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GENERAL INFORMATION

THE 8th HAI PHONG SCIENTIFIC CONFERENCE ON CANCER CONTROL (2026): A PREMIER ACADEMIC FORUM ON EMERGING TRENDS IN MODERN ONCOLOGY

On May 7-8, 2026, Viet Tiep Hospital, in collaboration with the Vietnam Cancer Association and the Hai Phong Department of Health, will host the 8th Hai Phong Scientific Conference on Cancer Control. The conference is expected to welcome nearly 400 participants, including distinguished scientists, leading oncology experts, physicians, and healthcare professionals from hospitals, medical universities, and healthcare institutions representing more than 20 provinces and cities across Vietnam.

The scientific program will feature more than 70 high-quality presentations, covering a broad spectrum of contemporary oncology, including immunotherapy, targeted therapy, molecular oncology, nuclear medicine, precision radiotherapy, minimally invasive surgery, multimodal treatment strategies, and personalized cancer care.

The conference agenda includes a specialized pre-conference training course entitled "Esophageal Cancer: Challenges and Advances in Treatment", together with a plenary session and multiple parallel scientific sessions. These sessions will focus on major oncology disciplines, including thoracic oncology, breast oncology, gastrointestinal and hepatobiliary cancers, gynecologic and genitourinary malignancies, hematologic oncology and molecular diagnostics, immunotherapy, nuclear medicine, radiation oncology, and oncology nursing.

Another highlight of the conference is the scientific session "Cancer Vaccines: Prospects and Challenges," which is expected to attract considerable interest from oncology professionals. The session will explore recent advances in the development of therapeutic cancer vaccines, one of the most promising frontiers in contemporary cancer research and precision medicine.

The Hai Phong Scientific Conference on Cancer Control has established itself as an important academic platform for sharing the latest scientific evidence, innovative technologies, advanced clinical techniques, and emerging directions in oncology. Beyond reflecting the continued progress of cancer prevention and treatment in Vietnam, the conference also demonstrates the country's growing integration into the global oncology community through scientific collaboration, technology transfer, and knowledge exchange. Ultimately, the conference aims to promote innovation, strengthen professional networking, and contribute to improving the quality of cancer prevention, diagnosis, treatment, and patient care for the Vietnamese population.

HEREDITARY BREAST AND OVARIAN CANCER (HBOC) SYNDROME

Nguyen Van Tung

ABSTRACT

Genetic factors account for approximately 5-7% of breast cancer cases and 15-20% of epithelial ovarian cancer cases. Germline mutations in genes such as *BRCA1/2, PALB2, TP53, CHEK2, ATM,* and *RAD51C/D* have been identified as contributing to varying degrees of cancer risk. Current evidence indicates that carriers of *BRCA* mutations have a cumulative lifetime risk of up to 60-80% for breast cancer and 15-45% for ovarian cancer. The advent of next-generation sequencing (NGS) has significantly improved mutation detection rates, while also posing challenges in the interpretation of variants of uncertain significance (VUS). In terms of treatment, large clinical trials have demonstrated the superior efficacy of PARP inhibitors in patients harboring *BRCA* mutations, based on the mechanism of synthetic lethality, leading to improvements in progression-free survival and other survival outcomes. In addition, genetic counseling plays a central role in risk assessment, guiding genetic testing, and supporting clinical decision-making. Risk-reducing strategies, including enhanced surveillance and prophylactic surgery, have shown clear effectiveness. However, the implementation of these approaches in developing countries remains limited and requires further improvement.

Keywords: Breast cancer, HBOC, germline mutations, BRCA.

1. INTRODUCTION

Hereditary Breast and Ovarian Cancer (HBOC) syndrome is a clinically significant entity in oncology and medical genetics, characterized by an increased risk of breast cancer, ovarian cancer, and several other malignancies due to germline mutations in tumor suppressor genes. Among these, *BRCA1* and *BRCA2* are the most extensively studied genes. Individuals harboring pathogenic variants in these genes have a cumulative lifetime risk of up to 60-80% for breast cancer and approximately 15-45% for ovarian cancer, which is substantially higher than that of the general population [1].

HBOC is commonly associated with clinical features such as early-onset breast cancer, bilateral breast cancer, triple-negative breast cancer, epithelial ovarian cancer, and a strong family history of related malignancies. In addition, this syndrome has been linked to other cancers, including pancreatic cancer, prostate cancer, and melanoma. Early identification of HBOC is crucial for optimizing screening strategies, implementing preventive measures, and guiding personalized treatment approaches.

In recent years, advances in next-generation sequencing (NGS) technologies have expanded the spectrum of genes implicated in HBOC beyond *BRCA1/2* to include multiple DNA repair

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genes. Concurrently, clinical guidelines from international organizations such as the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) have emphasized the importance of genetic testing and genetic counseling in the management of high-risk individuals.

This is a narrative review aimed at updating recent understanding of HBOC syndrome and its management strategies. The article also addresses some challenges in implementing professional recommendations related to this syndrome in the Vietnamese context.

2. GENES IN HEREDITARY BREAST AND OVARIAN CANCER SYNDROME

2.1. BRCA1/2 Genes

BRCA1 and *BRCA2* are tumor suppressor genes that play essential roles in DNA repair through the homologous recombination (HR) pathway. The proteins encoded by these genes are involved in the recognition and repair of DNA double-strand breaks, thereby maintaining genomic stability.

Germline mutations in *BRCA1/2* result in loss of protein function, leading to impaired DNA repair capacity. Consequently, genetic damage accumulates, causing chromosomal instability and promoting carcinogenesis. This mechanism is particularly relevant in tissues with high proliferative activity, such as the breast and ovarian epithelium.

An important related concept is "synthetic lethality" [2]. In BRCA-deficient cells, inhibition of alternative DNA repair pathways such as poly (ADP-ribose) polymerase (PARP) leads to selective tumor cell death. This provides the biological rationale for the use of PARP inhibitors in the treatment of BRCA-associated cancers.

In addition, *BRCA1* is involved in transcriptional regulation and cell cycle control, whereas *BRCA2* plays a more direct role in facilitating RAD51 binding to DNA during homologous recombination. These functional differences partly explain the distinct disease spectrum and phenotypic variations observed between *BRCA1* and *BRCA2* mutations.

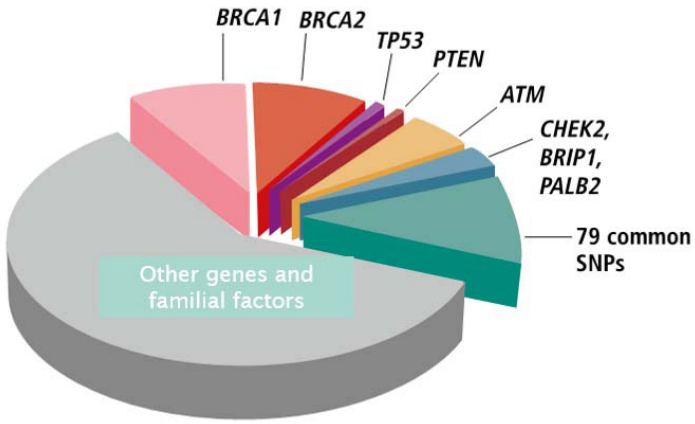

Fig.1. Breast and ovarian cancers - associated genes and familial factors

1. BalmahaJ, et al Ann Oncol 2011 (Supp 4): iv19-iv20
2. Venkitaraman AR. J Cell Sci 2001; 114:3591-3598

2.2. Other Susceptibility Genes

Beyond *BRCA1* and *BRCA2*, multiple additional genes have been identified as contributing to an increased risk of breast and ovarian cancers. These genes are primarily involved in DNA repair pathways or cell cycle regulation.

Figure 1 illustrates the distribution of genes associated with hereditary breast and ovarian cancer (HBOC), with *BRCA* mutations accounting for approximately 50% of cases, and the remaining proportion attributable to other susceptibility genes [3]for an individual, may be more efficient and less expensive than sequential testing. The authors assessed the frequency of deleterious germline mutations among individuals with breast cancer who were referred for BRCA1 and BRCA2 (BRCA1/2.

It is noteworthy that more than 50% of familial breast and ovarian cancer cases lack an identifiable pathogenic mutation. Conversely, up to 50% of individuals with confirmed germline mutations may not have a clearly documented family history.

Several commonly implicated non-*BRCA* genes and their associated cancer risks are summarized below:

PALB2 (Partner and Localizer of BRCA2): *PALB2* encodes a protein that directly interacts with BRCA2 and facilitates homologous recombination-mediated DNA repair. Germline mutations in *PALB2* confer a lifetime breast cancer risk of approximately 35-60%, representing a moderate-to-high risk category.

TP53 encodes the p53 protein, often referred to as the "guardian of the genome." Germline mutations result in Li-Fraumeni syndrome, which is associated with a broad spectrum of malignancies, including early-onset breast cancer. Unlike *BRCA* genes, *TP53* affects multiple oncogenic pathways, including apoptosis and cell cycle control.

CHEK2 encodes a key kinase involved in the DNA damage response. Mutations in *CHEK2* are associated with a moderate increase in breast cancer risk and are more frequently observed in European populations.

ATM plays a central role in DNA damage signaling. Germline mutations in *ATM* are associated with an increased risk of breast cancer and may also be linked to pancreatic cancer.

RAD51C and RAD51D: These genes are integral components of the homologous recombination repair pathway. Mutations in *RAD51C/D* are particularly associated with an elevated risk of ovarian cancer.

In addition, other genes such as *BRIP1, BARD1,* and *NBN* also contribute to cancer susceptibility, although with varying degrees of risk. This heterogeneity has led to the classification of susceptibility genes into high-, moderate-, and low-penetrance groups, which is essential for guiding risk stratification, screening strategies, and preventive interventions.

The use of multigene panel testing in clinical practice enables simultaneous detection of multiple pathogenic variants, thereby improving the diagnostic yield for HBOC. However, it also introduces challenges in interpreting variants of uncertain significance (VUS), which remain a critical issue in clinical genetics.

3. ROLE OF BRCA MUTATIONS IN THE TREATMENT OF BREAST AND OVARIAN CANCER

Germline *BRCA* mutations have been established as key therapeutic targets in the personalized management of breast and ovarian cancers. Evidence from phase III trials such as OLYMPIA, OLYMPIAD, SOLO-1, and SOLO-2 has defined the central role of poly (ADP-ribose) polymerase (PARP) inhibitors, particularly Olaparib in patients harboring *BRCA* mutations.

The biological rationale for this approach is based on the concept of "synthetic lethality," whereby tumor cells with *BRCA1/2* mutations, already deficient in homologous recombination–mediated DNA repair, become highly susceptible to PARP inhibition.

In breast cancer, the OLYMPIAD trial demonstrated the efficacy of olaparib in patients with metastatic HER2-negative breast cancer carrying germline *BRCA* mutations. The study reported a median progression-free survival (PFS) of 8.0 months compared with 3.8 months in the standard chemotherapy group (HR ≈ 0.51), along with improved response rates and quality of life. However, the overall survival (OS) benefit in the final analysis did not reach clear statistical significance (19.3 vs. 17.1 months). In contrast, the OLYMPIA trial, conducted in the adjuvant setting for high-risk early-stage breast cancer, demonstrated that olaparib significantly improved invasive disease-free survival (iDFS) and distant disease-free survival (dDFS), with a trend toward improved OS, thereby reinforcing the role of PARP inhibitors in early-stage disease [4].

In ovarian cancer, the SOLO-1 and SOLO-2 trials provide even more compelling evidence [5]niraparib, and rucaparib in patients with OC and discusses their role in disease management, with a focus on the use of PARPis as maintenance therapy in the United States (US. The SOLO-1 trial, involving newly diagnosed advanced-stage patients with *BRCA* mutations who responded to platinum-based chemotherapy, demonstrated an approximately 70% reduction in the risk of disease progression or death (HR ~0.30), with median PFS not reached compared to 13.8 months in the placebo group. Notably, after 6 years, approximately 48% of patients receiving olaparib remained progression-free compared to 21% in the control group, with sustained long-term benefits in extended follow-up analyses. Meanwhile, the SOLO-2 trial, conducted in patients with platinum-sensitive relapsed disease, showed that olaparib prolonged median PFS to 19.1 months compared with 5.5 months (HR ~0.30), while also improving quality-of-life measures and delaying time to subsequent therapy.

Overall, evidence from these four trials demonstrates that *BRCA*-targeted therapy with olaparib provides consistent survival benefits in both breast and ovarian cancers, with particularly pronounced efficacy in the maintenance setting of ovarian cancer. These findings have transformed clinical practice, establishing *BRCA* testing as an essential component of personalized cancer therapy. Other PARP inhibitors, such as niraparib and veliparib also demonstrated survival benefits in selected groups of ovarian cancer patients. However, these medication are currently not available in Vietnam.

4. DIAGNOSTIC TESTING FOR HEREDITARY BREAST AND OVARIAN CANCER (HBOC)

The diagnosis of HBOC is primarily based on genetic testing aimed at identifying germline mutations in susceptibility genes.

Currently, next-generation sequencing (NGS) is the most widely used method. NGS plays a pivotal role in detecting germline mutations in the *BRCA1* and *BRCA2* genes due to its ability to perform massively parallel sequencing with high coverage. This technology enables the simultaneous detection of multiple types of variants, including single-nucleotide variants, small insertions/deletions, and when combined with appropriate analytical approaches copy number variations (CNVs). Compared with conventional techniques, NGS offers advantages in terms of time and cost efficiency, as it allows the analysis of multiple cancer-associated genes in a single run, thereby improving diagnostic yield. However, NGS has certain limitations,

including the potential to miss large structural variants without complementary techniques, the identification of variants of uncertain significance (VUS), and the requirement for advanced bioinformatics infrastructure [6].

Genetic testing strategies may include single-gene analysis of *BRCA1/2* or the use of multigene panels. In addition, Multiplex Ligation-dependent Probe Amplification (MLPA) is employed to detect copy number variations.

Sanger sequencing, developed by Frederick Sanger and considered a first-generation sequencing method, is typically used when a specific mutation site is already known. This technique was instrumental in the Human Genome Project, completed in 2001 after more than a decade of global collaboration. Although it has lower sensitivity compared to modern sequencing technologies, Sanger sequencing remains useful for confirming NGS results when variant allele frequency is sufficiently high (approximately ≥25%), or when targeted sequencing of a specific gene or DNA fragment is required [7].

Genetic testing is commonly performed using peripheral blood or saliva samples. Results are interpreted according to the American College of Medical Genetics and Genomics (ACMG) classification system, which categorizes variants into five groups: pathogenic, likely pathogenic, variant of uncertain significance, likely benign, and benign.

