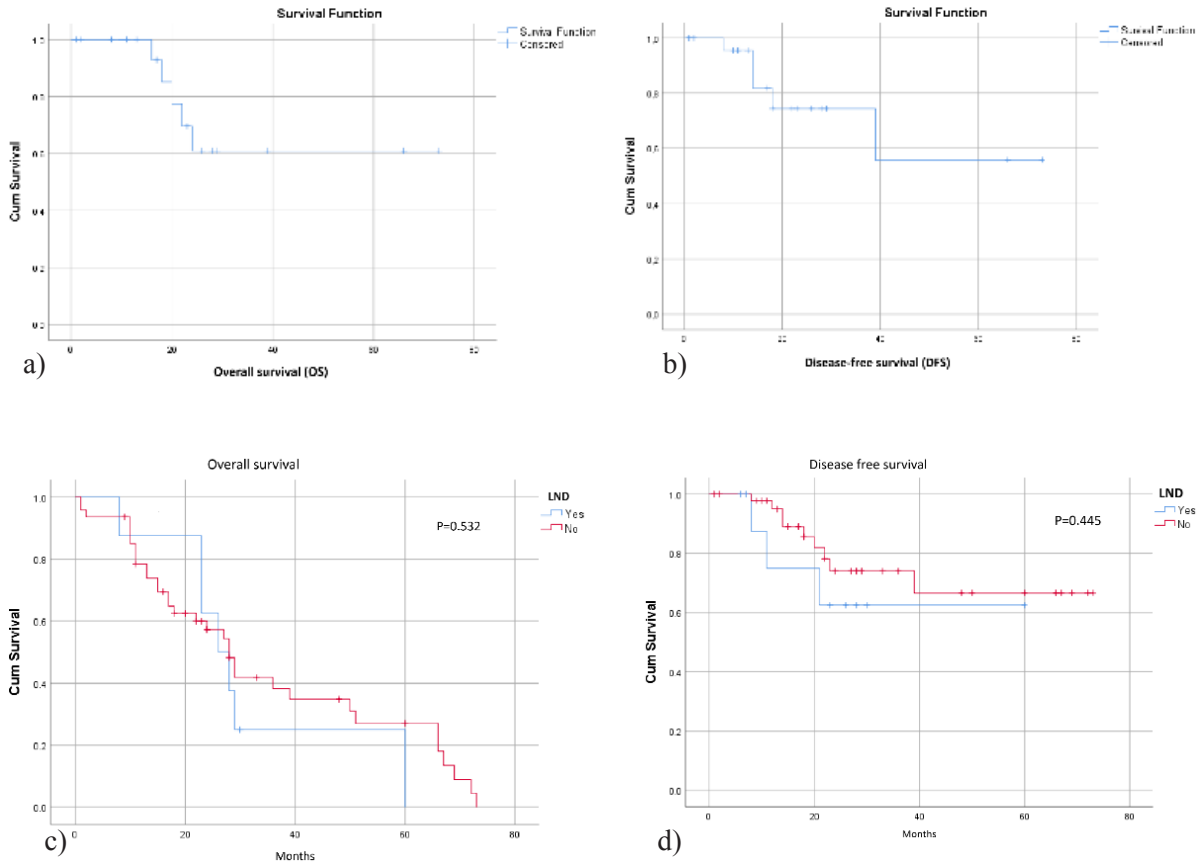

Fig 2. The survival outcomes of patients with malignant ampullary tumors after undergoing TDA. The overall survival (OS) (a) and the disease-free survival (DFS) rates (b) were showed. Additionally, based on whether lymph node dissection (LND) was performed, LND did not impact the 5-year DFS (c) or OS (d).

Risk factors affecting recurrence

Table 3 presents the uni- and multivariate analyses of risk factors influencing recurrence after TDA. Due to the limited patient sample and short follow-up duration, factors such as age, sex, tumor size, intraoperative transfusion, T classification, LN involvement, moderate/poor differentiation, lymphovascular invasion, perineural invasion, and adjuvant therapy were not linked to disease recurrence in the univariate analysis (all $p > 0.05$). In the multivariate analysis, perineural invasion emerged as an independent predictor of recurrence ($p=0.043$), while other factors like intraoperative transfusion, T classification, LN involvement, moderate/poor differentiation, lymphovascular invasion and adjuvant therapy did not show a significant association.

Table 3. Univariate and multivariate analysis of risk factors affecting recurrence in patients with malignant ampullary tumors (pTis/T1) undergoing transduodenal ampullectomy (TDA)

Variable	No	Univariate			Multivariate		
		HR	95% CI	p*	Exp(B)	95% CI	p*
Age, years							
≤ 60	25						
> 60	35	0.441	0.119-1.635	0.221			
Sex							
Male	29						
Female	28	1.226	0.395-3.811	0.724			
Tumor size							
< 18 mm	18						
≥ 18 mm	39	1.710	0.502-5.831	0.391			
Intraoperative transfusion							
No	53						
Yes	4	1.156	0.149-8.962	0.890			
T classification							
pTis	10						
pT1	15	0.408	0.051-3.265	0.398			
LN metastasis							
No	47						
Yes	10	1.656	0.445-6.161	0.452			
Differentiation							
Well	8						
Moderate/Poor	49	1.026	0.224-4.687	0.974			
Lymphovascular invasion							
No	21						
Yes	20	0.291	0.060-1.407	0.125			
Perineural invasion							
No	30						
Yes	14	2.044	0.456-9.162	0.350	0.096	0.010-0.931	0.043
Adjuvant therapy							
No	4						
Yes	40	0.040	0.000-606.610	0.512			

OR odds ratio; CI, confidence interval; Tis, carcinoma in situ; LN, lymph node. *p-values in multivariate analysis are from the Cox proportional hazard model.

4. DISCUSSION

The role of transduodenal ampullectomy (TDA) in the management of ampullary lesions has been a subject of debate, especially in comparison to pancreatoduodenectomy (PD) [9], [10]. TDA, first described by Halsted in 1899, represents a more localized surgical approach compared to the radical resection involved in PD, which was pioneered in its modern form by Whipple in 1940 [6], [9], [11].

Historically, PD became the standard surgical strategy for ampullary cancer [11]. However, PD is associated with a significant rate of postoperative complications, ranging from 33% to 52%. This has led to the application of TDA in patients who may not be suitable candidates for PD due to comorbidities [11].

Several studies, including a Korean multicenter study involving 486 patients, have compared the oncologic outcomes of TDA and PD for early ampulla of Vater (AoV) cancer (pTis-T2 stage) [11]. This study found that while the PPPD (pylorus-preserving pancreatoduodenectomy) group presented with more aggressive tumor behavior (larger size, higher T stage, poorer differentiation, lymphovascular invasion), the 5-year disease-free survival and overall survival did not differ significantly between the two groups when considering all T stages or only the Tis + T1 group. However, in T1 patients specifically, PPPD showed survival outcomes superior to those in the TDA group. Interestingly, lymph node dissection (LND) did not affect survival in the TDA group in this study. The authors concluded that PPPD should be the standard procedure for early AoV cancer.

Another study retrospectively reviewed 43 patients with early ampullary cancer who underwent either TDA or PD between 2001 and 2014 [6]. In this study, routine lymph node resection was performed during TDA. In our research, LND was performed in 53.6% of patients in the TDA group, with 20% showing positive LN involvement. In the PD group, the LN metastasis rate was 21.2%.

Some studies emphasized the role of intraoperative frozen pathological examination was used to confirm negative lymph node metastasis before proceeding with TDA [6]. If local resection criteria were not met, the operation was converted to the radical PD. That is also a limitation in our study due to the lack of equipment.