5. INDICATIONS FOR GERMLINE BRCA TESTING

Germline *BRCA* mutation testing is recommended for individuals identified as being at high risk for hereditary breast and ovarian cancer. These criteria are adapted from the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Cancer, with modifications to suit the Vietnamese population [8]. Individuals meeting any of the following criteria should be referred for pre-test genetic counseling:

1. Diagnosis of breast cancer before the age of 50.

2. Bilateral breast cancer (synchronous or metachronous).

3. Male breast cancer.

4. Triple-negative breast cancer.

5. Invasive lobular breast cancer with a personal or family history of diffuse gastric cancer.

6. Epithelial ovarian cancer.

7. Having at least one first-degree relative meeting any of the criteria listed in items 1 to 6.

8. Indication for germline *BRCA* testing to guide treatment decisions.

9. Having ≥3 relatives on the same side of the family with breast cancer and/or prostate cancer (at any age).

10. Having a first-degree relative with a known germline *BRCA* mutation or other high-risk breast cancer susceptibility gene mutation.

6. ROLE OF GENETIC COUNSELING

Genetic counseling is an essential component in the management of Hereditary Breast and Ovarian Cancer (HBOC) syndrome. This process includes risk assessment, interpretation of genetic testing, decision-making support, and provision of psychosocial care. All individuals indicated for germline *BRCA* or other HBOC-related genetic testing-whether for diagnostic or therapeutic purposes—should receive comprehensive pre-test and post-test genetic counseling [9].

Prior to testing, genetic counseling helps assess the likelihood of carrying a pathogenic variant and ensures that patients understand the benefits, limitations, and possible outcomes of testing. Post-test counseling focuses on interpreting the

results and developing appropriate surveillance or risk-reduction strategies.

In addition, genetic counseling plays a key role in identifying at-risk family members and facilitating cascade testing. This approach contributes to early detection and cancer prevention at the population level.

In Vietnam, the implementation of genetic counseling and testing services faces several challenges, including high costs, limited availability of trained specialists, and low public awareness. Furthermore, legal frameworks and health insurance systems have yet to provide comprehensive support for these services.

7. RISK-REDUCING STRATEGIES FOR BRCA MUTATION CARRIERS

7.1. Cancer screening and early detection

Individuals carrying, or related to carriers of, germline mutations associated with HBOC are recommended to undergo intensified screening programs for early detection of associated malignancies. Intensified screening refers to the use of more sensitive modalities, earlier initiation, and increased screening frequency. The following recommendations are adapted from ESMO guidelines for the management of HBOC [1].

Breast Cancer Screening:

- For individuals with *BRCA1/2* mutations, ESMO recommends initiating breast cancer screening either 5 years prior to the earliest age of diagnosis in the family or starting at age 30.

- The standard screening modality is breast magnetic resonance imaging (MRI) performed every 6 months.

- In settings where MRI is unavailable: For women aged 30–39 years: breast ultrasound combined with mammography may be considered. For women aged ≥40 years: mammography is recommended, with adjunctive ultrasound when indicated, particularly as breast density decreases with age.

Ovarian cancer screening for germline BRCA mutation (gBRCAm) carriers: according to ESMO's guidelines, screening for ovarian cancer in gBRCAm carriers may include transvaginal ultrasound combined with serum CA-125 measurement every 6 months, starting at the age when risk-reducing salpingo-oophorectomy is typically recommended.

7.2. Risk-Reducing Interventions

Risk-reducing interventions involve prophylactic surgical removal of organs at high risk of malignancy due to germline mutations associated with HBOC. These strategies are typically recommended for individuals confirmed to carry high-risk pathogenic variants. The most targeted organs for prophylactic surgery are breasts and ovaries.

Risk-Reducing Salpingo-Oophorectomy (RRSO): Prophylactic bilateral salpingo-oophorectomy has been shown to reduce overall mortality by up to 77%. Its effect on reducing breast cancer risk remains less clearly defined. RRSO is generally recommended after completion of childbearing, starting at age 35-40 years for *BRCA1* mutation carriers and 40-45 years for *BRCA2* mutation carriers.

Risk-Reducing Mastectomy: Prophylactic bilateral mastectomy can reduce the risk of breast cancer by up to 90%, not only in carriers of pathogenic *BRCA* variants but also in individuals with high-risk mutations in other genes such as *TP53, PTEN,* and *PALB2* [1,10].

For individuals who do not undergo prophylactic mastectomy, endocrine chemoprevention may reduce breast cancer risk by approximately 30-60%. Tamoxifen is commonly prescribed at a dose of 20

mg daily, or alternatively, aromatase inhibitors (AIs) may be used for a duration of 5 years.

8. CONCLUSIONS

Hereditary Breast and Ovarian Cancer (HBOC) syndrome represents a prototypical model of hereditary cancer, with a biological basis rooted in mutations of DNA repair genes, particularly *BRCA1/2*. Advances in genetic testing technologies have significantly expanded the capacity to identify and manage high-risk individuals. Genetic counseling plays a central role in optimizing the benefits of testing and supporting informed clinical decision making. At the same time, targeted therapies such as PARP inhibitors have substantially improved outcomes for patients harboring *BRCA* mutations. However, the widespread implementation of these services remains challenging, particularly in developing countries such as Vietnam. Therefore, comprehensive strategies are needed to enhance awareness, strengthen workforce training, and improve access to genetic services.

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PROGNOSTIC VALUE OF INFLAMMATORY AND IMMUNE INDICES IN NEOADJUVANT CONCURRENT CHEMORADIOTHERAPY FOR ESOPHAGEAL CANCER AT K HOSPITAL

Pham Khanh Toan*, Vo Van Xuan, Tran Trung Bach

ABSTRACT

Objectives: To evaluate the prognostic value of inflammatory–immune indices in patients with esophageal cancer treated with concurrent neoadjuvant chemoradiotherapy at K Hospital.

Subjects and Methods: This retrospective longitudinal study included 57 patients with middle-to-lower thoracic esophageal cancer, histologically confirmed squamous cell carcinoma, stage II–III according to the 8th edition of the AJCC staging system, who were treated with concurrent neoadjuvant chemoradiotherapy at K Hospital from January 2018 to December 2024. Clinical characteristics, paraclinical findings, treatment-related variables, and the NLR(Neutrophil/Lymphocyte), PLR(Platelet/Lymphocyte), and SII indices were collected. Optimal cut-off values were determined using time-dependent ROC curves based on mortality endpoints and the Youden index. Overall survival was analyzed using the Kaplan–Meier method, log-rank test, ROC analysis, and Cox regression.

Results: The median overall survival was 57 months; 3-year and 5-year overall survival rates were 73.3% and 41.9%, respectively. The optimal cut-off values for NLR, PLR, and SII were 5.3, 174.3, and 979.3. Patients with low SII had longer median survival than those with high SII (60 vs. 36 months; p=0.001). SII predicted 3-year overall survival with an AUC of 0.669 (p=0.035). In multivariable analysis, age >=60 years and nodal positivity were independent adverse prognostic factors, whereas low SII was an independent favorable prognostic factor (HR=0.131; 95% CI: 0.024-0.701; p=0.018).

Conclusions: Post-nCRT preoperative SII is a simple and clinically applicable index with prognostic value for overall survival in patients with locally advanced esophageal squamous cell carcinoma treated with neoadjuvant concurrent chemoradiotherapy.

Keywords: Esophageal cancer, concurrent neoadjuvant chemoradiotherapy, SII (Systemic Immune-Inflammation), NLR(Neutrophil/Lymphocyte), PLR(Platelet/Lymphocyte), overall survival.

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1. INTRODUCTION

Esophageal cancer (EC) is the sixth leading cause of cancer-related mortality and the eighth most common cancer worldwide. [1] Esophageal cancer is primarily classified into esophageal squamous cell carcinoma (ESCC) and adenocarcinoma, of which ESCC accounts for approximately 85% [2]. Studies have shown that neoadjuvant chemoradiotherapy (nCRT), neoadjuvant chemotherapy combined with immunotherapy, and neoadjuvant chemotherapy (nCT) alone are the main treatment modalities that improve survival outcomes in patients with resectable locally advanced ESCC. However, the prognosis of esophageal cancer remains limited. [3] Therefore, further studies are needed to identify independent factors that can predict the efficacy of nCRT in patients with locally advanced EC, thereby enabling personalized treatment strategies and more intensive surveillance.

Over the years, accumulating evidence has demonstrated that neutrophils, lymphocytes, platelets, and other inflammatory indices are closely associated with the prognosis of several solid tumors. [4]. Inflammatory–immune indices derived from peripheral blood parameters, such as PLR (platelet-to-lymphocyte ratio), SII (systemic immune–inflammation index), and NLR (neutrophil-to-lymphocyte ratio), which depend on neutrophil, platelet, and lymphocyte counts, have emerged as independent prognostic factors in various cancers in recent years. Currently, the mechanisms by which SII influences the prognosis of esophageal cancer remain unclear. Some studies suggest that neutrophils can activate endothelial and stromal cells, enhance adhesion of circulating tumor cells, and promote distant metastasis. Lymphocytes play a crucial role in anti-tumor immunity, whereas platelets, activated by tumor cells, may disrupt endothelial barriers, facilitating tumor metastasis and dissemination. [4], [5] Retrospective studies have shown that NLR, PLR, and SII have certain predictive value for the efficacy of neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer [6].

Regarding SII in patients with locally advanced ESCC undergoing nCRT, Zhang H et al. (2024) reported that improved overall survival (OS) was associated with lower SII (≤916.6 × 10^9 / L) in the neoadjuvant chemoradiotherapy group ($p = 0.034$). Patients with lower SII receiving nCRT had significantly better OS ($p < 0.001$). Furthermore, higher SII was associated with a lower resection rate ($p = 0.035$) [7].

In Vietnam, there has been little evidence on studies conducted to clarify the role of systemic inflammatory–immune indices in predicting survival outcomes in patients with locally advanced esophageal cancer treated with neoadjuvant concurrent chemoradiotherapy. Therefore, this study was carried out with the objective: "Assessment of the prognostic value of inflammatory–immune indices in neoadjuvant concurrent chemoradiotherapy for esophageal cancer at K Hospital".

2. SUBJECTS AND METHODS

2.1. Research subjects

This study included 57 patients with esophageal cancer who underwent neoadjuvant concurrent chemoradiotherapy at K Hospital from January 2018 to December 2024, meeting the inclusion and exclusion criteria.

Inclusion criteria:

- Patients with middle-to-lower third esophageal cancer with histologically confirmed squamous cell carcinoma (SCC).

- Locally advanced stage: cT1b–cT2, N (+); cT3–cT4a, any N (stage II–III according to the AJCC 8th edition).

- Indicated for neoadjuvant concurrent chemoradiotherapy.

- Complete medical records, including inflammatory–immune indices.

Exclusion criteria:

- Not meeting inclusion criteria.

- Distant metastatic disease (M1) according to the AJCC 8th edition.

- Presence of a second primary malignancy.

- Incomplete neoadjuvant chemoradiotherapy regimen, defined as failure to complete the planned concurrent chemotherapy cycles and/or radiotherapy course because of toxicity, disease progression, withdrawal, or other medical reasons.

- Not eligible for surgery or refusal of surgery.

- Patients who declined participation in the study.

2.2. Methods

Study design: Retrospective descriptive study with longitudinal follow-up.

Sampling method: Convenience sampling.

Research procedure:

- Select patients meeting inclusion and exclusion criteria.

- Collect clinical and paraclinical characteristics: age, sex, tumor features on endoscopy, and computed tomography imaging (location, size, morphology, characteristics).

- Collect treatment-related variables: chemotherapy regimen, radiotherapy technique, prescribed radiation dose and fractionation, treatment compliance, and the interval between completion of concurrent chemoradiotherapy and surgery. Radiotherapy was delivered using 3D-CRT or IMRT/VMAT according to institutional practice, with a preoperative dose/fractionation schedule recorded from the medical record. The inflammatory and immune indices used in this analysis were measured after completion of neoadjuvant chemoradiotherapy and within 1-2 weeks before surgery, using the most recent complete blood count before surgery. NLR was calculated as absolute neutrophil count/ absolute lymphocyte count; PLR as platelet count/ absolute lymphocyte count; and SII as platelet count x absolute neutrophil count/absolute lymphocyte count. Optimal cut-off values were determined using ROC curves based on 3-year mortality endpoints and the Youden index.

Periodically follow up and record overall survival. Follow-up was completed in September 2025.

Statistical analysis:

- Data were analyzed using SPSS version 26.0.

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

Associations between variables were assessed us- ing the chi-square (χ^2) test or Fisher's exact test.

- Spearman correlation analysis was used to evaluate the relationships between NLR, SII, and PLR.

- Overall survival (OS) was estimated using the Kaplan–Meier method.

- Differences between groups were analyzed using the log-rank test.

- Hazard ratios (HRs) were estimated using Cox proportional hazards regression. To reduce the risk of overfitting in this small cohort, multivariable models were limited to clinically relevant variables and variables with $p<0.10$ in univariate analysis; results were interpreted as exploratory.

- Predictive performance was assessed using the area under the curve (AUC) of time-dependent ROC analysis to evaluate the prognostic value of SII for 1-year and 3-year overall survival.

A p-value < 0.05 was considered statistically significant.

3. RESULTS

3.1. Clinical and paraclinical characteristics and treatment regimens

Table 1. Clinical and paraclinical characteristics and treatment regimens

Characteristics		n	Percentage (%)
Age	≥60	32	56.1
	<60	25	43.9
	Total	57	100
	Mean	60.5±6.6 (48-75)	
Gender	Male	56	98.2
	Female	1	1.8
Tumor location	Middle third	23	40.4
	Lower third	34	59.6
Tumor length	≤ 7 cm	33	57.9
	>7 cm	24	42.1
T stage	T1	1	1.8
	T2	25	43.9
	T3	25	43.9
	T4	6	10.4
N stage	N0	16	28.1
	N1-2	41	71.9
Chemotherapy regimen	CF	7	12.3
	TC	50	87.7
Radiotherapy technique	3D-CRT	15	26.3
	IMRT/VMAT	42	73.7

Comment: The mean age of the study population was 60.5 ± 6.6 years. Patients aged ≥60 years accounted for the majority (56.1%). The oldest patient was 75 years and the youngest was 48 years. Most patients were male (98.2%). Tumors located in the lower third of the esophagus were predominant (59.6%), followed by the middle third (40.4%). Tumor length ≤7 cm was more common than >7 cm, accounting for 57.9% and 42.1%, respectively. T1–2 stage accounted for 45.7%, while 54.3% were in T3–4 stage. The majority of patients had nodal metastasis (N1–2),

accounting for 71.9%. Most patients (87.7%) received the TC concurrent chemotherapy regimen. A total of 73.7% of patients were treated with IMRT/VMAT radiotherapy techniques.