A systematic review and meta-analysis comparing endoscopic ampullectomy (EA), surgical ampullectomy (SA, which includes TDA), and PD for ampullary lesions found that SA and PD had significantly higher pooled R0 resection rates compared to EA [12]. The pooled R0 rate for SA was 96.4%, while for PD it was 98.9%, and for EA it was 76.6%. However, the rates of adverse events were 28.3% for SA, 44.7% for PD and 24.7% for EA. Recurrence rates were 9.4% for SA, 14.2% for PD, and 13.0% for EA, with no significant differences observed. This meta-analysis indicates that surgical interventions (SA and PD) achieve better complete resection but may be associated with a higher risk of complications, particularly PD. The authors noted significant heterogeneity and limitations in the included studies.

A single-institution study analyzing 60 patients with AoV neoplasms undergoing either TDA (n=23) or PD (n=37) between 2006 and 2020 aimed to compare surgical outcomes and survival [13]. This study found no significant differences in overall survival and recurrence-free survival between the two groups. However, similar to the Korean multicenter study, the PD group had more lymph node metastasis and perineural invasion. The authors suggested that TDA could be considered a feasible option for carefully selected early-stage

AoV cancers (pTis-T1N0M0), especially in patients with comorbidities. They also emphasized that TDA should be accompanied by lymph node dissection, and further research is needed to determine the appropriate extent of LND. In our study, recurrence rates and patterns were similar between the two groups. The 5-year disease-free survival (DFS) rates showed no significant difference between the TDA and PD groups, regardless of the inclusion of T2 cases (Fig. 2a, b).

The technical aspects of TDA involve a duodenotomy, identification and marking of the bile and pancreatic ducts, and circumferential dissection of the ampulla with a margin [9]. Reconstruction involves approximating the ducts to the duodenal wall [10]. Intraoperative frozen section analysis is crucial to ensure negative resection margins and to guide the decision to proceed with TDA or convert to PD if necessary [9].

In our study, over a median follow-up period of 23 months (ranging from 1 to 73 months), the recurrence rates was 17.9%. 3 patients were reoperated while 2 others experienced palliative care.

In conclusion, while PD remains the standard of care for resectable ampullary cancer due to its potentially superior outcomes in certain early-stage tumors and more comprehensive lymphadenectomy, TDA appears to be a viable option for carefully selected early-stage lesions and in patients with significant comorbidities that increase the risk associated with PD [11], [13]. Proper patient selection based on thorough pre-operative staging, including endoscopic ultrasound (EUS), and meticulous surgical technique with intraoperative margin assessment are essential for successful outcomes with TDA [9]. Further prospective, well-designed studies are needed to definitively define the indications for TDA in the modern management of ampullary lesions [10].

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DISCLOSURE

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REFERRENCES

[1]. Jorge Albores-Saavedra, Arnold M Schwartz, Kristen Batich, et al (2009). Cancers of the ampulla of vater: demographics, morphology, and survival based on 5,625 cases from the SEER program. *Journal of surgical oncology*. 100 (7), 598-605.

[2]. Dirk J Gouma, Rutger CI van Geenen, Thomas M van Gulik, et al (2000). Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. *Annals of surgery*. 232 (6), 786-795.

[3]. Joon Seong Park, Dong Sup Yoon, Kyung Sik Kim, et al (2007). Factors influencing recurrence after curative resection for ampulla of Vater carcinoma. *Journal of surgical oncology*. 95 (4), 286-290.

[4]. Marek Sierzega, Krystyna Nowak, Jan Kulig, et al (2009). Lymph node involvement in ampullary cancer: the importance of the number, ratio, and location of metastatic nodes. *Journal of surgical oncology*. 100 (1), 19-24.

[5]. Yoo-Seok Yoon, Sun-Whe Kim, Sang Jae Park, et al (2005). Clinicopathologic analysis of early ampullary cancers with a focus on the feasibility of ampullectomy. *Annals of surgery*. 242 (1), 92-100.

[6]. Yang Gao, Yayun Zhu, Xiuyan Huang, et al (2016). Transduodenal ampullectomy provides a less invasive technique to cure early ampullary cancer. *BMC surgery*. 16 1-8.

[7]. Daniel Dindo, Nicolas Demartines, Pierre-Alain Clavien (2004). Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of surgery*. 240 (2), 205-213.

[8]. Claudio Bassi, Giovanni Marchegiani, Christos Dervenis, et al (2017). The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. *surgery*. 161 (3), 584-591.

[9]. Fabio Francesco di Mola, Paolo Panaccio, Tommaso Grottola, et al (2021). Transduodenal surgical ampullectomy: a procedure that requires a multidisciplinary approach. *Updates in Surgery*. 1-9.

[10]. Darren L Scroggie, Vasileios K Mavroeidis (2021). Surgical ampullectomy: A comprehensive review. *World Journal of Gastrointestinal Surgery*. 13 (11), 1338.

[11]. Seung-Soo Hong, Sung-Sik Han, Wooil Kwon, et al (2021). Comparison of oncologic outcomes between transduodenal ampullectomy and pancreatoduodenectomy in ampulla of vater cancer: Korean multicenter study. *Cancers*. 13 (9), 2038.

[12]. Christian Heise, Einas Abou Ali, Dirk Hasenclever, et al (2020). Systematic review with meta-analysis: endoscopic and surgical resection for ampullary lesions. *Journal of clinical medicine*. 9 (11), 3622.

[13]. Eun-Ki Min, Seung Soo Hong, Ji Su Kim, et al (2022). Surgical outcomes and comparative analysis of transduodenal ampullectomy and pancreaticoduodenectomy: a single-center study. *Annals of surgical oncology*. 1-12.

RESULTS OF SURGICAL TREATMENT OF MEDULLOBLASTOMAS AT VIETNAM NATIONAL CANCER HOSPITAL

Nguyen Duc Lien*, Hoang Thi Thuy Linh

ABSTRACT

Objective: Evaluate the results of surgical treatment of medulloblastoma at Vietnam National Cancer Hospital.

Subjects and methods: The study subjects include patients who underwent surgery and chemotherapy and radiotherapy at Vietnam National Cancer Hospital from January 2019 to December 2023, with pathological result of medulloblastoma, with complete medical records and MRI scans. Excluding cases of recurrent medulloblastoma, cases that only received surgery, refused chemotherapy or radiotherapy after surgery or cases that did not receive adequate treatment regimen. The study is cross-sectional, retrospective and prospective.

Results: A total of 45 patients underwent surgery: Total or near-total tumor removal (accounting for 93.3%), partial tumor removal 3/45 (6.7%), the overall complication rate after surgery was 11.1%. Results of 5-year follow-up after postoperative chemoradiotherapy: the overall survival rate and progression-free survival rate were 54.3±11.1 and 50.8±8.5, respectively. The high-risk group had a median survival of 34.3 months, the intermediate-risk group had a median survival of 64.7 months, the difference was statistically significant with p=0.001.

Conclusion: Histopathological types, molecular subgroups and risk stratification are important prognosticators, and are associated with overall and progression-free survival of MB patients

Key words: Medulloblastomas; neurosurgery; Risk stratification of MB.

1. INTRODUCTION

Medulloblastoma is the most common malignant brain tumor in children, accounting for about 15-20% of all primary tumors of the central nervous system and 30-40% of tumors in the posterior fossa[1,2]. Multimodal treatment including surgery, radiotherapy and chemotherapy has been widely applied in most patients. However, the overall survival rate is low, the rate of late complications related to treatment is high and this is a major challenge for pediatric oncologists and neurosurgery. Currently, medulloblastoma risk stratification is based on pathological type, tumor extent on magnetic resonance imaging and cerebrospinal fluid cytology (Chang classification system), extent of tumor resection and age; medulloblastoma is classified into three groups: standard risk, high risk and poor risk (children under 3 years old) with different treatment regimens and prognosis[3,4]. We conducted this study with the aim of: Evaluating the results of surgical treatment of medulloblastoma at Vietnam National Cancer Hospital.

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2. SUBJECT AND STUDY METHOD

2.1. Subject

Inclusion criteria: patients who underwent

surgery and chemotherapy and radiotherapy at Vietnam National Cancer Hospital from January 2019 to December 2023. Pathologically diagnosed as medulloblastoma, with complete medical records and MRI scans.

Exclusion criteria: cases of recurrent medulloblastoma, cases that only underwent surgery, refused chemotherapy or radiotherapy after surgery Or cases that did not receive adequate treatment regimen.

2.2. Method

Cross-sectional, retrospective and prospective descriptive study. Study according to a unified medical record form, data on radiographs, pathological results, surgical methods, treatment regimens based on archived medical records and archived films. Evaluation of re-examination results based on clinical examination, MRI examination.

Risk stratification: 3 groups.

+ Standard risk: Over 3 years old, no metastasis in cerebrospinal fluid, residual tumor volume after surgery less than 1.5 cm^2, Pathology: classical or Desmoplatic

+ High risk: Over 3 years old, metastasis M1-M4, residual tumor volume after surgery more than 1.5 cm^2, pathology: large cell, anaplastic

+ Bad risk: Under 3 years old, in all types of pathology

Data processing: Descriptive statistics of quantitative variables: Mean, standard deviation, maximum value, minimum value. Description of qualitative variables by frequency and frequency (%). X2 comparison test, comparisons are statistically significant with $p < 0.05$. In case the sample is less than 5, use Fisher test. SPSS 20.0 software is used to process data.

Research ethics: This is a descriptive study, not a treatment intervention. The treatment regimen for medulloblastoma has been included in the 2021 Vietnamese cancer diagnosis and treatment guidelines by the Ministry of Health.

3. RESULTS

A total of 45 patients who met the inclusion and exclusion criteria were included in the study. The male/female ratio was 1.25/1, the youngest age was 3.1 years old, the oldest was 15 years old, the average age was 9.09 ± 3.28 years old. The size of the tumor on the preoperative brain MRI was less than 3 cm, accounting for 22.2%, the size was over 3cm, accounting for 77.8%. Surgical treatment results: 22/45 patients (48.9%) had total tumor removal, 20/45 (44.4%) had near-total tumor removal, 3/45 (6.7%) had partial tumor removal. The number of patients who underwent ventriculoperitoneal shunt surgery to treat hydrocephalus before tumor resection was 23/45 patients (51.1%). Postoperative complications: death (0%), cerebrospinal fluid leakage in 2/45 patients (4.4%), surgical site bleeding requiring reoperation in 1/45 (2.2%), post-tumor resection ventricular dilatation in 2/45 patients (4.4%). Pathological results: classical medulloblastoma (88.9%), desmoplastic/nodular medulloblastoma (4.4%), diffuse nodular medulloblastoma (2.2%), large/anaplastic medulloblastoma (4.4%).

Treatment results at 5-year follow-up, the overall survival rate and progression-free survival rate were 54.3±11.1 and 50.8±8.5, respectively. There were 14/45 patients who died during the follow-up period (31.1%). The survival time of the total tumor resection group was 53.9 months, which was longer than that of the near-total tumor resection group (51 months) and the partial tumor resection group (16.6 months) ($p=0.002$).

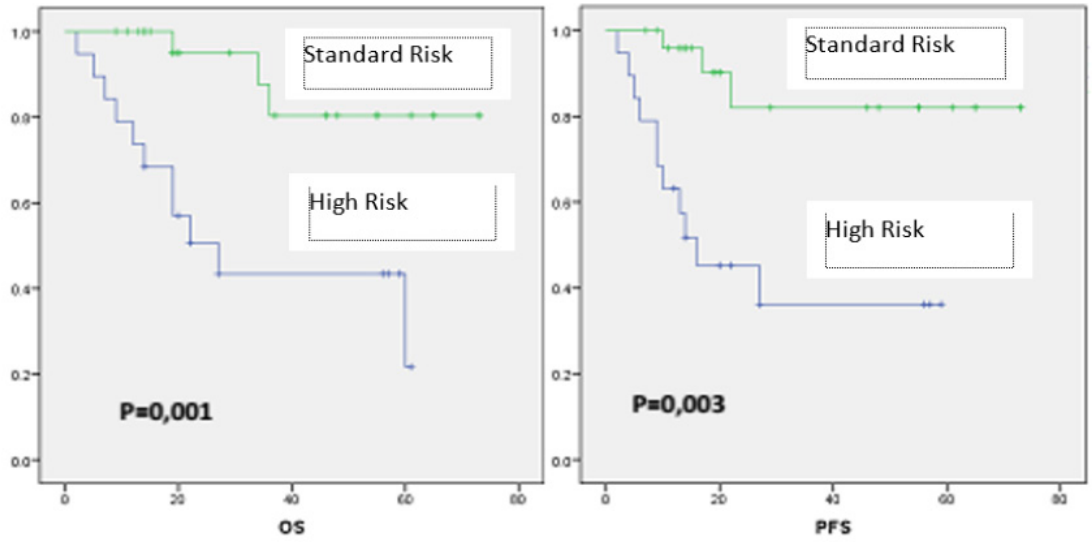

Figure 1: OS and PFS according to medulloblastoma risk stratification

Comments: the high-risk group had an average survival time of 34.3 months, the intermediate-risk group had an average survival time of 64.7 months, the difference was statistically significant with p=0.001.

4. DISCUSSION

Medulloblastoma (MB) is the most common malignant brain tumor in the pediatric population. Traditionally, MB has been classified as average- or high-risk, depending on patient age, presence of metastasis, extent of postsurgical residual disease, and histology in clinical risk stratification and treatment has been degraded in high-risk patients. A total of 45 patients were analyzed in this study: the mean age of the patient group in the study was 9.09 years old, of which the majority were children aged 7-15 years old (68.9%). The youngest patient was 3.1 years old, the oldest was 15 years old. Thus, our study group of patients was mainly in the standard-risk and high-risk stratification groups, with no poor-risk group.

In this study, all patients underwent tumor removal surgery under a microscope. Surgical results: Total or near-total tumor removal (93.3%), partial tumor removal 3/45 (6.7%). There were 3 cases of partial tumor removal due to tumor infiltration into the floor of the fourth ventricle and cerebellar peduncle, with a high risk of affecting respiratory and motor function if these structures are damaged. The rate of total/near-total tumor removal in the study of Pham Thanh Tuan[1] (2022) was 98.6%, of Haque[4] (2020) was 60%. Evaluation of postoperative chemotherapy and radiotherapy results: overall survival time of the total tumor removal group was 53.9 months, the near-total tumor removal group (51 months) and the partial tumor removal group (16.6 months). Thus, the total/near-total tumor removal group had better results than the partial tumor removal group (p = 0.002). The authors all agree that maximal tumor resection is very important, and that tumor size after surgery of less than 1.5 cm is a prognostic factor in the treatment of medulloblastoma[3,4,5].

In this study, 35 patients were admitted to the hospital with signs of increased intracranial pressure, of which 27/45 (60%) had hydrocephalus on MRI, all of whom were treated with medical treatment. However, 23 patients did not respond

to medical treatment, and their prognosis could not wait until tumor removal surgery, so they underwent ventriculoperitoneal shunting (51.1%). Three patients had ventriculoperitoneal shunting due to postoperative hydrocephalus. Postoperative complications: death (0%), cerebrospinal fluid leakage in 2/45 patients (4.4%), surgical site bleeding requiring reoperation in 1/45 (2.2%), post-tumor resection ventricular hydrocephalus in 2/45 patients (4.4%), and overall postoperative complication rate was 5/45 (11.1%). In case of postoperative bleeding, reoperation and hemostasis are required, and the ventricles are drained out, the patient is stable after 2 weeks of active treatment. Due to the characteristics of medulloblastoma, which is a soft tumor and has many blood vessels, in cases where the tumor cannot be completely removed, it is necessary to avoid bruising the remaining tumor tissue, and specialized hemostatic materials such as Floceal should be used. In Muzumdar's study of 211 patients who underwent surgery for medulloblastoma, 40 patients had postoperative complications (18.9%), of which postoperative complications were: 15 patients with surgical fossa hematoma, 1 patient with subdural hematoma, 22 patients with meningitis and cerebrospinal fluid leakage and 2 patients with postoperative blindness[5].