3.2. Inflammatory-immune indices

Table 2. Inflammatory-immune indices

Index	n	%
NLR		
≤5.3	51	89.5
>5.3	6	10.5
PLR		
≤174.3	38	66.7
>174.3	19	33.3
SII		
≤979.3	42	73.7
>979.3	15	26.3

Comment: Using ROC curve analysis based on mortality at the specified time point and the Youden index, the optimal cut-off values for inflammatory-immune indices were determined as follows: SII 979.3, NLR 5.3, and PLR 174.3. The majority of patients were in the low SII group (73.7%) and had NLR ≤5.3 (89.5%); approximately one-third had PLR >174.3 (33.3%).

3.3. Association between SII, NLR levels and related factors

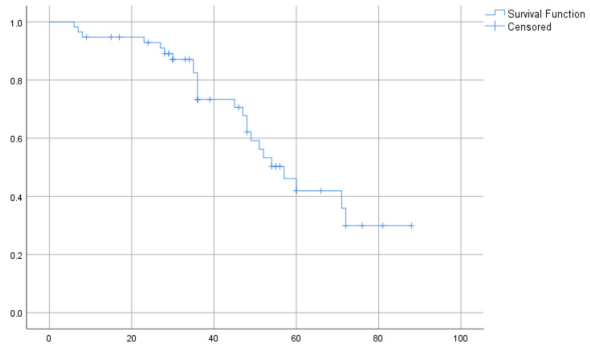
Table 3. Association between SII, NLR levels and related factors

Characteritics		SII		p	NLR		p
		High (n)	Low (n)		High (n)	Low (n)	
Age group	≥60	8	17	0.546	1	31	0.077
	<60	7	25		5	20	
Gender	Male	14	41	0.461	6	49	1.000
	Female	1	1		0	2	
T stage	T1-2	8	18	0.554	2	24	0.678
	T3-4	7	24		4	27	
N stage	N0	6	10	0.317	1	15	0.665
	N(+)	9	32		5	36	
Tumor location	Middle third	8	26	0.760	5	29	0.385
	Lower third	7	16		1	11	

Characteritics		SII		p	NLR		p
		High (n)	Low (n)		High (n)	Low (n)	
Tumor length	≤ 7cm	9	24	0.847	1	32	0.073
	>7cm	6	18		5	19	
Chemotherapy regimen	CF	4	3	0.070	2	5	0.153
	TC	11	39		4	46	
Radiotherapy technique	3D	6	9	0.949	5	10	0.197
	IMRT/VMAT	13	29		3	39	

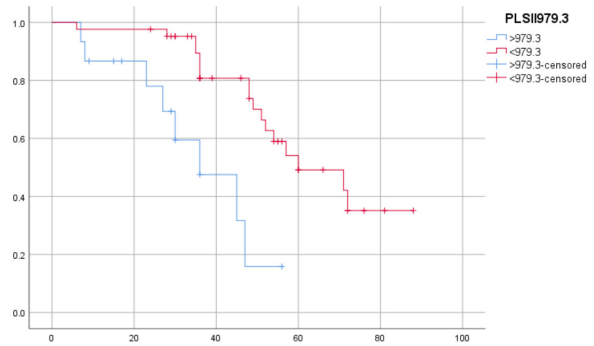
Comment: No statistically significant associations were observed between SII or NLR and age, sex, T/N stage, tumor length, chemotherapy regimen, or radiotherapy technique ($p > 0.05$). Borderline trends toward significance were noted for NLR with age ($p = 0.077$) and tumor length ($p = 0.073$), and for SII with chemotherapy regimen ($p = 0.070$).

3.4. Overall survival (OS)



Trung vị	ĐLC	95% CI
57.00	5.300	46.613-67.387

Figure 1. Overall survival of the study population



SII	Trung vị	ĐLC	95% CI	Log Rank (Mantel-Cox): 11.991 (p=0,001)
>979.3	36.000	8.492	19.355-52.645	
<979.3	60.000	9.909	40.578-79.422	

Figure 2. Overall survival according to SII groups

Comment: Among the 57 patients, the 3-year overall survival rate was 73.3% and the 5-year overall survival rate was 41.9%, with a median overall survival of 57 ± 5.3 months (95% CI: 46.4-67.4 months). The median overall survival was 36 months (95% CI: 19–52) in the high SII group and 60 months (95% CI: 46–67) in the low SII group. The corresponding 3-year overall survival rates were 47.5% and 80.8%, respectively (log-rank = 11.991; $p = 0.001$).

3.5. ROC curve of SII for predicting overall survival

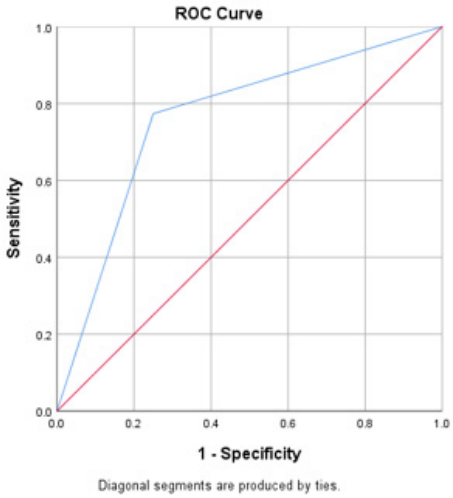


Figure 3. ROC curve of SII for predicting 1-year overall survival

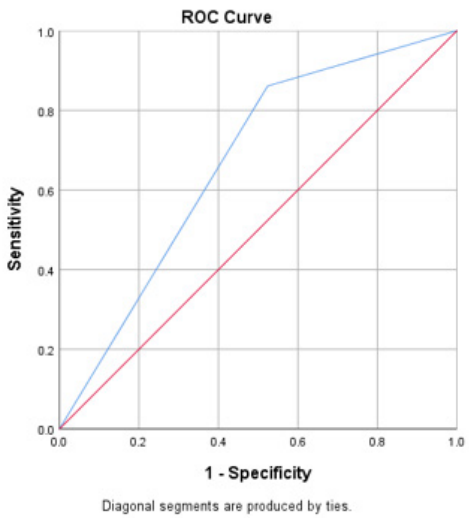


Figure 4. ROC curve of SII for predicting 3-year overall survival

Comment: Preoperative SII following neoadjuvant chemoradiotherapy showed a trend toward predicting 1-year overall survival (AUC = 0.762; 95% CI: 0.506-1.000), although this did not reach statistical significance (p = 0.083). For 3-year overall survival, SII demonstrated an AUC of 0.669 (95% CI: 0.516-0.882; p = 0.035), indicating a moderate but statistically significant ability to stratify long-term mortality risk.

3.6. Univariate and multivariable Cox proportional hazards regression analysis for overall survival

Table 4. Univariate and multivariable Cox proportional hazards regression model for overall survival

Characteristics	Univariate analysis			Multivariable analysis		
	HR	95% CI	p	HR	95% CI	p
Age group (≥60/<60)	1.879	0.879-4.285	0.136	6.602	1.821-20.195	0.003
T stage (T3-4/T1-2)	2.139	0.923-4.953	0.076	2.433	0.772-7.665	0.129
N stage (N+/N0)	2.210	0.757-6.451	0.147	5.228	1.328-20.579	0.018
Tumor location (Middle/Lower third)	1.054	0.471-2.359	0.898			
Tumor length (>7cm/≤7cm)	2.830	1.249-6.414	0.013	1.062	0.319-3.542	0.922
Chemotherapy (TC/CF)	1.414	0.480-4.162	0.529			
SII (≤979.3/>979.3)	0.225	0.089-0.567	0.002	0.131	0.024-0.701	0.018
PLR (≤174.3/>174.3)	0.131	0.044-0.389	<0.001	0.656	0.213-2.016	0.462
NLR (≤5.3/>5.3)	0.566	0.255-1.256	0.162	0.326	0.048-2.238	0.254

Comment: In univariate analysis, tumor length >7 cm was associated with poorer overall survival (HR = 2.830; p = 0.013); both SII and PLR were statistically significant (SII: HR = 0.225; p = 0.002; PLR: HR = 0.131; p < 0.001). Multivariable analysis demonstrated that age ≥60 years and positive nodal status (N+) were independent adverse prognostic factors for overall survival (HR = 6.602; 95% CI: 1.821-20.195; p = 0.003) and (HR = 5.228; 95% CI: 1.328-20.579; p = 0.018), respectively. PLR and NLR were no longer significant after adjustment. Notably, low SII was identified as an independent favorable prognostic factor for overall survival (HR = 0.131; 95% CI: 0.024-0.701; p = 0.018).

4. DISCUSSION

In this cohort of 57 patients, the mean age was 60.5 +/- 6.6 years, and most patients were male (98.2%), which is consistent with the epidemiological pattern of esophageal squamous cell carcinoma. Tumors were most frequently located in the lower third of the esophagus (59.6%), and most patients had locally advanced disease with nodal positivity (71.9%). These baseline findings are broadly comparable with previous cohorts of locally advanced ESCC treated with neoadjuvant chemoradiotherapy, including the study by Zhang H et al [7].

Most patients received the TC regimen (paclitaxel-carboplatin) and IMRT/VMAT was used in 73.7% of cases. These treatment characteristics reflect current institutional practice for patients eligible for neoadjuvant concurrent chemoradiotherapy followed by surgery. Because radiation dose, chemotherapy regimen, surgical approach, and patient condition may influence survival, they should be considered when interpreting associations between inflammatory indices and overall survival.

The biological mechanisms underlying inflammatory–immune indices are closely related to the role of inflammation in cancer progression. Neutrophils can activate endothelial and stromal cells, enhance the adhesion of circulating tumor cells, and promote metastasis. Lymphocytes play a key role in anti-tumor immune responses, whereas platelets, activated by tumor cells, facilitate tumor dissemination and metastasis. Therefore, these indices reflect the balance between tumor-promoting inflammation and anti-tumor immunity. In our study, the optimal cut-off values were SII = 979.3, NLR = 5.3, and PLR = 174.3. Based on these thresholds, 73.7% of patients had SII ≤979.3, 89.5% had NLR ≤5.3, and 66.7% had PLR ≤174.3. Zhang H et al. (2024) reported a similar SII cut-off of ≤916.6 × 10^9/L. [7] Zheng Z et al. (2021) reported a lower NLR cut-off (2.20), which may be explained by differences in study populations, cut-off determination methods (ROC curve vs. Cut-off Finder), and disease stages [9].

We did not observe statistically significant associations between SII and clinical factors such as age, sex, T/N stage, radiotherapy technique, or chemotherapy regimen (p > 0.05), consistent with Zhang's findings. [7] However, borderline trends were observed between SII and chemotherapy regimen (p = 0.070), and between NLR with age and tumor length (p = 0.077 and p = 0.073), suggesting a potential relationship between inflammatory response and treatment or tumor burden that warrants further investigation.

The median overall survival (OS) in our study was 57 ± 5.3 months, with 3-year and 5-year OS rates of 73.3% and 41.9%, respectively. These outcomes are better than those reported by Zhang et al. (median OS: 40 months; 3-year OS: 52.6%). [7] This may reflect differences in treatment strategies, radiotherapy techniques, and surgical management.

Our findings confirm the important prognostic role of SII. Zhang H et al. (2024) also demonstrated that patients with lower SII (≤916.6×10^9/L) had significantly better OS when treated with neoadjuvant chemoradiotherapy (p < 0.001). [7]

A meta-analysis by Gao GH reported that elevated SII was significantly associated with shorter OS in patients with surgically resected ESCC (HR: 1.34; 95% CI: 1.15–1.53; $p < 0.001$), supporting the role of SII as a prognostic biomarker. [5] The underlying mechanisms may include: (1) elevated neutrophils reflecting systemic inflammation that promotes tumor progression; (2) decreased lymphocytes indicating impaired anti-tumor immunity; and (3) increased platelets facilitating tumor embolism formation and immune evasion.

ROC curve analysis is a key method for evaluating predictive performance. The area under the curve (AUC) reflects discriminatory ability, with AUC >0.7 indicating good predictive value. In our study, SII showed an AUC of 0.762 for 1-year OS ($p = 0.083$) and 0.669 for 3-year OS ($p = 0.035$), indicating moderate predictive performance. Compared with Zhang et al. (AUC: 0.725 for 1-year and 0.634 for 3-year OS), our results suggest slightly improved predictive accuracy. [7] Thus, SII is a non-invasive, simple, and clinically applicable biomarker.

Univariate Cox analysis identified several prognostic factors, including tumor stage, tumor size, tumor length, treatment response, and inflammatory indices. Zhou XL et al. (2017) reported that elevated baseline NLR was independently associated with poorer progression-free survival (PFS) and OS (HR = 1.529 for PFS; HR = 1.856 for OS; $p < 0.001$). [8] Zheng Z et al. also confirmed the prognostic value of NLR and PLR in univariate analysis. [9]

Multivariable analysis is essential to identify independent prognostic factors. Zhang H et al. (2024) demonstrated that low SII (≤916.6 × 10^9/L) was an independent predictor of improved OS ($p = 0.040$), along with neoadjuvant chemoradiotherapy ($p = 0.034$). [7] Furthermore, higher SII was associated with a lower resection rate ($p = 0.035$), suggesting its role in predicting treatment response and surgical eligibility.

In our study, multivariable analysis identified three independent prognostic factors: age ≥60 (HR = 6.602; $p = 0.003$), 1/3 (HR = 5.528; $p = 0.018$), and low SII as a protective factor (HR = 0.131; $p = 0.018$). These findings are consistent with Zhang et al., in which SII was the strongest independent prognostic factor. [7] Therefore, SII is not only an inflammatory marker but also a valuable tool for clinical risk stratification in esophageal cancer.

Other studies have also confirmed the prognostic value of inflammatory-immune indices. Zheng Z identified NLR as an independent prognostic factor in resectable ESCC. [9] Man Q et al. (2024) reported that NLR, PLR, and TNM stage were independent predictors of both PFS and OS. [10] Additionally, studies evaluating PLR and SII in patients undergoing neoadjuvant chemoradiotherapy have demonstrated that both indices serve as independent prognostic factors.

Study limitations

This study has several limitations. First, the retrospective single-center design and small sample size may limit statistical power and external validity. Second, selection bias is possible because only patients who completed neoadjuvant chemoradiotherapy and proceeded to surgery were included; therefore, the findings may not apply to patients who were medically inoperable, refused surgery, or progressed before surgery. Third, inflammatory and immune indices were measured after nCRT and before surgery rather than at baseline; these indices may be affected by radiation-related inflammation, infection, leukopenia, nutritional status, or treatment toxicity. Fourth, the ROC-derived cut-off values were not externally validated and should be confirmed in larger independent cohorts. Fifth, the limited number of events increased the risk of overfitting in Cox regression, despite restricting the multivariable model. Finally, some important variables such as ECOG performance status,

pathological complete response, surgical margin status, disease-free survival, and recurrence patterns were not available for comprehensive analysis.