Evaluation of treatment results, with a 5-year follow-up period, the overall survival rate and progression-free survival rate were 54.3±11.1 and 50.8±8.5, respectively. There were 14/45 patients who died during the follow-up period (31.1%). In combination with clinical and pathological outcome indicators, molecular markers are not only prognostically important but will also facilitate the use of targeted therapies, such as GDC-0449, a novel SHH pathway inhibitor, particularly in infants and adults[5]. In the current study, the high-risk group has an average survival time of 34.3 months, the average risk group 64.7 months, the difference is statistically significant with p = 0.001. Nalita[6] et al. reported 84.4% and 42.8% OS rates of standard-risk and high-risk groups, respectively. Sirachainan[7] et al. reported OS rates of standard-risk and high-risk groups of 58–85% and 32–70%, respectively. Thompson[8] et al. reported that patients with postsurgical residual tumor $>1.5\,cm^2$ (an indicator of high-risk disease) had worse PFS and required aggressive treatment options. Juraschka[9] conclude clinical trials should incorporate key molecular profiles, including subgroup information, genetic, cytogenetic, and epigenetic changes, of this diverse disease entity that can suggest precise patients' outcomes or predict rational treatment strategies. The rarity of some WHO subtypes of MB; specifically, medulloblastoma with extensive nodularity, is considered a limitation of this study. Larger studies including all the histopathological types of medulloblastoma are recommended

5. CONCLUSION

Research results of 45 patients undergoing surgery and radiotherapy for medulloblastoma: Total or near-total tumor resection (93.3%), partial tumor resection 3/45 (6.7%), overall postoperative complication rate was 11.1%. With a 5-year follow-up period, the overall survival rate and progression-free survival rate were 54.3±11.1 and 50.8±8.5, respectively; the high-risk group had an average survival time of 34.3 months, the intermediate-risk group had an average survival time of 64.7 months, the difference was statistically significant with p=0.001.

In conclusion, histopathological types, molecular subgroups and risk stratification are important prognosticators and are associated with overall and progression-free survival of MB patients

REFERENCES

[1]. Pham Thanh Tuân. Kết quả phẫu thuật u nguyên bào tuỷ tại bệnh viện hữu nghị việt đức. Tạp chí y học Việt Nam 2022, Tập 510, số 1, tr 231-235.

[2]. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro-Oncol. 2021;23(8):1231-1251

[3]. Dhall G. Medulloblastoma. J Child Neurol. 2009;24(11):1418-1430

[4]. Haque W, Verma V, Brian Butler E, Teh BS.Prognostic role of themotherapy, radiotherapy dose, and extent of surgical resection in adult medulloblastoma. Journal of Clinical Neuroscience. 2020;76:154-160.

[5]. Muzumdar D, Deshpande A, Kumar R, et al. Medulloblastoma in childhood-King Edward Memorial hospital surgical experience and review: Comparative analysis of the case series of 365 patients. J Pediatr Neurosci. 2011;6(Suppl1):S78

[6]. Nalita N, Ratanalert S, Kanjanapradit K, Chotsampancharoen T, Tunthanathip T. Survival and prognostic factors in pediatric patients with medulloblastoma in southern Thailand. J Pediatr Neurosci. 2018;13(2):150–7.

[7]. Sirachainan N, Nuchprayoon I, Thanarattanakorn P, Pakakasama S, Lusawat A, Visudibhan A, et al. Outcome of medulloblastoma in children treated with reduced-dose radiation therapy plus adjuvant chemotherapy. J Clin Neurosci. 2011;18(4):515–59.

[8]. Thompson EM, Hielscher T, Bouffet E, Remke M, Luu B, Gururangan S, et al. Prognostic value of medulloblastoma extent of resection after accounting for molecular subgroup: a retrospective integrated clinical and molecular analysis. Lancet Oncol. 2016;17(4):484–95

[9]. Juraschka K, Taylor MD. Medulloblastoma in the age of molecular subgroups: a review. JNSPG 75th Anniversary Invited Review Article. J Neurosurg Pediatr. 2019;24(4): 353-63

TREATMENT OUTCOMES OF BORDERLINE OVARIAN TUMORS AT VIETNAM NATIONAL CANCER HOSPITAL

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Abstract

Background: Borderline ovarian tumors (BOTs), comprising 10–20% of epithelial ovarian neoplasms, are characterized by atypical epithelial proliferation without stromal invasion and typically exhibit favorable prognosis. This study delineates the clinical and pathological characteristics of BOT patients and evaluates recurrence and survival outcomes following surgical treatment at Vietnam National Cancer Hospital.

Methods: A combined retrospective and prospective cohort study was conducted on 64 patients with histologically confirmed BOT, treated surgically between January 2018 and December 2023. Data on clinical presentation, imaging, pathology, treatment modalities, and outcomes were analyzed.

Results: The median age was 46.0 years (range: 16–77), with 59.4% of patients aged <50 years. Serous BOT predominated (78.1%), followed by mucinous (18.7%). Most patients (75.0%) presented at FIGO stage I. Fertility-sparing surgery was performed in 35.9% of cases, and 14.1% underwent laparoscopy. Adjuvant chemotherapy was administered to 20.3% of patients. Over a median follow-up of 33.6 months, two patients (3.1%) experienced recurrence, and one died.

Conclusions: BOT patients at Vietnam National Cancer Hospital are predominantly young, with early-stage serous tumors. The low recurrence rate and limited mortality suggest a favorable prognosis, though fertility-sparing surgery may require vigilant surveillance.

Keywords: Borderline ovarian tumor; serous; mucinous; fertility-sparing surgery; recurrence.

1. INTRODUCTION

Borderline ovarian tumors (BOTs), or tumors of low malignant potential, constitute 10–20% of epithelial ovarian neoplasms and are defined by atypical epithelial proliferation without stromal invasion [1]. Predominantly affecting younger women, with approximately one-third diagnosed before age 40, BOTs pose unique challenges in balancing oncologic safety with fertility preservation [2]. Most BOTs present at FIGO stage I (70–85%), conferring excellent prognosis, though recurrence risk is elevated with conservative surgical approaches [3]. Serous and mucinous subtypes account for the majority of cases, with serous BOTs comprising 50–55% and mucinous 35–45% [4].

Despite increasing global incidence, data on BOT characteristics and outcomes in Vietnam remain scarce [5]. This study aims to characterize the clinical, radiological, and pathological features of BOT patients treated at Vietnam National Cancer Hospital and to evaluate recurrence and survival outcomes, thereby informing evidence-based management strategies in a resource-constrained setting.

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2. MATERIALS AND METHODS

2.1. Study population

This study enrolled 64 patients with histologically confirmed BOT, treated surgically at Vietnam National Cancer Hospital, Hanoi, Vietnam, from January 2018 to December 2023.

2.2. Eligibility criteria

Inclusion Criteria:

+ Histologically confirmed BOT based on surgical specimens.

+ Complete medical records with clinical, radiological, pathological, and follow-up data.

Exclusion Criteria:

+ Patient refusal to participate.

+ Incomplete medical records precluding analysis.

2.3. Study design

A hybrid retrospective and prospective, non-randomized cohort study was conducted. Data were abstracted from medical records, encompassing demographic characteristics, tumor markers (CA125), imaging findings, histopathological subtype, FIGO stage, surgical interventions, adjuvant therapies, and clinical outcomes.

2.4. Procedures

+ Data Collection: Extracted variables included age, CA125 levels, ultrasound/CT/MRI findings, histological subtype, FIGO stage, surgical approach (fertility-sparing vs. radical, laparoscopic vs. laparotomic), and adjuvant chemotherapy use.

+ Outcome Measures: Recurrence, progression-free survival (PFS) and overall survival (OS) were recorded. PFS was defined as the interval from surgery to recurrence or last follow-up; OS was defined as the interval from surgery to death or last follow-up.

+ Histopathological Assessment: BOT subtypes were classified per the 2014 World Health Organization criteria [1]. FIGO staging followed the 8th edition AJCC/UICC guidelines [6].

+ Statistical Analysis: Continuous variables were reported as medians (interquartile ranges), and categorical variables as frequencies (percentages). Univariate Cox regression identified prognostic factors for PFS, with variables yielding $p \leq 0.10$ included in multivariate models. Survival curves were generated using the Kaplan-Meier method, with differences assessed via log-rank tests. A p-value ≤ 0.05 denoted statistical significance. Analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY).

2.5. Ethical approval

The study was approved by the Research Ethics Committee of Vietnam National Cancer Hospital

3. RESULTS

3.1. Clinical and pathological characteristics

Among 64 patients, the median age was 46.0 years (range: 16–77), with 59.4% aged <50 years. Serum CA125 was elevated (>35 U/ml) in 67.2% of cases (median: 39.6 U/ml, range: 8.9–5074.0). Radiologically, tumors were located on the left side in 17.2%, right side in 23.4%, bilateral in 6.3% and không xác định rõ vị trí in 53.1% due to large tumor size. Ascites was observed in 15.6% of patients.

Serous BOT was the predominant subtype (78.1%), followed by mucinous (18.7%) and Brenner (3.1%); no endometrioid cases were identified. FIGO stage I accounted for 75.0% of cases, followed by stage II (12.5%), stage III (10.9%), and stage IV (1.6%).

Table 1: Clinical and Pathological Characteristics of BOT Patients

Characteristic	Value
Age, median (range), years	46.0 (16-77)
CA125, median (range), U/ml	39.6 (8.9-5074.0)
CA125 >35 U/ml, n (%)	43 (67.2)
Tumor Location, n (%)	
- Left	11 (17.2)
- Right	15 (23.4)
- Bilateral	4 (6.3)
- Undetermined	34 (53.1)
Histological Subtype, n (%)	
- Serous	50 (78.1)
- Mucinous	12 (18.7)
- Brenner	2 (3.1)
FIGO Stage, n (%)	
- I	48 (75.0)
- II	8 (12.5)
- III	7 (10.9)
- IV	1 (1.6)

3.2. Treatment Characteristics

Fertility-sparing surgery (FSS), aimed at preserving reproductive potential in younger patients with ovarian cancer, was performed in 23 patients (35.9%). This included unilateral salpingo-oophorectomy with omentectomy in 15 cases, oophorectomy in 6 cases, and unilateral salpingo-oophorectomy with lymphadenectomy in 2 cases. Radical surgery, comprising bilateral salpingo-oophorectomy, omentectomy, and hysterectomy, was performed in 41 patients (64.1%). Laparoscopic surgery was utilized in 9 cases (14.1%). Adjuvant chemotherapy was administered to 13 patients (20.3%), primarily those with stage III–IV disease.

Table 2: Treatment Characteristics

Treatment	n (%)
Surgery Type	
- Fertility-sparing	23 (35.9)
- Radical	41 (64.1)
Surgical Approach	
- Laparoscopic	9 (14.1)
- Laparotomic	55 (85.9)
Adjuvant Chemotherapy	
- Yes	13 (20.3)
- No	51 (79.7)

3.3. Recurrence and Survival Outcomes

Over a median follow-up of 33.6 months (range: 1–130), two patients (3.1%) experienced recurrence,

both with mucinous BOT (stages IA and IC). One patient died of disease progression. Due to the limited sample size and only one recorded death, there is insufficient data to fully evaluate survival outcomes. However, the overall prognosis for BOTs appears highly favorable.

4. DISCUSSION

This study provides a comprehensive analysis of the clinical characteristics, treatment modalities, and outcomes of 64 patients with borderline ovarian tumors (BOTs) treated at Vietnam National Cancer Hospital, offering valuable insights into the management of this unique entity in a resource-constrained setting. With a median age of 46.0 years and a predominance of serous BOTs (78.1%), our cohort aligns closely with global trends, where serous histology accounts for 50–55% of cases [1,2]. Due to the limited sample size and only one recorded death, there is insufficient data to fully evaluate survival outcomes. However, the overall prognosis for BOTs appears highly favorable, consistent with international reports.

The predominance of FIGO stage I disease (75.0%) in our cohort is consistent with international data, where 70-85% of BOTs are diagnosed at an early stage [3,4]. This early presentation likely contributes to the favorable prognosis observed, mirroring findings from a Swiss single-center study by Kipp et al., which reported a similarly low recurrence rate (2.4%) among 42 patients, predominantly with stage I disease [5]. However, our study diverges from larger multicenter cohorts, such as the French FRANCOGYN study, which reported a higher recurrence rate (7.5%) among 493 patients, with advanced FIGO stage and invasive implants identified as significant risk factors [6]. The absence of invasive peritoneal implants in our cohort may partly explain the lower recurrence rate, though this could also reflect understaging due to limited intraoperative frozen section use (performed in only 64% of cases compared to 87% in tertiary European centers) [7].

Fertility-sparing surgery (FSS), performed in 35.9% of our patients, is a critical option for younger women but requires careful consideration due to potential recurrence risks, as evidenced by international studies. A meta-analysis by Vasconcelos et al. reported a recurrence rate of 17% in FSS cohorts, significantly higher than the 5% observed with radical surgery [8]. Notably, both recurrences in our study occurred in patients with mucinous BOTs, contrasting with the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) cohort, where serous BOTs with micropapillary patterns were more prone to relapse [9]. This discrepancy may reflect regional differences in histological distribution, as mucinous BOTs predominate in East Asia (e.g., 68–76% in Korea and Japan) compared to serous BOTs in Western countries (60–74% in the USA and Europe) [10]. Lifestyle factors, such as smoking, which is strongly associated with mucinous BOTs (OR=2.10, 95% CI 1.22–3.60), may contribute to this variation, though such data were not collected in our study [11].

The use of adjuvant chemotherapy in 20.3% of our patients, primarily for stage III–IV disease, contrasts with current European Society for Medical Oncology (ESMO) guidelines, which do not recommend adjuvant therapy for BOTs regardless of stage due to lack of survival benefit [12]. This practice may reflect regional preferences or concerns about understaging in advanced cases, as seen in a German multicenter survey where 15% of clinicians administered chemotherapy for "high-risk" BOTs [7]. In contrast, a Gynecologic Oncology Group study by Sutton et al. found no improvement in disease-free survival with cisplatin-based regimens, suggesting overtreatment in our cohort [13]. Future studies should explore the cost-effectiveness and clinical utility of adjuvant therapy in low-resource settings like Vietnam, where access to long-term surveillance may be limited.

Preoperative diagnostic challenges were evident, with 53.1% of tumors classified as không xác định rõ vị trí due to large size, aligning with Fischerova et al., who reported only 69% accuracy in preoperative ultrasound for BOTs [14]. The high rate of elevated CA125 (67.2%) in our cohort is consistent with

global reports but underscores its limited specificity, as noted in a South Korean study where the Risk of Malignancy Index (RMI) outperformed single-marker CA125 for distinguishing BOTs from benign tumors [15]. These findings highlight the need for advanced imaging (e.g., MRI) and novel biomarkers, such as the CPH-I index, which has shown superior diagnostic accuracy for BOTs in recent studies [16].