5. CONCLUSION

The systemic immune–inflammation index (SII) has prognostic value for overall survival in patients with locally advanced esophageal squamous cell carcinoma treated with neoadjuvant concurrent chemoradiotherapy. Low SII is an independent favorable prognostic factor, whereas age ≥60 years and positive nodal status are independent adverse prognostic factors. SII is a simple, readily applicable biomarker with potential utility for clinical risk stratification.

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RESULTS OF QUALITY CONTROL IN PATHOLOGY THROUGH THE EXTERNAL QUALITY ASSESSMENT PROGRAM IMPLEMENTED IN VIETNAM DURING THE PERIOD 2021-2025

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ABSTRACT

External quality assessment (EQA) is an important tool to control quality tests. In the period from 2007 to 2025, the Center for standardization and quality control in medical laboratory (CSQL) has continuously developed and implemented a wide range of EQA programs, ranging from routine to specialized schemes, with the aim of supporting laboratories in improving testing quality. The number of laboratories participating in EQA by CSQL has rapidly increased from 50 participants (2007) to 3,800 participants (2025). The Pathology EQA program has been implemented since 2021. After five years of implementation, Pathology laboratories have shown increasing attention in participation as part of their effort to enhance analytical quality at their institutions.

This study aims to evaluate the quality control results of pathological examination in the period 2021-2025 through data analysis from the Pathological EQA Program implemented by CSQL. This study is based on EQA data collected from all Pathology laboratories participating in the program. The main indicators reflecting the quality control results include number of participants, number of histopathologies analyzed and evaluated the proportion of acceptable analytical results and frequency of recorded errors types (e.g. diagnostic errors, technical errors). The data were analyzed using descriptive statistics and trend analysis methods.

The research results show that the number of Pathology Departments nationwide participating has increased every year since 2021 with 09 Pathology Departments participating, increasing to 40 Pathology Departments participating in 2025. The percentage of participating hospital models

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including specialized hospitals 39%, general hospitals 39%, private general hospitals 11% and private laboratories 11%. The number of histopathology groups evaluated increased from 7 to 18 different tissue groups including general and specialized fields, the number of samples (number of cases) analyzed is 18 (in 2021) increased to 156 cases (in 2025). Statistics show that some types of tissues are commonly deployed according to the model and characteristics of each Pathology laboratory (including stomach, gastric biopsy, uterus, breast, thyroid, colon, liver, lung, brain,...).

Keywords: External quality assessment, pathology, quality assurance.

1. INTRODUCTION

Pathology plays a fundamental role in modern medicine by providing definitive diagnoses for a wide range of diseases, particularly malignancies, thereby guiding appropriate treatment strategies. Due to its complexity and high level of expertise required, ensuring quality in pathology testing is essential to prevent diagnostic errors and inappropriate clinical decisions.

Quality in pathology is evaluated based on three key criteria: accuracy, timeliness, and completeness of diagnostic reports [1]. Errors in any of these aspects may lead to serious consequences, including misdiagnosis, delayed treatment, and increased mortality risk [1]. Quality management in pathology requires a comprehensive approach covering all phases of the testing process: Pre-analytical errors: patient misidentification, incorrect specimen site, specimen loss, non-representative samples, insufficient clinical information, Analytical errors: false positive/negative results, incorrect classification (benign vs malignant), grading errors, Post-analytical errors: incomplete or incorrect reports, transcription errors. Therefore, quality management must focus not only on minimizing random errors but also on detecting and preventing systematic technical and interpretative errors that may directly impact patient outcomes.

The Center for Standardization and Quality Control in Medical Laboratory (CSQL) is the first institution in Vietnam to implement a national EQA program in pathology, alongside international providers such as UK NEQAS, CAP, Labquality, and the Royal College of Pathologists. After five years of implementation, this study was conducted to evaluate the effectiveness of pathology quality management through the national EQA program and to provide direction for further improvement.

2. MATERIALS AND METHODS

2.1. Materials

The study included all EQA data from pathology laboratories participating in the program from 2021 to 2025.

Collected information included: hospital name, laboratory identification code (anonymized), facility type (specialized or general hospital), and ownership (public or private).

All case-related data and EQA slides were anonymized according to the program's confidentiality procedures.

2.2. Methods

This study employed a retrospective, descriptive cross-sectional method to analyze the results of the EQA GPB program implementation nationwide from 2021 to 2025.

Data were continuously collected from the management system of the Center. All administrative and specimen data were anonymized.

Outcome indicators included number of participating laboratories, number of EQA rounds, laboratory classification, number of samples evaluated, proportion of acceptable results, and frequency of errors.

Diverse models: The EQA program closely followed the disease patterns at PGPB, helping to keep quality management focused and aligned with actual needs

2.3. Evaluation framework and Acceptance Criteria

Evaluation criteria: EQA results were evaluated by a panel of experts on a scale of 0-5 for each evaluation category, including: technique (tissue preparation, tissue fixation, cutting, staining, and complete slide preparation) and diagnostic evaluation (accuracy of diagnosis and interpretation of results).

Table 1: Outpatient evaluation framework for the external audit program

Content evaluation	
Technical evaluation	**Diagnostic evaluation**
Sufficient tissue quantity as described macroscopically	No results
The section is positioned between the slides, without wrinkles, folds, or tissue tears	Results lacking microscopic description or inconclusive disease findings
The lamination completely covers the cut piece, with no air bubbles	The microscopic description and diagnosis are inappropriate
The cut pieces have the appropriate thickness and absorb color evenly	The microscopic description and pathological conclusions do not fully match the tissue sample
The nuclear and cytoplasmic components stain correctly, and the nuclear membrane and chromatin are clearly visible	The microscopic description and pathological findings are entirely consistent with the tissue sample
Sufficient tissue quantity as described macroscopically	The microscopic description and pathological findings are entirely consistent with the tissue sample and include reasonable recommendations

This evaluation standard references the quality control requirements of ISO 15189 and framework evaluation references from international EQA organizations (CAP, UK NEQAS).

The unit of analysis was individual cases. The aggregated results were calculated per case, summarizing general data for each period and cycle (year) of each PGPB and the overall statistical results of the program.

2.4. Expert panel and standard answer development process

Establishing a "gold standard": The gold standard was developed through a consensus consultation by a panel of experts based on original specimens and clinical data. The expert panel consisted of pathology specialists from central and provincial/city hospitals with extensive professional experience and was selected by the

science and technology council of the Center for Clinical Laboratory Technology. The expert panel was established according to Decision No. 91/ QD-KCXN dated April 16, 2024, and Decision No. 212/QD-KCXN.

Each specimen was independently scored by at least three members of the expert panel. If consensus was not reached, the specimen was sent for further consultation.

Specimens submitted to the expert panel were fully encrypted (using a coding process to anonymize participating pathology laboratories) to ensure objectivity. The study used encrypted and anonymized secondary administrative data. The reported results were based solely on aggregated data.

2.5. Data collection and statistical analysis of results

He evaluation results were continuously monitored from the first year of implementation (2021) to 2025.

Data was calculated using Excel 2010 software.

3. RESULTS AND DISCUSSION

3.1. Number of laboratories participating in external quality control over the years

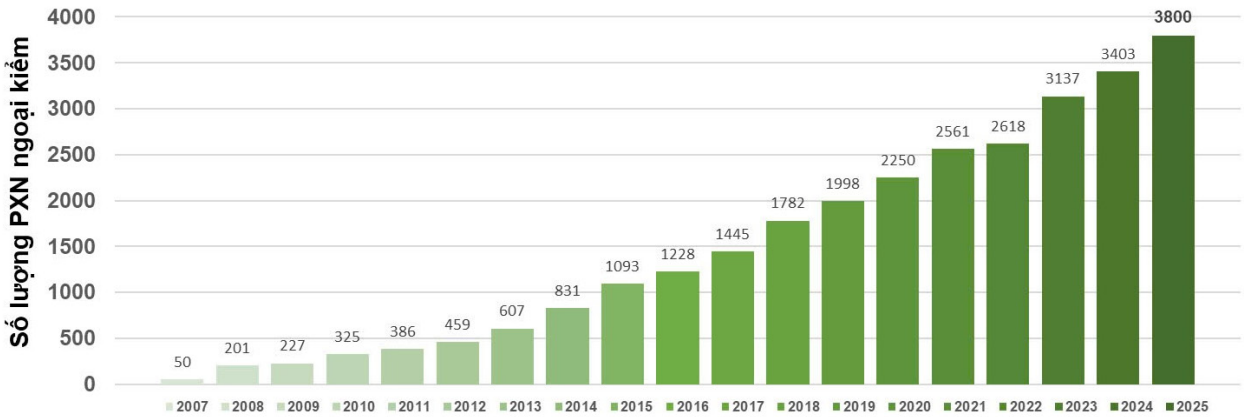

Figure 1: Total number of laboratories participating in EQA programs at CSQL (2007-2025)

Statistics show that the focus on quality management in laboratory testing, from routine to specialized, has increased over the years, from 50 laboratories (in 2007) to 3.800 laboratories (in 2025).

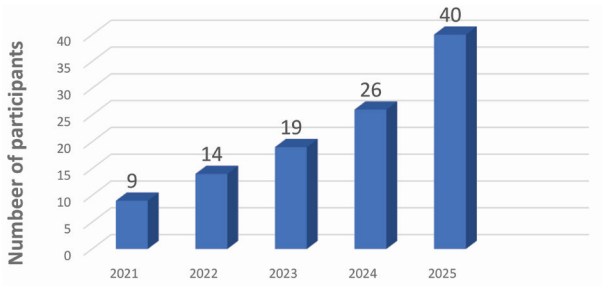

Figure 2: Number of Pathology labs participating in external audits over the years

Research on the implementation of external quality control shows an increase in the number

of participating laboratories in the external quality control program, from 9 laboratories (in 2021), the first year the Center for Laboratory Quality Control officially implemented the program, to 40 laboratories (in 2025). This continuous upward trend reflects the interest of healthcare facilities in quality control of laboratory testing and confirms the effectiveness of the external quality control program for laboratories.

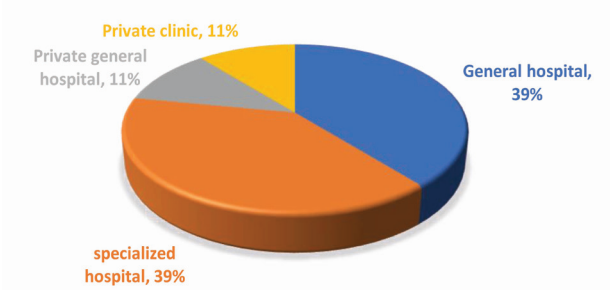

Figure 3: Statistics of hospitals/laboratories participating in the EQA pathology

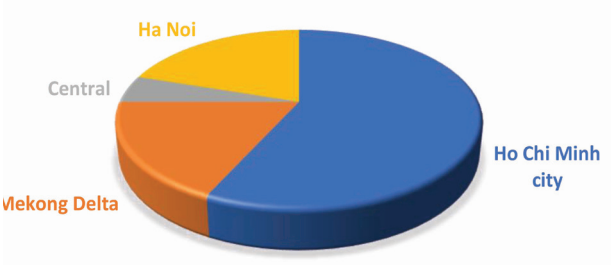

Figure 4: Geographical distribution of hospital/ laboratories participating in the EQA pathology

Geographic distribution statistics show that the majority of participating laboratories are concentrated in 3 regions Ho Chi Minh city: 57%; Ha Noi city: 20%; Mekong Delta: 18%; behide 5% participants in central.

3.2. Statistical analysis of the quantity and characteristics of histopathological tissues in external quality assessment

Table 2: Statistics on the number and types of tissues subjected to external quality assessment over the years

2021		2022		2023		2024		2025	
Tissue	**Quantity**	**Tissue**	**Quantity**	**Tissue**	**Quantity**	**Tissue**	**Quantity**	**Tissue**	**Quantity**
Colon	7	Colon	8	Uterus and ovaries	12	Lung tissue	13	Stomach biopsy	20
Breast tissue	5	Thyroid gland	8	Breast tissue	8	Stomach	11	Stomach	18
Stomach-biopsy	2	Breast tissue	8	Lung	8	Liver tissue	11	Uterus	18
Thyroid gland	1	Ovaries	7	Stom-ach biopsy	7	Cervix	9	Ovaries	16
Stomach polyps	1	Brain tumor	5	Brain tumor	6	Kidney	7	Liver tissue	12

2021		2022		2023		2024		2025	
Tissue	**Quantity**	**Tissue**	**Quantity**	**Tissue**	**Quantity**	**Tissue**	**Quantity**	**Tissue**	**Quantity**
Colon polyps	1	Stomach biopsy	4	Colon	5	Breast tumors	7	Thyroid gland	12
Appendix	1	Prostate gland	3	Prostate gland	4	Ovaries	6	Kidney tissue	10
-	-	Bladder	2	Bladder	3	Stomach	6	Lung tumors	10
-	-	Lung	2	Liver tissue	3	Colon	6	Stomach	8
-	-	Gallbladder	2	Thyroid gland	3	Brain tumor	6	Colon	8
-	-	salivary glands	2	Kidney	2	Thyroid gland	3	Colon	6
-	-	Stomach	1	Gallbladder	2	Cervical lymph nodes	2	Stomach	4
-	-	Colon polyps	1	Salivary glands	2	Nasal tumor	2	Breast tissue	4
-	-	Gallbladder	1	Nasal tumor	2	Jaw angle region	1	Testis	2
-	-	Jaw angle region	1	Jaw angle region	1	Submandibular gland	1	Prostate gland	2
-	-	-	-	Brain	1	Salivary glands	1	Nasal tumor	2
-	-	-	-	Larynx	1	Prostate gland	1	Brain tumor	2
-	-	-	-	Submandibular gland	1	Nasopharynx	1	Bone tumor	2

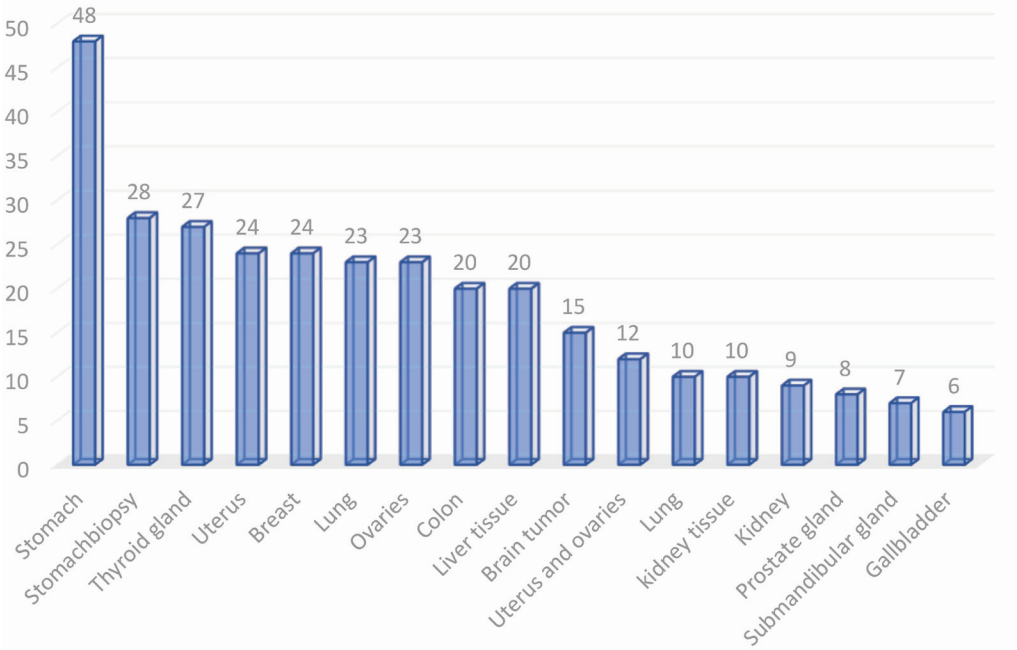

Figure 5: Statistics of the most frequently deployed tissue types over 5 years

The external quality control program for tissue samples at the CSQL was implemented with a focus on disease patterns and aligns with the list of procedures currently being performed by the tissue sample processing units. Therefore, the diversity of tissue types performed over the years is evident (Table 1), and the tissue types most frequently subjected to external quality control by the tissue sample processing units over the past five years are shown (Figure 4). This demonstrates that the external quality control program has met the needs for quality control of the techniques performed by the tissue sample processing units, focusing on the correct techniques and aligning with the list of techniques being implemented at the unit, thus improving diagnostic work at the unit.