Our study's low recurrence rate may also reflect genetic or environmental factors specific to the Vietnamese population. A Lund University study suggested that BOTs share familial risks with invasive cancers, potentially linked to mutations in KRAS and BRAF, which were prevalent in 43% and 57% of BOTs, respectively [17]. However, molecular profiling was not performed in our cohort, limiting our ability to explore these associations. Additionally, lifestyle factors, such as lower smoking prevalence among Vietnamese women compared to Western populations, may reduce the incidence of mucinous BOTs, contributing to the predominance of serous histology [11]. Future research should investigate these hypotheses using genomic and epidemiological approaches to elucidate regional differences in BOT pathogenesis.

Limitations of this study include its modest sample size (n=64), which restricts the generalizability of findings, and the short median follow-up (33.6 months), which may underestimate late recurrences, as Silva et al. recommended a minimum 10-year follow-up for BOTs [18]. The hybrid retrospective-prospective design introduces potential selection bias, and the lack of centralized pathology review may affect histological accuracy. Furthermore, the absence of data on molecular markers (e.g., KRAS, BRAF) and lifestyle factors (e.g., smoking, oral contraceptive use) limits our ability to fully contextualize our findings within the global landscape. Despite these constraints, our study is among the first to provide detailed insights into BOT management in Vietnam, contributing to the sparse literature from Southeast Asia.

In conclusion, this study highlights the favorable prognosis of BOTs in a Vietnamese cohort, with a low recurrence rate, particularly for early-stage serous tumors. The use of FSS underscores the need for rigorous surveillance, especially in young patients. Future studies should prioritize molecular characterization, long-term follow-up and the development of cost-effective diagnostic tools to further refine the management of BOTs globally and in Southeast Asia.

5. CONCLUSION

Patients with BOT at Vietnam National Cancer Hospital are predominantly young, presenting with early-stage serous tumors. The low recurrence rate and limited mortality suggest a favorable prognosis, though fertility-sparing surgery may require rigorous follow-up.

REFERENCES

[1]. Hauptmann S, Friedrich K, Redline R, Avril S. Ovarian borderline tumors in the 2014 WHO classification: evolving concepts and diagnostic criteria. Virchows Arch. 2017;470:125–142. https://doi.org/10.1007/s00428-016-2040-8

[2]. Skírnisdóttir I, Garmo H, Wilander E, Holmberg L. Borderline ovarian tumors in Sweden 1960–2005: trends in incidence and age at diagnosis compared to ovarian cancer. Int J Cancer. 2008;123:1897–1901. https://doi.org/10.1002/ijc.23786

[3]. Zanetta G, Rota S, Chiari S, Bonazzi C, Bratina G, Mangioni C. Behavior of borderline tumors with particular interest to persistence, recurrence, and progression to invasive carcinoma: a prospective study. J Clin Oncol. 2001;19:2658–2664. https://doi.org/10.1200/JCO.2001.19.10.2658

[4]. Fischerova D, Zikan M, Dundr P, Cibula D. Diagnosis, treatment, and follow-up of borderline ovarian tumors. Oncologist. 2012;17:1515–1533. https://doi.org/10.1634/theoncologist.2012-0139

[5]. Kipp B, Vidal A, Lenick D, Christmann-Schmid C. Management of borderline ovarian tumors (BOT): results of a retrospective, single-center study in Switzerland. J Ovarian Res. 2023;16:20. https://doi.org/10.1186/s13048-023-01104-4

[6]. Bourdel N, Chabert P, Gremeau AS, et al. Risk factors for recurrence of borderline ovarian tumors in France: a multicenter retrospective study by the FRANCOGYN group. J Gynecol Obstet Hum Reprod. 2020;49:101745. https://doi.org/10.1016/j.jogoh.2020.101745

[7]. Du Bois A, Heitz F, Harter P. Clinical management of borderline ovarian tumors: results of a multicentre survey of 323 clinics in Germany. Br J Cancer. 2009;100:1731–1738. https://doi.org/10.1038/sj.bjc.6605066

[8]. Vasconcelos I, de Sousa Mendes M. Conservative surgery in ovarian borderline tumours: a meta-analysis with emphasis on recurrence risk. Eur J Cancer. 2015;51:620–631. https://doi.org/10.1016/j.ejca.2015.01.004

[9]. Du Bois A, Ewald-Riegler N, de Gregorio N, et al. Borderline tumours of the ovary: a cohort study of the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Study Group. Eur J Cancer. 2013;49:1905–1914. https://doi.org/10.1016/j.ejca.2013.01.035

[10]. Song T, Choi CH, Lee YY, et al. Histologic distribution of borderline ovarian tumors worldwide: a systematic review. J Gynecol Oncol. 2013;24:44–

[11]. https://doi.org/10.3802/jgo.2013.24.1.44 [11]. Rasmussen CB, Kjaer SK, Albieri V, et al. Lifestyle factors and borderline ovarian tumors: a Danish case-control study. Int J Cancer. 2017;140:1310–1319. https://doi.org/10.1002/ijc.30546

[12]. Du Bois A, Trillsch F, Mahner S, Heitz F, Harter P. Management of borderline ovarian tumors. Ann Oncol. 2016;27(Suppl 1):i20–i22. https://doi.org/10.1093/annonc/mdw090

[13]. Sutton GP, Bundy BN, Omura GA. Stage III ovarian tumors of low malignant potential treated with cisplatin combination therapy (a Gynecologic Oncology Group study). Gynecol Oncol. 1991;41:230–233. https://doi.org/10.1016/0090-8258(91)90314-U

[14]. Fischerova D, Zikan M, Dundr P, Cibula D. Diagnosis, treatment, and follow-up of borderline ovarian tumors. Oncologist. 2012;17:1515–1533. https://doi.org/10.1634/theoncologist.2012-0139

[15]. Kim JH, Cho HJ, Park JH, et al. Diagnostic extended usefulness of RMI: comparison of four risk of malignancy index in preoperative differentiation of borderline ovarian tumors. Arch Gynecol Obstet. 2019;300:1283–1291. https://doi.org/10.1007/s00404-019-05285-7

[16]. Huang K, Li Y, Wang J, et al. A diagnostic system combining inflammation and tumor biomarkers for epithelial ovarian tumors. Front Oncol. 2023;13:1096382. https://doi.org/10.3389/fonc.2023.1096382

[17]. Zheng G, Yu H, Kanerva A, Försti A, Sundquist K, Hemminki K. Borderline ovarian tumors share familial risks with themselves and invasive cancers. Cancer Epidemiol Biomarkers Prev. 2018;27:1358–1363. https://doi.org/10.1158/1055-9965.EPI-18-0503

[18]. Silva EG, Gershenson DM, Malpica A, Deavers M. The recurrence and the overall survival rates of ovarian serous borderline neoplasms with noninvasive implants is time dependent. Am J Surg Pathol. 2006;30:1367–1371. https://doi.org/10.1097/01.pas.0000213299.11649.fa

HORNER'S SYNDROME FOLLOWING THYROID SURGERY: A CASE REPORT AND LITERATURE REVIEW

Ngo Xuan Quy[1*], Nguyen Thi Phuong Lan[2], Ngo Quoc Duy[1, 2]

ABSTRACT

Objective: Horner's syndrome (HS) occurs due to damage to the cervical sympathetic nerve pathway and is considered a rare complication following thyroid surgery with an incidence of approximately 0.2%. This paper reports a case of HS that developed after thyroid surgery and provides a literature review of this rare complication.

Case report: A 29-year-old female patient diagnosed with suspected right thyroid cancer cT3bN0M0 underwent total thyroidectomy and central neck dissection. On the second postoperative day, the patient developed right-sided ptosis and miosis (right pupil 2mm compared to left pupil 4mm). The patient was diagnosed with HS secondary to thyroid surgery. After 3 months of follow-up, the symptoms showed no improvement.

Conclusion: HS following thyroid surgery is a rare complication that may result from various mechanisms such as direct injury to the cervical sympathetic chain, hematoma compression, ischemia, or traction of the cervical sympathetic chain. Standardized surgical procedures and refined surgical techniques are necessary to prevent this complication. Patients should be counseled about the possibility of permanent injury and long-term aesthetic impact.

Keywords: Horner's syndrome; thyroid surgery; complication; ptosis; miosis.

1. INTRODUCTION

Horner's syndrome (HS) was first described in 1853 by Bernard, and later in more detail by Horner in 1869 [1]. This syndrome is characterized by the classic triad of symptoms: ptosis (drooping of the upper eyelid), miosis (pupillary constriction) and anhidrosis (decreased sweating) on the ipsilateral side of the face. HS occurs due to disruption of the cervical sympathetic nerve pathway and is considered a rare complication following thyroid surgery with an incidence of approximately 0.2% [2].

Kaelin and colleagues reported the first case of HS following thyroid surgery in 1915 [3]. In the context of increasing global incidence of thyroid cancer [4], [5] and surgery remaining the primary treatment option, understanding rare complications such as HS is of significant importance.

In this report, we present a case of HS that developed after total thyroidectomy and central neck dissection, while also providing a comprehensive literature review of this rare complication.

2. CASE REPORT

A 29-year-old female patient was admitted to the hospital after incidentally discovering a thyroid

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nodule during a routine health check-up. Thyroid ultrasound revealed: a right lobe hypoechoic nodule with irregular margins and calcifications measuring 10×13 mm (TIRADS 5), with evidence of capsular invasion into the strap muscles. No abnormal cervical lymph nodes were detected. The fine-needle aspiration (FNA) biopsy result under ultrasound guidance of the right lobe nodule indicated papillary thyroid carcinoma (category V).

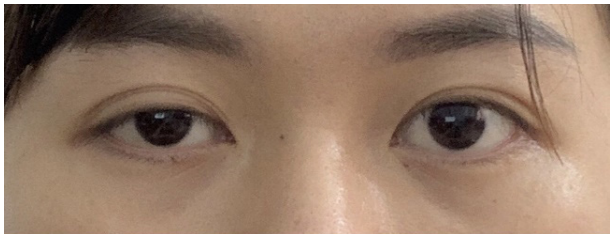

Figure 1a: 2 days after thyroid surgery

Figure 1b: 1 month after thyroid surgery

The patient was diagnosed with right thyroid lobe cancer cT3bN0M0 and underwent total thyroidectomy with central neck dissection, preserving the parathyroid glands and recurrent laryngeal nerves. Intraoperative assessment showed: a firm right lobe tumor approximately 13mm in size with capsular invasion into the strap muscles. Postoperative histopathology results confirmed papillary thyroid carcinoma in the right lobe; 3/3 central neck lymph nodes showed chronic inflammation. Postoperative staging was pT3bN0M0.

On the second postoperative day, the patient developed right-sided ptosis. Physical examination revealed: right ptosis (right upper eyelid covering nearly 4 mm of the corneal limbus) and anisocoria (right pupil 2 mm, left pupil 4 mm). Anhidrosis on the ipsilateral side could not be determined. The patient was diagnosed with Horner's syndrome secondary to thyroid surgery. No other complications such as hypocalcemia or recurrent laryngeal nerve palsy were observed. The patient received conservative treatment and follow-up. After 3 months, the HS symptoms showed no improvement.

3. DISCUSSION

3.1. Epidemiology

HS is rare with an incidence rate of approximately 2.93 per 100,000 people. The 10-year cumulative incidence of HS in adults is reported to be 2.95 per 100,000 adults. This rate is lower in children, at approximately 1.42-2.12 per 100,000 children [6] mainly characterized by symptoms including ptosis, miosis and anhidrosis on the affected face, is a condition that is well documented but rarely reported as a postoperative complication of thyroidectomy, particularly in endoscopic thyroid surgery (ETS. HS can occur at any age and is not dependent on ethnicity. Notably, the incidence of HS following thyroid surgery is only about 0.2-0.3% [2], despite neck surgery, particularly thyroid surgery, being considered a primary cause of HS. This demonstrates that it is truly a rare complication in clinical practice.

3.2. Neuroanatomy and pathophysiology

The ocular sympathetic pathway consists of three neurons [7]. The first neuron (central) originates from the hypothalamus, passes through the brainstem and spinal cord, and synapses with the second neuron in the lower cervical or upper thoracic spinal cord. The second neuron (preganglionic) originates from the spinal nuclei, passes through the upper thoracic cavity, through the inferior and middle cervical ganglia, and synapses with the superior cervical ganglion. The third neuron (postganglionic) originates from the superior cervical ganglion, travels along the carotid arterial system to reach the orbit and eye. Potential causes of HS following thyroid surgery include: postoperative hematoma compressing the cervical sympathetic chain; nerve damage due to ischemia caused by ligation of lateral

branches of the inferior thyroid artery; stretching of the cervical sympathetic chain by surgical instruments; damage to the connecting branches between the cervical sympathetic chain and the recurrent laryngeal nerve; or direct injury to the cervical sympathetic chain [1]. According to Min et al. [6]mainly characterized by symptoms including ptosis, miosis, and anhidrosis on the affected face, is a condition that is well documented but rarely reported as a postoperative complication of thyroidectomy, particularly in endoscopic thyroid surgery (ETS, HS is more common after total thyroidectomy with lymph node dissection, particularly lateral neck dissection. However, HS can also occur after simple thyroid lobectomy or thyroid lobectomy with central cervical lymph node dissection.

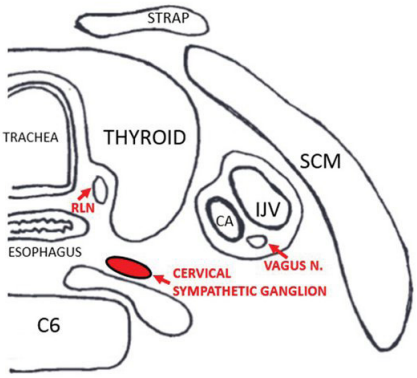

Figure 2: The mechanisms of Horner's syndrome following thyroid surgery

3.3. Clinical features

HS is the result of disruption of the ocular sympathetic pathway, causing three main symptoms. First, ptosis due to paralysis of Müller's muscle, which is innervated by the sympathetic nervous system. Second, miosis due to the loss of pupillary dilation effect of the sympathetic nervous system. Third, facial anhidrosis on the ipsilateral side, a symptom less common than the first two. In our case, the patient presented with the first two symptoms, consistent with other reports in the literature. HS typically manifests within a few hours to 3 days after surgery [6]mainly characterized by symptoms including ptosis, miosis, and anhidrosis on the affected face, is a condition that is well documented but rarely reported as a postoperative complication of thyroidectomy, particularly in endoscopic thyroid surgery (ETS, which is consistent with our case where the patient developed symptoms on the second day after surgery.

3.4. Prognosis and treatment

The prognosis of HS depends on the mechanism of injury. If the injury is related to hematoma, inflammation, or ligation of peripheral branches of the inferior thyroid artery, HS may resolve spontaneously [8]. However, up to 70% of HS cases following thyroid surgery have permanent damage or incomplete recovery, with only 30% experiencing complete recovery but requiring an extended period (from 20 days to 15 months) [1]. This explains why after 3 months of follow-up, our patient still showed no improvement in symptoms. Treatment of HS following thyroid surgery is generally conservative [9] which follows a complex anatomical course through the head and neck. Neck surgery may cause injury to this pathway, causing loss of sympathetic innervation producing the eponymous Horner's syndrome (ipsilateral ptosis, miosis and anhidrosis. Some studies suggest the use of short-term neurotropic therapy such as vitamin

B1 and B12 [6]mainly characterized by symptoms including ptosis, miosis, and anhidrosis on the affected face, is a condition that is well documented but rarely reported as a postoperative complication of thyroidectomy, particularly in endoscopic thyroid surgery (ETS, or short-term oral steroids [10] to stimulate nerve cell repair and reduce symptoms. For persistent HS cases causing aesthetic concerns, apraclonidine eye drops may be used as a short-term option, however, the duration and frequency of use need to be closely monitored due to dose-dependent toxicity [9]which follows a complex anatomical course through the head and neck. Neck surgery may cause injury to this pathway, causing loss of sympathetic innervation producing the eponymous Horner's syndrome (ipsilateral ptosis, miosis and anhidrosis.