Case distribution and difficulty level (malignant/benign): In the total number of cases (18 cases in 2021 to 156 cases in 2025), the proportion of malignant/benign cases was balanced to ensure representativeness of the practical work of the clinical Pathology Laboratories. Specifically, the proportion of malignant cases (e.g., Carcinoma 39) is maintained at 30-40% of the total cases annually, with the remainder being benign tumors, sarcomas, or other pathologies. The proportion of cases requiring staging or difficult diagnosis is maintained at 15-20% to challenge the Pathology Laboratories, as reflected in the number of Carcinoma cases evaluated. The distribution of pathologies or case difficulty levels will be adjusted over time depending on the number of participants in the program and quality improvements through annual external quality control data.

3.3. Results of external audits over the years

To comprehensively evaluate the performance of the Pathology Laboratories, the approach includes all three stages of the testing process,

from the technical preparation of specimens to the analysis and reporting of results. The study showed that the external quality control results over the five years of the participating pathology laboratories were relatively good.

Table 3: Statistics on the implementation results of the pathology laboratories over 5 years

		2021	2022	2023	2024	2025
Results of implementation	Acceptable results	100%	100%	99%	100%	99%
	Results for review	0%	0%	1%	0%	1%
	Unacceptable results	0%	0%	0%	0%	0%
Number of cases evaluated Carcinoma		9	20	20	26	22(*)

(*) 2025: At the time of compiling research results, the evaluation results of sample batch 02 were not yet available, so the reported data was based on data up to the end of August 2025.

The research results show that the external quality assessment (EQA) performance of the histopathology laboratories was being maintained at a relatively high level of good evaluation (Figure 5), with the percentage of results requiring technical review or evaluation being approximately 1%. Several technical errors were recorded and commented on directly in the result analysis reports sent to the EQA: tissue fixation technique, slice thickness, staining accuracy of the staining method, or contaminated specimens, etc. Some errors in result evaluation include: incomplete microscopic description, determination of the degree of tumor cell invasion, lack of clinical orientation, etc.). Technical and diagnostic errors were directly recorded by the expert panel in coded result evaluation forms sent with the external quality control slides. Statistics also show the number of cases with recorded carcinomas performed over the years and the percentage of EQA s with correspondingly satisfactory external quality control results. This result was significant in ensuring the role of histopathology in the diagnosis and treatment of malignant diseases.

The current program uses a specific scoring system; however, the conclusions regarding quality standards are currently "good," "needs improvement," and "unacceptable." This needs to be adjusted with more specific evaluation levels to correspond to the statistical evaluation scale, ensuring a more accurate reflection of quality and contributing to the improvement of laboratory quality.

Selection Bias: Participation in the EQA program is voluntary. Therefore, PGPBs with better capabilities and a focus on quality management tend to participate earlier and more regularly. However, the continuous increase in the number of participating pathology laboratories over the years (from 9 to 40) shows that the program is gradually expanding its coverage, minimizing the impact of this bias. pathology laboratories need to actively participate in EQA to gain an objective view of their unit's quality, thereby enabling effective corrective and preventive actions to achieve reliable diagnostic results.

4. CONCLUSION

Quality management of histopathology was not just a technical process but a comprehensive

system requiring close coordination from many different aspects. In Vietnam, significant progress has been made in implementing the external quality control program for histopathology to support histopathology laboratories.

EQA data has demonstrated that the results of quality management in histopathology testing in Vietnam have shown significant improvements during the 2021-2025 period. The participation rate in the program has increased, along with the maintenance of satisfactory evaluation results in external quality control by histopathology laboratories, and the diversification of histopathology techniques suitable for practical implementation at the units. The research results show that the program has contributed to improving quality management at histopathology laboratories nationwide.

5. RECOMMENDATIONS

To further improve quality control results in the field of Pathology, the author proposes the following recommendations:

- When receiving non-conforming external quality control results, the pathology laboratories needs to study recommendations from the external quality control program implementing unit and have a plan for corrective and preventive measures, applying some statistical quality assurance tools suitable to the unit's reality [4].

- The current external quality control program needs to be expanded to include more types of specimens, disease groups and more specialized techniques such as immunohistochemistry and in situ hybridization [5]. This will help meet the increasing needs of pathology laboratories in quality control.

- Develop a more advanced online EQA management system, allowing virtual sample submission, rapid feedback and more in-depth data analysis, while facilitating the continuous collection and analysis of pathology laboratories quality control results.

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SURGICAL TREATMENT OUTCOMES OF FACIAL BASAL CELL CARCINOMA AT VIET TIEP FRIENDSHIP HOSPITAL

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ABSTRACT

Objective: To evaluate the treatment outcomes of facial basal cell carcinoma.

Patients and methods: A descriptive study was conducted on patients with facial basal cell carcinoma treated at Viet Tiep Friendship Hospital from January 2023 to March 2026.

Results: The study included 29 patients with facial basal cell carcinoma. The mean age was 72.03 ± 14.65 years (range: 39-100 years), with the 60-80year age group accounting for the highest proportion (44.8%). Females predominated (62%). The disease duration was mainly less than 3 years (96.5%), with less than 1 year accounting for 51.7%. The most common tumor location was the cheek (34.5%). Tumor size <2 cm accounted for 55.2%, and a surgical margin of 5-10 mm was used in 96.6% of cases. Local flap reconstruction was the most frequently used technique, with rotation flaps accounting for 34,5%. No intraoperative complications occurred in 86% of patients. The rate of good early postoperative outcomes was 93.1%. At the 3-month follow-up, 95.8% of flaps demonstrated good color and thickness, while 93.1% showed good scar outcomes, indicating favorable functional and aesthetic results.

Keywords: Skin cancer, basal cell carcinoma, facial area.

1. INTRODUCTION

Skin cancer is one of the most common malignancies, particularly prevalent among Caucasians and individuals living in regions with high levels of ultraviolet radiation exposure. According to the World Health Organization [1], the incidence of skin cancer has increased significantly in recent decades. Each year, approximately 2-3 million cases of non-melanoma skin cancer and around 132,000 cases of melanoma are reported worldwide [1]. The three main types of skin cancer include basal cell carcinoma, squamous cell carcinoma, and adnexal skin tumors.

Basal cell carcinoma (BCC) is the most common type of skin cancer, arising from the basal layer of the epidermis and skin adnexal structures. It generally has a favorable prognosis, with rare lymphatic or distant metastasis, and accounts for approximately 70-80% of all skin cancer cases. Lesions typically occur in sun-exposed areas such as the head, face, neck, and arms, with the facial

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region being the most frequently affected site [2,3]. The disease mainly progresses through local invasion and may extend into adjacent structures such as subcutaneous tissue, cartilage, or bone.

Wide local excision combined with reconstructive surgery is the main treatment approach, aiming for complete tumor removal while restoring both function and aesthetic appearance of the facial region. In recent years, Viet Tiep Friendship Hospital has routinely implemented various advanced excision and reconstruction techniques, achieving notable functional and cosmetic outcomes. However, comprehensive studies describing the clinical, paraclinical characteristics and surgical outcomes of facial basal cell carcinoma at this institution remain limited and require further investigation.

2. SUBJECTS AND METHODS

2.1. Study subjects

The study included 29 patients diagnosed with facial basal cell carcinoma who underwent surgical tumor excision and reconstruction of the defect using local flaps or primary closure at the Oncology and Nuclear Medicine Center, Viet Tiep Friendship Hospital, during the period from January 2023 to March 2026.

Inclusion criteria

- Patients with histopathologically confirmed facial basal cell carcinoma who underwent complete tumor excision and reconstruction of the resulting defect.

- Patients with complete medical records sufficient for study analysis.

- Patients who consented to participate in the study and attended postoperative follow-up visits.

Exclusion criteria

- Patients treated with other surgical approaches.

- Patients with distant metastasis or those who could not undergo curative surgery.

- Patients with severe general condition (ASA > 4).

- Patients with incomplete medical records.

2.2. Study methods

This study was designed as a descriptive study combining both retrospective and prospective components, including a total of 29 patients with facial basal cell carcinoma treated at the Oncology and Nuclear Medicine Center, Viet Tiep Friendship Hospital, from January 2023 to March 2026. The retrospective phase, conducted from January 2023 to January 2025, included 19 cases, while the prospective phase, from February 2025 to March 2026, comprised 10 cases. A convenience sampling method was applied.

All patients underwent wide local excision of the tumor with oncologically appropriate safety margins. Surgical specimens were submitted for histopathological examination to confirm the diagnosis and assess margin status, which was classified as negative (R0) or positive (R1).

Following tumor excision, the reconstructive technique was selected based on the location, size, and characteristics of the defect, including primary closure or local flap reconstruction (advancement, rotation, or transposition flaps).

Postoperative outcomes were assessed during hospitalization and at 3 months postoperatively based on flap viability, adequacy of defect coverage, wound healing, deformity, and postoperative complications. Outcomes were categorized as good, fair, or poor according to predefined criteria.

A good outcome was defined as complete flap survival, satisfactory functional restoration, and favorable aesthetic results (flat, supple scars with good color match and no contracture). Scar quality was further evaluated using the Vancouver Scar Scale.

3. RESULTS

3.1. Age

Table 1. Age groups in the study

Age group	Number	Percentage (%)
< 60	5	17.3
60 - 80	13	44.8
> 80	11	37.9
Total	29	100.0
$\bar{X}$ ± SD (min - max)	72.03 ± 14.65 (39 - 100)	

The mean age was 72.03 ± 14.65 years, with the oldest patient being 100 years old and the youngest 39 years old.

The majority of patients were in the 60-80 years age group, accounting for 44.8% of the study population.

3.2. Gender

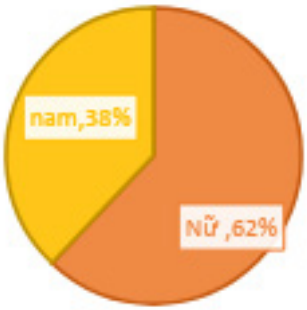


Chart 1: Gender distribution

Female patients predominated, accounting for 62%, while male patients accounted for 38%.

3.3. Duration of disease onset

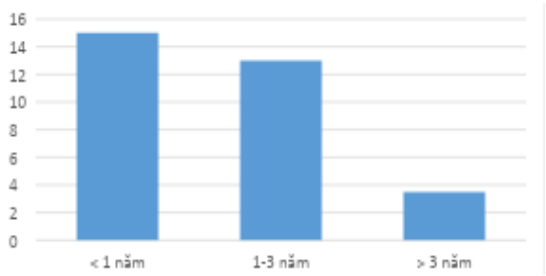


Chart 2: Duration of disease onset

The duration of disease was mainly less than 3 years (96.5%), with the highest proportion occurring within <1 year (51.7%).

3.4 Tumor location

Table 2. Tumor location

Lesion location	Number	Percentage %
Eye	6	20.7
Nose	7	24.1
Cheek	10	34.5
Lip	1	3.4
Forehead	5	17.3
Total	29	100%

The cheek region was the most common tumor location, accounting for 34.5%.

3.5. Tumor size

Chart 3: Tumor size

Tumor size < 2 cm accounted for the highest proportion, at 55.2%.

3.6. Tumor surgical margin

Table 3. Tumor surgical margin

Tumor surgical margin	Number	Percentage (%)
3 - 4 mm	1	3.4%
5 - 10 mm	28	96.6%
Total	29	100.0%

Surgical margins of 5-10 mm accounted for the majority of cases (96.6%), while margins of 3-4 mm accounted for 3.1%.

3.7. Methods of defect reconstruction

Table 4. Methods of defect reconstruction

Surgical reconstruction methods		Number	Percentage (%)
Primary closure		5	17.2
Local flap reconstruction	Rotation flap	10	34.5
	Advancement flap	8	27.6
	Transposition flap	6	20.7
	Total	29	100

Local flap reconstruction was the most commonly used method for defect repair. Among these, rotation flaps were the most frequently performed technique (34.5%), followed by advancement flaps (27.6%) and transposition flaps (20.7%). Primary closure accounted for a lower proportion of cases (17.2%).

3.8. Intraoperative and postoperative complications

Most patients had no complications (86%). Surgical site infection occurred in 10% of cases, while postoperative bleeding accounted for 4%.

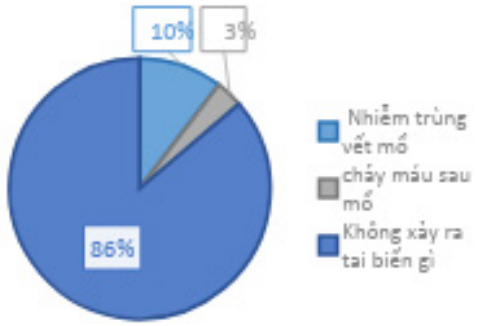


Chart 4: Intraoperative and postoperative complications

3.9. Evaluation of early surgical outcomes

Table 5. Early surgical outcomes

Evaluation criteria of early surgical outcomes	Good	Fair	Bad	Total
Flap viability	23 (95.8%)	1 (4.2%)	0 (0.0%)	24
Coverage function	22 (91.7%)	2 (8.3%)	0 (0.0%)	24
Wound condition	27 (93.1%)	2 (6.9%)	0 (0.0%)	29
Donor site condition	24 (100.0%)	0 (0.0%)	0 (0.0%)	24
Overall surgical outcome evaluation	27 (93.1%)	2 (6.9%)	0 (0.0%)	29

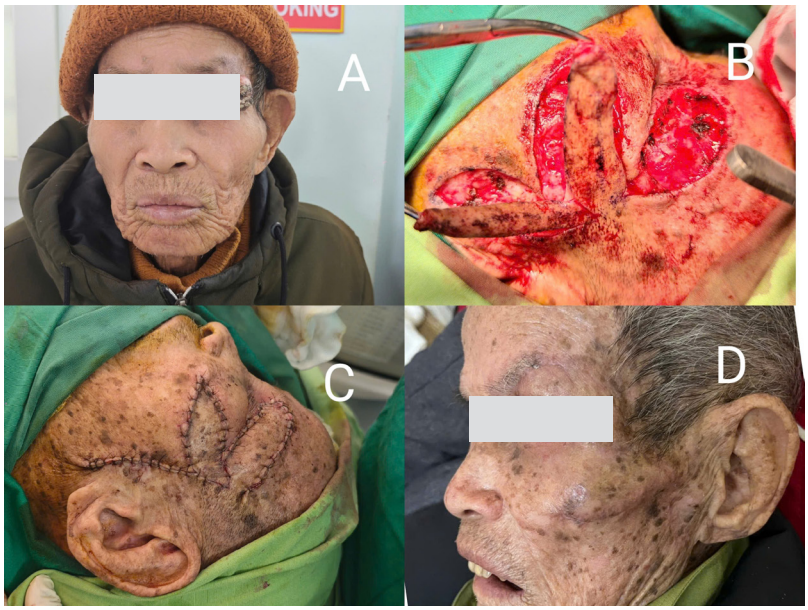
Flap survival was excellent in 95.8% of cases. Coverage function was good in 91.7% of patients, wound healing was good in 93.1%, and the overall surgical outcome was good in 93.1% of cases.

3.10. Evaluation of outcomes at 3 months after surgery

Table 6. Outcomes at 3 months postoperatively

Evaluation criteria	Good	Fair	Bad	Total
Flap color	23 (95.8%)	1 (4.2%)	0 (0.0%)	24
Flap thickness	23 (95.8%)	1 (4.2%)	0 (0.0%)	24
Scar condition	27 (93.1%)	2 (6.9%)	0 (0.0%)	29
Donor site condition	24 (100.0%)	0 (0.0%)	0 (0.0%)	24

Flap color and thickness were rated as good in 95.8% of cases. Scar condition was good in 93.1% of patients, while the donor site condition was good in 100% of cases.



Picture 1. Case report: 90-year-old male with basal cell carcinoma of the left eyelid

(A) Basal cell carcinoma located in the left eyelid region; (B) A transposition flap was raised and mobilized to cover the defect; (C) The flap was sutured into the defect site; (D) Three months postoperatively: the flap was completely viable, fully covered the defect, with good flap contour and satisfactory scar healing.

4. DISCUSSION

4.1. Age and Gender

Basal cell carcinoma can occur at various ages but is more commonly seen in elderly patients. In our study, the youngest patient was 39 years old and the oldest was 100 years old, with a mean age of 72.03 ± 14.65 years. This result is consistent

with Nguyễn Trần Thúc Huân (2023), who reported a mean age of 72.2 ± 12.8 years [4], and Dương Mạnh Chiến (2022), who reported a mean age of 68 ± 13.1 years [5]. The most common age group was 60-80 years (44.8%), followed by patients over 80 years (37.9%). These findings are consistent with the epidemiological characteristics of basal cell carcinoma, which typically occurs in older individuals due to the cumulative long-term effects of ultraviolet radiation exposure on the skin.

Regarding gender distribution, females accounted for 62% and males 38%, indicating a higher prevalence in females. This result is similar to Nguyễn Trần Thúc Huân (2023), who reported 85.3% females and 14.7% males [4], and Dương Mạnh Chiến (2022), who reported 54.5% females and 45.5% males [5].

4.2. Duration of disease detection

In our study, the duration of disease was mainly less than 3 years, accounting for 96.5%, of which cases detected within less than 1 year accounted for 51.7%. Patients with a longer disease duration were less common. This suggests that most patients presented with lesions that had been present for a certain period but were not yet at an advanced stage. However, in cancer management in general, early detection and treatment remain crucial in limiting tumor progression and local invasion.

4.3. Tumor characteristics

Regarding tumor location, the cheek was the most frequently affected site, accounting for 34.5%, followed by the nose at 24.1%. This result is consistent with Nguyễn Trần Thúc Huân (2023) [4], who reported the nose as the most common site (37.1%), followed by the cheek (31.4%). These are areas that are frequently exposed to direct sunlight, which is in line with the pathogenesis of basal cell carcinoma.

Regarding tumor size, lesions <2 cm accounted for 55.2%, while those measuring 2-5 cm accounted for 44.8%. Similarly, Nguyễn Trần Thúc Huân (2023) reported that tumors <2 cm accounted for 94.2% [4]. Most patients were diagnosed when the tumor was still relatively small, facilitating complete surgical excision and effective reconstruction of the resulting defect.

4.4. Surgical and reconstructive methods

In our study, surgical margins of 5-10 mm accounted for the majority of cases (96.6%), while margins of 3-4 mm accounted for only 3.1%. This rate is higher than that reported by Nguyễn Trần Thúc Huân (2023), which was 71.4% [4]. Selecting an adequate surgical margin helps ensure oncological safety and reduces the risk of local recurrence.

After tumor excision, local flap reconstruction was the most commonly used method. Among these, rotation flaps accounted for 34.5%, advancement flaps 27.6%, and transposition flaps 20.7%, while primary closure accounted for 17.2%. Compared with Dương Mạnh Chiến (2022), who reported rotation flaps at 53.6%, transposition flaps at 25%, and advancement flaps at 24% [5], our study showed a relatively different distribution. Local flaps have advantages in terms of color, thickness, and tissue characteristics similarity, which generally provide good aesthetic outcomes.

Intraoperative complications were uncommon, with 86% of patients experiencing no complications. Surgical site infection occurred in 10% of cases and postoperative bleeding in 4%, indicating that the surgical approach was relatively safe.

4.5. Evaluation of surgical outcomes

Primary closure cases were evaluated based on wound healing status. For cases reconstructed

with flaps (local or regional flaps), the assessment criteria included flap perfusion, flap condition, and healing at both the recipient and donor sites. Early postoperative outcomes showed that 95.8% of flaps had good viability, 91.7% achieved good coverage function, and 93.1% demonstrated good wound healing. Overall surgical outcomes were classified as good in 93.1% of cases and moderate in 6.9%, with no poor outcomes reported.

At 3 months postoperatively, flap color and thickness were rated as good in 95.8% of cases, scar condition was good in 93.1%, and donor site outcomes were good in 100% of cases. The facial region, with its rich vascular network and good skin elasticity, allows local flap reconstruction to achieve favorable functional and aesthetic results.

4.6. Limitations of the study

This study has several limitations. The relatively small sample size (n = 29) and the use of convenience sampling may limit the generalizability of the findings. The combined retrospective–prospective design may introduce heterogeneity in data collection. In addition, the short follow-up period (3 months) precludes adequate assessment of long-term outcomes, including recurrence and late aesthetic results.

5. CONCLUSION

In a study of 29 patients with facial basal cell carcinoma treated surgically at the Oncology and Nuclear Medicine Center, Viet Tiep Friendship Hospital, the mean age was 72.03±14.65 years, with the 60-80 age group accounting for 44.8%, and females comprising 62% of cases. The disease duration was mainly less than 3 years (96.5%), of which cases diagnosed within less than 1 year accounted for 51.7%. The most common tumor location was the cheek (34.5%), and most lesions were smaller than 2 cm (55.2%). Wide local excision with 5-10 mm surgical margins (96.6%), combined with local flap reconstruction, yielded favorable outcomes. Overall, good surgical results were achieved in 93.1% of cases, flap survival was good in 95.8%, and coverage function was satisfactory in 91.7%. At 3 months postoperatively, good outcomes were observed in flap color and thickness in 95.8% of cases and in scar condition in 93.1%, indicating that this approach is safe, effective, and provides both functional and aesthetic benefits in facial reconstruction. Future studies with larger cohorts and longer follow-up periods (over 5 years) are recommended to accurately assess long-term recurrence and late cosmetic outcomes.

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CASE REPORT: A PATIENT WITH LARGE CELL NEUROENDOCRINE CARCINOMA OF UNKNOWN ORIGIN ACHIEVED AN EXCELLENT RESPONSE TO TEMOZOLOMIDE TREATMENT AFTER FAILURE OF TWO PREVIOUS CHEMOTHERAPY REGIMEN

Pham Tuan Anh

ABSTRACT

Abstract: Large-cell neuroendocrine carcinoma of unknown primary origin is a rare entity with limited data, primarily from retrospective analyses or case reports. We herein present the case of a 71-year-old female with stage IV disease and extensive nodal involvement. After limited success with Etoposide-Carboplatin and then FOLFIRI, the patient achieved a remarkable clinical and radiological response to Temozolomide. Through this case, we summarized key clinical, paraclinical, and treatment outcome data from the literature.

Keywords: Euroendocrine carcinoma, Cancer of unknown primary, Temozolomide.

1. INTRODUCTION

Cancers of unknown primary account for approximately 2% of all malignancies, among which neuroendocrine tumors represent less than 5%. Large-cell neuroendocrine carcinoma of unknown primary is an exceptionally rare entity, with very limited data available in the literature. Most retrospective analyses have focused on neuroendocrine carcinomas (NECs) in general, with little attention given to the large-cell subtype specifically.

As with other forms of NEC, first-line treatment for stage IV disease typically consists of a Platinum-Etoposide doublet. Although response rates are relatively favorable (approximately 60-70%), the duration of response is generally short. In subsequent lines of therapy, regimens such as Irinotecan, Paclitaxel, Topotecan, and Temozolomide have demonstrated low disease control rates, and no regimen has consistently shown clear superior efficacy.

Herein, we report a clinical case of stage IV large-cell neuroendocrine carcinoma of unknown primary that achieved a remarkable response to Temozolomide as third-line therapy.

2. CASE REPORT

Our case was a 71-year-old female with no significant past medical history. She presented to K Hospital due to self-examination of a left cervical lymph node. Her performance status was generally good. Peripheral lymph node

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examination revealed a left supraclavicular lymph node approximately 2 cm in size, firm, and with limited mobility. No other abnormalities were identified on systemic examination.

An excisional biopsy of the cervical lymph node was performed. Histopathological examination and immunohistochemistry confirmed large-cell neuroendocrine carcinoma (LCNEC), with the following profile: Chromogranin (+), synaptophysin (+), CDX-2 (−), napsin A (−), and TTF-1 (−).

A whole-body PET-CT scan demonstrated hypermetabolic lymphadenopathy involving cervical levels IV–V (maximum diameter 26 mm, SUVmax 10.1), mediastinal lymph nodes (maximum 14 mm, SUVmax 5.6), and abdominal lymph nodes predominantly in the right renal hilum region (maximum 17 mm, SUVmax 8.4). Based on clinical and imaging findings, the patient was diagnosed with neuroendocrine carcinoma of unknown primary, stage IV. Additional biomarkers, including PD-L1 expression and microsatellite instability (MSI) status, were negative.

Following multidisciplinary discussion and consultation with the patient and her family, first-line chemotherapy with Etoposide–Carboplatin was initiated. The treatment was well tolerated, with only mild fatigue lasting 3–5 days after each cycle and no other reported adverse events. After three cycles of EP, clinical examination showed minimal change in the size of the left supraclavicular lymph node. Computed tomography (CT) imaging demonstrated stable disease, with no significant change in cervical, mediastinal, or abdominal lymph nodes and no new lesions.

Given the patient's and family's preference for a more aggressive approach, Atezolizumab (anti–PD-L1) was added to the regimen (EP–Atezolizumab). However, after three cycles, the best response remained stable disease, with a 16% increase in the sum of lesion diameters (SLD) according to RECIST 1.1 criteria. Maintenance therapy with Atezolizumab was subsequently administered.

After two cycles of maintenance therapy, the patient reported enlargement and increased pain of right cervical lymph nodes. Follow-up CT imaging revealed disease progression, with enlargement of all previously identified lesions, including cervical lymph nodes (largest 28 × 39 mm), mediastinal lymph nodes (largest 30 × 46 mm), and retroperitoneal lymph nodes (largest 24 × 42 mm).

Considering the patient's relatively preserved condition and strong treatment intent, second-line chemotherapy with FOLFIRI was initiated. After four cycles, the disease continued to progress clinically and radiologically. The patient developed worsening abdominal pain, occasionally severe. CT imaging showed further enlargement of lymph node masses, with the largest abdominal lesion measuring 38 × 54 mm, associated with surrounding infiltration, consistent with the patient's symptoms.

After two lines of combination chemotherapy with suboptimal response and declining performance status, treatment options were discussed, including best supportive care versus exploratory oral chemotherapy with temozolomide. The patient and her family opted for the latter. Temozolomide was administered at a dose of 150-200 mg/m²/day orally on days 1–5 of a 28-day cycle. No dose reduction was required. The treatment was well tolerated. No grade ≥3 hematologic or non-hematologic toxicities were observed. The patient reported only mild fatigue (grade 1–2).

Remarkably, within the first month of Temozolomide therapy, the patient demonstrated significant clinical improvement. Bilateral

cervical lymph nodes decreased in size from approximately 4 cm to 1 cm. Abdominal pain resolved completely.

After two months of treatment, imaging assessment showed a near-complete response. The largest cervical lymph node decreased from 40 × 42 mm to 7 mm, the largest mediastinal lymph node from 30 × 46 mm to 12 mm, and abdominal lymphadenopathy was no longer detectable (previously up to 38 × 54 mm). Tumor markers also showed a dramatic decline: neuron-specific enolase (NSE) decreased from 4720 to 14 ng/mL, and pro-gastrin-releasing peptide (proGRP) from >5000 to 145 pg/mL.

The disease remained stable after four months of treatment. However, at the six-month evaluation, lymph node lesions began to increase in size again, with the largest cervical, mediastinal, and retroperitoneal lymph nodes measuring 14 mm, 24 mm, and 20 mm, respectively. At this stage, the patient and her family decided to discontinue specific anti-cancer treatment and focus on palliative care.

3. DISCUSSION

Cancers of unknown primary account for approximately 2% of all malignancies, of which neuroendocrine tumors comprise less than 5%. Neuroendocrine carcinomas (NECs) are poorly differentiated neoplasms that are typically diagnosed at an advanced or metastatic stage and are associated with a poor prognosis.