3.4. Prevention of complications

To prevent HS following thyroid surgery, thorough preoperative assessment of the characteristics, size, and location of the lesion is essential. Establishing standardized surgical procedures and performing refined surgical techniques to avoid damage to neural structures play an important role. Close postoperative monitoring also helps in early detection of complications and timely intervention. Although HS does not affect visual function, the aesthetic impact can cause anxiety and psychological effects for patients. Therefore, patients need to be thoroughly counseled before surgery about this risk.

4. CONCLUSION

Horner's syndrome following thyroid surgery is a rare complication with an incidence of approximately 0.2%. Our case illustrates this rare complication and emphasizes the importance of early recognition, close monitoring, and comprehensive counseling for patients regarding the possibility of permanent injury and long-term aesthetic impact.

REFERENCES

[1]. Cozzaglio L., Coladonato M., Doci R., et al. (2008). Horner's syndrome as a complication of thyroidectomy: report of a case. *Surg Today*, 38(12), 1114–1116.

[2]. Lee Y.S., Nam K.-H., Chung W.Y., et al. (2010). Postoperative Complications of Thyroid Cancer in a Single Center Experience. *J Korean Med Sci*, 25(4), 541–545.

[3]. Kaelin W. (1915). Über Störungen von seiten des Halssympathicus bei einfacher Struma und im Anschluß an deren operative Behandlung. *Dtsch Z Für Chir*, 134(5), 395–423.

[4]. Kim J., Gosnell J.E., and Roman S.A. (2020). Geographic influences in the global rise of thyroid cancer. *Nat Rev Endocrinol*, 16(1), 17–29.

[5]. Wang J., Yu F., Shang Y., et al. (2020). Thyroid cancer: incidence and mortality trends in China, 2005-2015. *Endocrine*, 68(1), 163–173.

[6]. Min Y., Chen H., Wang X., et al. (2021). Case report and literature review: Horner syndrome subsequent to endoscopic thyroid surgery. *BMC Surg*, 21(1), 36.

[7]. Knyazer B., Smolar J., Lazar I., et al. (2017). Iatrogenic Horner Syndrome: Etiology, Diagnosis and Outcomes. *Isr Med Assoc J IMAJ*, 19(1), 34–38.

[8]. Demiral M., Binay C., Simsek E., et al. (2017). Horner Syndrome Secondary to Thyroid Surgery. *Case Rep Endocrinol*, 2017, 1689039.

[9]. Palmer E.M., Sonoo P., Jawaid I., et al. Post-operative Horner's Syndrome Following Total Thyroidectomy: A Case Report. *Cureus*, 14(8), e27742.

[10]. Huang L., Tang X., and Su L. (2018). Horner's Syndrome after Thyroidectomy: Two Cases Report. *Open J Prev Med*, 8(12), 325–329.

RECENT ADVANCES IN IMMUNOTHERAPY FOR HEPATOCELLULAR CARCINOMA

April 19 is recognized annually as World Liver Day, providing an important opportunity for both the medical community and the general public to raise awareness about liver diseases in general, particularly hepatocellular carcinoma (HCC) - a condition that continues to pose a significant global and national healthcare burden. According to GLOBOCAN 2022, liver cancer currently ranks second in incidence and remains the leading cause of cancer-related mortality in Vietnam [1]. The majority of patients are diagnosed at an advanced stage, resulting in limited treatment options and a poor prognosis.

Sorafenib was the first targeted systemic therapy approved by the FDA in 2007 for the treatment of unresectable HCC. More than a decade later, Lenvatinib, a next-generation targeted agent, was introduced as a first-line treatment option for advanced-stage HCC, offering additional therapeutic choices for patients. While these represented significant therapeutic advancements, the advent of the immunotherapy era has introduced a new paradigm in the management of HCC, bringing renewed hope through novel combinations such as Tremelimumab + Durvalumab (known as STRIDE) and Atezolizumab + Bevacizumab.

The IMbrave150 trial demonstrated the superior efficacy of the Atezolizumab + Bevacizumab combination in the treatment of HCC. This regimen integrates Atezolizumab (an anti-PD-L1 immunotherapy agent) with Bevacizumab (an anti-angiogenic monoclonal antibody). Clinical results showed a marked improvement in overall survival (OS), with a median OS of 19.2 months compared to 13.4 months in the Sorafenib arm [2].

The combination of Tremelimumab (anti-CTLA-4) and Durvalumab (anti-PD-L1) exerts its effect by reactivating the immune system and enhancing anti-tumor immune responses. Findings from the HIMALAYA trial - a randomized, phase III, multicenter global study - revealed a significant improvement in OS with the STRIDE regimen versus Sorafenib monotherapy, achieving a 5-year survival rate of 19.6% compared to just 9.4% in the Sorafenib group [3]. This marks the first time a systemic treatment regimen has shown a substantial long-term survival benefit in advanced HCC.

Both regimens have been approved by the FDA as first-line systemic therapies and are recommended as preferred options in international treatment guidelines for patients with unresectable HCC who are no longer candidates for curative surgery or locoregional therapy [4]. These immunotherapeutic advancements have expanded the therapeutic arsenal, offering comprehensive improvements in clinical outcomes for patients with hepatocellular carcinoma.

REFERENCES

[1]. GLOBOCAN 2022: Incidence, Mortality, and Prevalence Database - World Health Organization (WHO).

[2]. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol. 2022 Apr;76(4):862-873. doi: 10.1016/j.jhep.2021.11.030. Epub 2021 Dec 11. PMID: 34902530.

[3]. Lorenza Rimassa, Five-year overall survival update from the HIMALAYA study of tremelimumab plus durvalumab in unresectable HCC, Published online April 11, 2025; DOI: 10.1016/j.jhep.2025.03.033

[4]. NCCN Hepatocellular Carcinoma version 4.2024; Hepatocellular Carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up 2025; BCLC 2022

ARTICLE SUBMISSION GUIDELINES FOR THE VIETNAM JOURNAL OF ONCOLOGY

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Manuscripts should be concise and formatted on A4 paper, using Times New Roman, font size 12, single spacing, and justified alignment. Margins should be set at: top 2 cm, bottom 2 cm, left 2 cm, and right 3 cm. Illustrations and tables must be clear and succinct. The structure should include:

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ABSTRACT (in English): Bold, uppercase, font size 12, upright. Abstract text should be italicized, font size 11. Section headings (Background/Objectives, Methods, Results, Conclusions, Keywords) should be italicized.

c. Main section titles: Use Roman numerals (I, II, III...) in uppercase and bold.

d. Subheadings: Use numbering (e.g., 1.1, 1.2...), bold, indented one tab; sub-subheadings (e.g., 2.1.1, 2.1.2...) should be bold, italicized, and indented similarly.

2.2. Tables and Figures

- Table content should use font size 11, with bold headers. Table titles should be italicized, bold, font size 12. Tables may extend across the whole page width. If a table continues onto a second page, the header row must be repeated.
- Figures reproduced from other sources must include a proper citation. Authors are responsible for obtaining permission to reuse such figures. Use consistent labels (e.g., Figure 1, Figure 2, and Table 1, Table 2). Tables must be clear and easy to read (avoid overly complex designs or font sizes smaller than 10). Place table titles above the table, and figure or chart titles below the image.

2.3. References

- Citations must include recent studies published within the past 5 years and should not exceed 15 references.
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2.4. Page Numbering

Page numbers should be centered at the bottom of each page.

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