In patients with NEC of known primary origin, the literature reports high response rates (approximately 66%) with Platinum-based chemotherapy (Carboplatin or Cisplatin) in combination with Etoposide. Similarly, this doublet regimen has demonstrated activity in NEC of unknown primary and is considered the standard first-line treatment. In the largest published case series to date (n = 99), the objective response rate (ORR) reached up to 70.[1]

More recently, immune checkpoint inhibitors (ICIs) have demonstrated clinical efficacy in neuroendocrine malignancies such as Merkel cell carcinoma of the skin and small-cell lung cancer. However, data supporting their benefit in other neuroendocrine tumor subtypes remain limited. The non-randomized prospective LANCE study, published in June 2024, evaluated the addition of atezolizumab to standard chemotherapy in the first-line treatment of large-cell neuroendocrine carcinoma (LCNEC) of the lung. Owing to the rarity of this disease, only 17 patients were enrolled, including 10 patients treated with four cycles of Etoposide–Carboplatin plus Atezolizumab followed by maintenance therapy with the checkpoint inhibitor, and 7 patients treated with chemotherapy alone.

After a median follow-up of 23.3 months, the Atezolizumab-containing arm demonstrated improved 24-month overall survival (OS) rates (45.7% vs. 14.3%) and longer median OS (not reached vs. 8.2 months; hazard ratio [HR] = 0.37; 95% confidence interval [CI], 0.10–1.05) compared with the EP-only arm. Although limited by the small sample size, these findings provide preliminary evidence supporting the addition of Atezolizumab to first-line chemotherapy in metastatic pulmonary LCNEC.

Based on the findings of the LANCE study, we incorporated atezolizumab into the EP regimen in our patient with the aim of achieving a deeper and more durable response. With this first-line approach, the patient achieved a progression-free survival (PFS) of 6 months, which represents a clinically meaningful outcome in the context of the poor prognosis associated with LCNEC.

In subsequent lines of therapy, according to the National Comprehensive Cancer Network guidelines, several regimens have demonstrated clinical activity, primarily based on retrospective

studies, including FOLFOX, FOLFIRI, and temozolomide with or without capecitabine. In a retrospective analysis of 64 patients with extrapulmonary NEC who progressed after first-line platinum–etoposide therapy, regimens such as irinotecan, paclitaxel, topotecan, temozolomide, and paclitaxel–topotecan did not demonstrate clear superiority, with a median progression-free survival (PFS) of approximately 2 months and a median overall survival (OS) of 6–7 months. In our case, we selected the FOLFIRI regimen to optimize treatment tolerability and preserve quality of life. However, after only four cycles (approximately 2 months), the disease continued to progress both clinically and radiologically.

In the absence of standard third-line therapy for extrapulmonary NEC, temozolomide was selected based on its oral administration, tolerability, and reported activity in retrospective studies. Additionally, the patient's declining performance status and preference favored a less intensive regimen. Administered on a 5-day schedule every 28-day cycle, this regimen is convenient, does not require hospitalization, and is associated with a favorable toxicity profile. Moreover, the continuation of active anticancer therapy contributed positively to the patient's psychological well-being and treatment outlook. The patient achieved a near-complete response at the first evaluation after 2 months of treatment, with disease stabilization maintained for up to 6 months. Given the rarity of large-cell neuroendocrine carcinoma (LCNEC) of unknown primary, available evidence is limited and largely derived from retrospective analyses and case reports. Consequently, treatment recommendations are often extrapolated from data on small-cell neuroendocrine carcinoma, particularly small-cell lung cancer, due to shared histopathological characteristics. Evidence regarding the efficacy of temozolomide in LCNEC of unknown primary remains particularly scarce.

In a phase II study (2021) by Noritoshi Kobayashi et al., evaluating temozolomide monotherapy following platinum–etoposide therapy, only one patient with unknown primary tumor was included among 13 patients with extrapulmonary NEC. Unlike our case, that patient experienced disease progression at the first assessment, with a progression-free survival (PFS) of only 1.8 months. Another retrospective analysis by Staffan Welin et al. (2011) evaluated temozolomide, with or without capecitabine, in patients with extrapulmonary NEC. However, only 5 of 25 enrolled patients had tumors of unknown primary origin, and detailed data regarding histological subtypes (large-cell vs. small-cell), treatment response, and survival outcomes for this subgroup were not specifically reported. Taken together, our case represents one of the few reports demonstrating a significant clinical benefit of temozolomide in a patient with stage IV large-cell neuroendocrine carcinoma of unknown primary.

Are there any factors that may predict response to Temozolomide in neuroendocrine carcinoma? A meta-analysis of 11 studies demonstrated that patients with neuroendocrine tumors harboring O6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation or low MGMT protein expression achieved higher objective response rates to alkylating agents than those without these features. [5]

The MGMT gene is located on chromosome 10q26 and encodes a DNA repair enzyme capable of rapidly reversing DNA damage induced by alkylating agents, thereby maintaining genomic stability.[6] The promoter region of the MGMT gene contains 97 CpG sites. Methylation of these CpG sites may lead to alterations in chromatin structure, inhibit the binding of transcription factors to the promoter region, and ultimately result in gene silencing. In other words, MGMT promoter methylation suppresses MGMT enzyme

activity, rendering tumor cells more sensitive to alkylating agents such as temozolomide. However, in routine clinical practice at K Hospital, as well as in Vietnam more broadly, testing for MGMT promoter methylation status is not yet widely available and remains costly.

Despite the remarkable response observed in this case, the efficacy of temozolomide in LCNEC remains uncertain due to limited data and heterogeneity of reported studies. The observed benefit may reflect underlying biological factors, including potential MGMT deficiency, although this was not assessed in our patient.

4. CONCLUSION

We report a case of stage IV large-cell neuroendocrine carcinoma of unknown primary that achieved a dramatic response to temozolomide. This case provides additional clinical evidence supporting the potential role of temozolomide in this rare and challenging disease.

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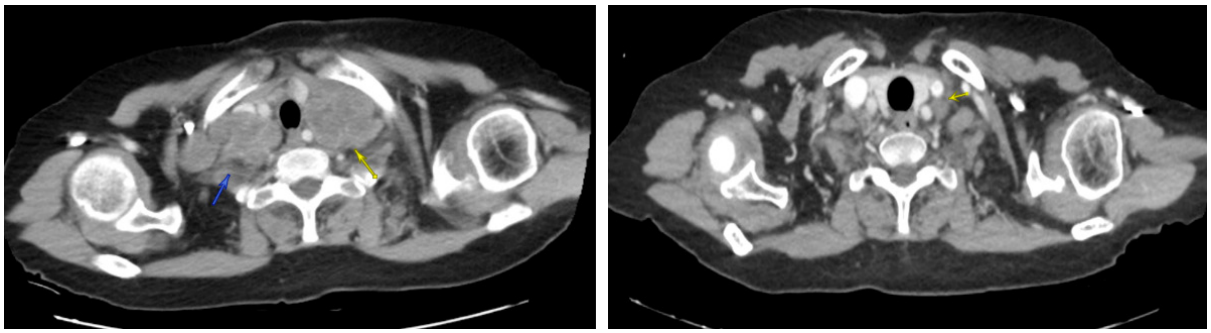

Figure 1. CT scan of the neck before and after Temozolomide treatment

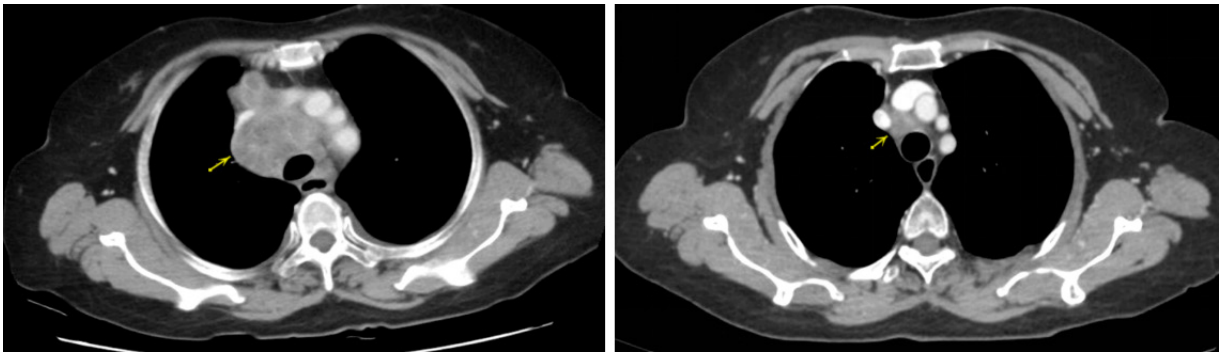

Figure 2. CT scan of the chest before and after Temozolomide treatment

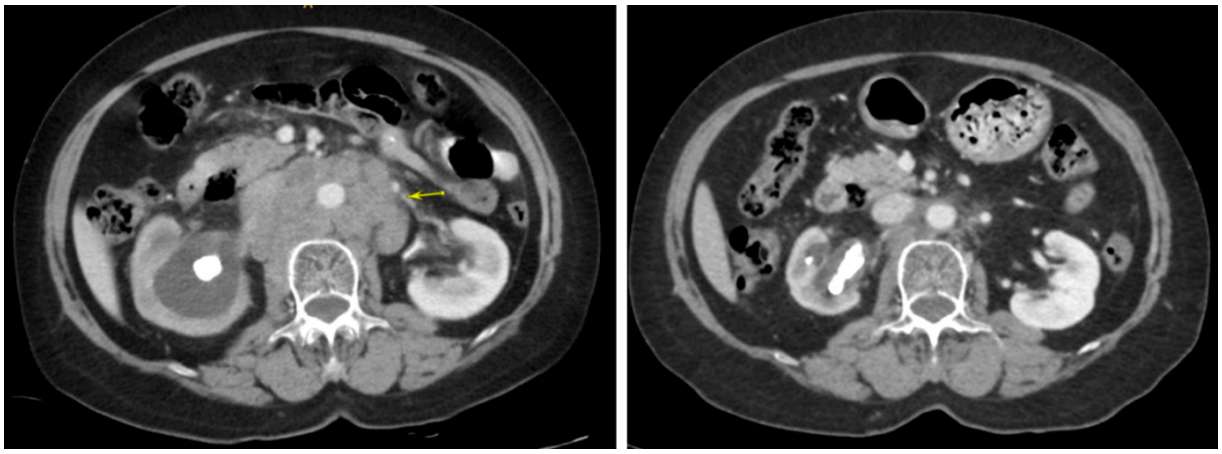

Figure 3. CT scan of the abdomen before and after Temozolomide treatment

CHARACTERISTICS OF LYMPH NODE METASTASIS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER UNDERGOING LOBECTOMY AND SYSTEMIC LYMPH NODE DISSECTION AT HANOI ONCOLOGY HOSPITAL

Phan Le Thang, Pham Dac Dong*, Nguyen Van An, Pham Van Hoan

ABSTRACT

Objective: To evaluate characteristics of lymph node metastasis in patients with non-small cell lung cancer who underwent surgery.

Methods: Retrospective study on patients with stage I-IIIA non-small cell lung cancer who underwent lobectomy and lymph node dissection at Hanoi Oncology Hospital from September 2023 to September 2025.

Results: There were 144 patients enrolled in the study. The incidence of lung cancer increased with age, with a mean age of 57 ± 11.08 (35-79). The male/female ratio was nearly equal. Right-sided lung tumors were more common than left-sided tumors; most of these tumors were ≤3 cm with spiculated margins. The majority of patients were in stages I and II, accounting for 96.5%. Thoracoscopic surgery was performed in 95.8% of patients. The average number of lymph nodes dissected per patient was 11.32 ± 4.58. The rate of lymph node metastasis was 33.6%, in which N1 metastasis accounted for 27.6% and N2 metastasis for 6%. Lymph node metastasis was positively correlated with lymph node size and primary tumor size; the difference was statistically significant ($p<0.05$). There was no statistically significant difference in the rate of lymph node metastasis according to factors such as primary tumor location, pleural invasion, and histopathological type.

Conclusion: Lymph node metastasis in non-small cell lung cancer accounted for 33.6%, including N1 metastasis in 27.6% and N2 metastasis in 6%. The likelihood of lymph node metastasis increased in proportion to lymph node size and primary tumor size. There was no difference in the rate of lymph node metastasis according to factors such as primary tumor location, pleural invasion, and histopathological type.

Keywords: NSCLC, lobectomy, lymph node dissection, lymph node metastasis.

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1. INTRODUCTION

Lung cancer is one of the most common cancers globally and in Vietnam. According to GLOBOCAN 2022, lung cancer ranked third in incidence with 24,426 new cases and second in cancer-related mortality with 22,597 deaths in Vietnam [1].

In clinical practice, lung cancer is divided into two main groups: small cell lung cancer, which accounts for about 15%, and non-small cell lung cancer (NSCLC), which accounts for about 85%. Surgery remains the main treatment modality and is especially important for stage I-IIIA NSCLC. To achieve radical resection, in addition to lobectomy, regional lymph node dissection according to the nodal map is required to remove all lesions [2].

The pulmonary lymph node system is divided into 14 groups. Regional lymph node dissection serves both a curative purpose and provides specimens for histopathological diagnosis to accurately determine metastasis in each nodal group, thereby enabling correct staging and prognosis. This is a major operation; therefore, identifying which nodal groups are commonly metastatic is extremely important in order to remove all involved lymph nodes, and reduce the risk of recurrence, improve survival, and avoid unnecessary extensive lymph node dissection that may be dangerous and may cause complications. Studies have shown that lymph node metastasis occurs in 20-40% of patients with non-small cell lung cancer and is associated with certain factors such as the location, size, and invasive characteristics of the primary tumor [3]. However, there have been relatively few studies on this topic in Vietnam. Therefore, we conducted this study in order to evaluate the characteristics of lymph node metastasis in patients with non-small cell lung cancer who underwent lobectomy and systemic lymph node dissection.

2. STUDY SUBJECTS AND METHODS

2.1. Study subjects

The study subjects included 144 patients with stage I, II, and IIIA non-small cell lung cancer who underwent surgical treatment at Hanoi Oncology Hospital from September 2023 to September 2025 according to the following criteria.

2.1.1 Inclusion criteria

- Patients diagnosed with lung cancer at stage I, II, or IIIA (according to IASLC), based on histopathology from needle biopsy or frozen section, who underwent lobectomy and N1/N2 lymph node dissection.

- Postoperative histopathology confirmed non-small cell lung cancer.

- Patients were fit for general anesthesia, lobectomy, and lymph node dissection (general condition, cardiovascular status, and respiratory function).

2.1.2 Exclusion criteria

- Patients who had received neoadjuvant chemoradiotherapy, because assessment of tumor and lymph node size would no longer be accurate, or those with another concomitant cancer.

- Patients who had undergone surgery before the study period and later developed local recurrence requiring reoperation.

- The disease was assessed as beyond the surgical stage (IIIB, IV) during surgery.

2.2. Data collection process

- Step 1: Select patients according to the study criteria.

- Step 2: Collect clinical and paraclinical information and determine disease stage.

- Step 3: Collect/extract data regarding surgical

characteristics and postoperative outcomes from medical records, surgery (thoracoscopic: 138 cases; open surgery: 6 cases).

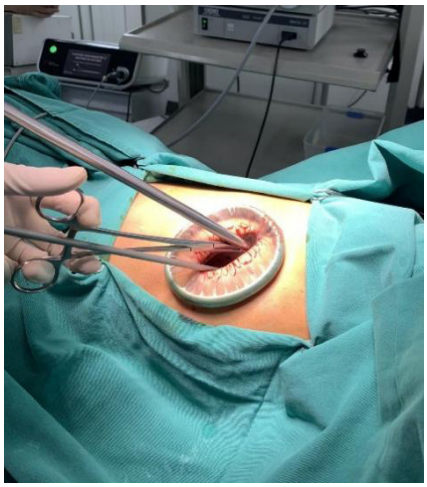

Figure 1: Thoracic incision in single-port thoracoscopic surgery

Surgical procedure: Double-lumen endotracheal anesthesia was used to collapse the affected lung. A 4-5 cm skin incision was made through the 4-5th or 5-6th intercostal space depending on the patient. A soft wound protector was used. Alternatively, conventional thoracotomy was performed. The artery, vein, and bronchus were dissected and divided using a stapler; the lung lobe was removed in a specimen bag; and lymph node dissection was performed using an ultrasonic scalpel or LigaSure, a minimum of one N1 and three N2 stations sampled. Hemostasis was secured, a chest drain was placed, and the operation was completed. Specimens were sent for examination and postoperative follow-up was performed.

2.3. Study methods

The study was conducted using a retrospective descriptive design. Data were collected using a standardized study record form and analyzed with SPSS 20.0 software. Differences were considered statistically significant if $p \leq 0.05$.

3. RESULTS

3.1. General characteristics of the study patients

Table 1. Gender distribution by age group

Age	Gender (n=144)	
	Male (n=71; 49.3%)	Female (n=73; 50.7%)
≤ 40	0 (0%)	1 (0.7%)
40-60	31(21.5%)	35 (24.3%)
≥ 60	40 (27.8%)	37 (25.7%)
Total	71 (49.3%)	73 (50.7%)

Totally 144 patients were enrolled in the study with 49.3% patients were males and 50.7% were females

According to the above table 1, mean age was 57 ± 11.08 (35-79). The rate of lung cancer increased with age. The male/female ratio was nearly equal.

Table 2. Tumor location and size on computed tomography and preoperative staging

Tumor location	Number of patients		Percentage %		
Right lung					
Upper lobe	34		23.6		
Middle lobe	13		9.0		
Lower lobe	41		28.5		
Left lung					
Upper lobe	21		14.6		
Lower lobe	35		24.3		
Tumor size	Mean: 3.1 ± 1.91 (1.1-6.1)				
Tumor size ≤ 3 cm	86		59.7		
3 < tumor size ≤ 5 cm	53		36.8		
5 < tumor size ≤ 7 cm	5		3,5		
Stage	IA	IB	IIA	IIB	IIIA
Patients (n)	20	55	39	25	5
Rate (%)	13.9	38.2	27.1	17.3	3.5

The above Table 2 showed that right-sided lung tumors were more common than left-sided tumors, mainly in the lower lobes on both sides. Most tumors were smaller than 3 cm. Most patients were in early stages I and II; stage IIIA accounted for only 3.5%.

3.2. Surgical characteristics and lymph node metastasis

3.2.1. General surgical characteristics

Table 3. General surgical characteristics

Characteristics	Number of patients	Percentage
Surgical method		
Thoracoscopic surgery	138	95.8
Open surgery	6	4.2
Frozen section		
Yes	14	9.7
No	130	90.3
Surgical complications		
No	141	97.9
Pulmonary artery injury	3	2.1

According to the Table 3 above, most patients underwent thoracoscopic surgery (95.8%) and had preoperative histopathology (90.3%). In terms of surgical complications there were 3 cases of pulmonary artery injury during lymph node dissection.

3.2.2. Characteristics of lymph node metastasis

Table 4. Dissected regional lymph nodes

Lymph node size	N1 nodes (n %)	N2 nodes (n %)	Overall (n%)
≤ 10 mm	623 (54.4)	310 (63.9)	933 (57.2)
10-15 mm	420 (36.7)	130 (26.8)	550 (33.7)
15-20 mm	87 (7.6)	42 (8.7)	129 (8.0)
> 20 mm	15 (1.3)	3 (0.6)	18 (1.1)
Total	1.145 (100)	485 (100)	1.630 (100)

According to the Table 4 above, the average number of lymph nodes dissected per patient was 11.32±4.58. The fewest nodes dissected in one patient was 3 and the highest was 27; the smallest lymph node measured 4 mm and the largest 28 mm in diameter.

Table 5. Rate of metastasis by regional lymph node groups

	N1 nodes (n %)	N2 nodes (n %)	Overall (n%)
Positive nodes	450 (39.3)	97 (20)	547 (33.6)
Negative nodes	695 (60.7)	388 (80)	1.083 (66.4)
Total	1.145 (100)	485 (100)	1.630 (100)

The above Table 5 showed that the lymph node metastasis rate was 33.6%. Among positive nodes, metastasis occurred mainly in N1 nodes, accounting for 70.2% of all metastatic nodes.

Table 6. Relationship between lymph node size and metastatic potential

Lymph node size	Overall N1 N2		Total	p
	Positive	Negative		
≤ 10 mm	186 (19.9%)	747 (80.1%)	933 (100%)	0,01
10-15 mm	261 (47.4%)	289 (52.5%)	550 (100%)	
15-20 mm	82 (63.6%)	47 (36.4%)	129 (100%)	
> 20 mm	18 (100%)	0 (0%)	18 (100%)	
Total	547	1083		

According to the above Table 6, the larger the lymph node is, the higher the likelihood of metastasis is. Among nodes ≤10 mm, only 19.9% were positive; this rate increased progressively, reaching 100% in nodes >20 mm.

Table 7. Relationship between primary tumor size and lymph node metastasis

Tumor size	No lymph node metastasis	N1 lymph node metastasis	N2 lymph node metastasis	Total (%)	p
≤ 3 cm	52 (60.5)	21(24.4)	13 (15.1)	86 (100)	0,018
3-5 cm	21 (39.6)	31 (58.5)	1 (1.2)	53(100)	
5-7 cm	1 (20)	2 (40)	2 (40)	5 (100)	

Table 7 above showed that the rate of lymph node metastasis increased in proportion with the tumor size; the difference was statistically significant (p = 0.018).

Table 8. Relationship between pleural invasion and lymph node metastasis

Pleural invasion	No lymph node metastasis	N1 lymph node metastasis	N2 lymph node metastasis	p
Yes	27 (36.5%)	29 (53.7%)	9 (56.3%)	0.534
No	47 (63.5%)	25 (46.3%)	7 (43.7%)	
Total	74 (100%)	54 (100%)	16 (100%)	

According to the above Table 8, there was no relationship between the appearance of pleural invasion and lymph node metastasis.

Table 9. Relationship between tumor location and lymph node metastasis

Tumor location	No lymph node metastasis	N1 lymph node metastasis	N2 lymph node metastasis	p
Right upper lobe	24 (16.7%)	8 (5.6%)	2 (1.4%)	0.195
Right middle lobe	7 (4.9%)	5 (3.5%)	1 (0.7%)	
Right lower lobe	25 (17.4%)	11 (7.6%)	5 (3.5%)	
Left upper lobe	11 (7.6%)	6 (4.1%)	4 (2.8%)	
Left lower lobe	7 (4.8%)	24 (16.6%)	4 (2.8%)	

Table 9 above showed that lymph node metastasis was not related to tumor location; metastasis was commonly observed in the right upper lobe and both lower lobes.

Table 10. Relationship between histopathology and lymph node metastasis

Histopathology	No lymph node metastasis	N1 + N2 lymph node metastasis	Total	p
Adenocarcinoma	65 (53.7%)	56 (46.3%)	121 (100%)	0,205
Squamous cell carcinoma	9 (39.2%)	14 (60.8%)	23 (100%)	
Other types	0	0	0	

According to the above Table 10, lymph node metastasis did not depend on the histopathological characteristics of the tumor.

4. DISCUSSION

4.1. Characteristics of lymph node metastasis

Most patients in our study group did not have lymph node metastasis; only 33.6% had nodal metastasis, most of which was N1 metastasis, accounting for 70.2%. This result is consistent with previous studies. For example,in the study by Le Hai Son et al., the rate of lymph node metastasis was 38.1%, and isolated N1 or N2 station metastasis accounted for a high proportion [4]. Studies have shown that lymph node metastasis in non-small cell lung cancer occurs in 20-40% of patients and is associated with characteristics such as the location, size, invasive nature of the primary tumor, and the anthropological characteristics of the study population [3,4].

4.2. Relationship between lymph node metastasis and selected tumor characteristics

In this study, we found that the rate of lymph node metastasis was associated with lymph node size and primary tumor size. However, there was no statistically significant relationship between the rate of lymph node metastasis and factors such as age, sex of the study group, tumor location, histopathological characteristics, or occurring of pleural invasion.

In many studies, most authors have reported that lymph node metastasis is related to tumor size. According to a study at Military Central Hospital 108, the rate of lymph node metastasis was 59.3% for tumors <5 cm and 66.7% for tumors >5 cm and <7 cm; the metastatic pattern was related to the size of the primary tumor [4]. Studies by JinLong Zhao et al. [5] and Pham Cam Phuong et al. [6] also showed a correlation between tumor size and the risk of lymph node metastasis in lung cancer: the larger the primary tumor is, the higher the rate of lymph node metastasis is.

In our study, the rate of lymph node metastasis increased in proportion to lymph node size: among nodes ≤10 mm, only 19.9% were positive, and this rate rose progressively to 100% in the group of nodes >20 mm. Studies in Vietnam and worldwide have consistently shown that lymph node size is directly proportional to the likelihood of metastasis, especially in nodes >20 mm, in which the metastasis rate is nearly 100%. According to Tadasu Kohno (2012) (n=160), the rate of lymph node metastasis was 15% in nodes ≤10 mm, 61.2% in nodes 11-20 mm, and 94% in nodes >20 mm [7]. Mai Trong Khoa's study (2013) in 33 patients reported rates of 8.2% for nodes ≤10 mm, 61.6% for nodes 11-20 mm, and 100% for nodes >20 mm [8].

The study by Le Hai Son [4] showed that N1 lymph node metastasis was common in tumors located in the right upper lobe or left lower lobe; superior N2 lymph node metastasis was commonly seen in right upper lobe tumors,

aortopulmonary region nodes in left upper lobe tumors, and subcarinal nodes in tumors located in both lower lobes. However, our study and some others did not find a relationship between tumor location and the likelihood of lymph node metastasis [6]. These differences among studies may be due to differences in sampling method, sample size, and variation in surgeons' indications for surgery. Therefore, the relationship between age, tumor size, and tumor location and the risk of lymph node metastasis should be further studied systematically with larger sample sizes and standardized surgical indications.

5. CONCLUSION

Lymph node metastasis in non-small cell lung cancer accounted for 33.6%, with N1 metastasis being the most common in 27.6% and N2 metastasis in 6%. The likelihood of lymph node metastasis increased in proportion to lymph node size and primary tumor size, and the difference was statistically significant ($p<0.05$). There was no difference in the rate of lymph node metastasis according to factors such as primary tumor location, pleural invasion, and histopathological type. This research provides us with a preliminary insight into the prognosis of lymph node metastasis in patients with non-small cell lung cancer.

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OLIGOMETASTATIC BREAST CANCER: DEFINITIONS, DIAGNOSTIC ADVANCES, AND TREATMENT STRATEGIES

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ABSTRACT

Background: Oligometastatic breast cancer (OMBC) is considered an transitional state between locally confined and widespread metastaticbreast cancer. It is characterized by a limited number of metastatic lesions (commonly ≤5 lesions across ≤2 organs) and a potentially favorable response to definitive local therapies such as surgery or stereotactic body radiation therapy (SBRT).

Objective: To review recent advances in imaging and molecular biology in OMBC, elucidate the potential for long-term disease control through multimodal treatment strategies, and discuss ongoing challenges in standardizing diagnosis and management.

Content: Although metastatic breast cancer has traditionally been regarded as incurable, accumulating evidence suggests that a selected subgroup of patients with OMBC may achieve prolonged disease-free survival following aggressive treatment. However, there remains significant heterogeneity in the definition of OMBC across studies, including variations in imaging criteria, number and location of metastatic lesions, timing of metastasis (de novo versus metachronous), and molecular characteristics. The ESTRO-EORTC classification system has proposed 17 criteria for comprehensive assessment and distinguishes among different OMBC states, including genuine, induced, and repeat oligometastatic disease.

Most currently available data on OMBC management derive from retrospective studies and small phase II trials, while evidence from randomized controlled trials remains limited. This lack of high-level evidence poses challenges in standardizing treatment strategies, particularly regarding the role of local therapies in the context of increasingly personalized systemic treatment.

Recent advances in tumor biology and diagnostic technologies have opened new perspectives. Molecular biomarkers such as PIK3CA mutations, YAP/TAZ expression, and circulating tumor

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DNA (ctDNA) dynamics show promise in risk stratification, patient selection, and early detection of recurrence. Meanwhile, modern imaging modalities, including whole-body PET/CT with specific tracers, enable more accurate identification of metastatic burden and support appropriate classification of OMBC.

Conclusion: OMBC represents a distinct subgroup of breast cancer with unique prognostic implications and potential for improved outcomes. Accurate characterization of tumor biology combined with individualized treatment strategies may optimize clinical outcomes. Large-scale randomized trials are warranted to validate the benefit of aggressive interventions and to establish standardized treatment guidelines for this patient population.

Keywords: Oligometastatic breast cancer (OMBC); Stereotactic body radiation therapy (SBRT); Multimodal therapy; ESTRO-EORTC classification; Circulating tumor DNA (ctDNA); PET/CT imaging; Molecular biology; Personalized treatment.

1. INTRODUCTION

Oligometastasis in the Era of Advances in Diagnosis and Treatment

Randomized trials such as SABR-COMET have demonstrated that comprehensive metastasis-directed therapy may improve progression-free survival (PFS) and overall survival (OS), while also suggesting the potential for durable disease control and, in selected cases, long-term remission in patients with oligometastatic disease. The rigorous study design and well-defined patient population have strengthened the clinical validity of these findings. However, the EA2108 trial in patients with stage IV breast cancer did not demonstrate a survival benefit with the addition of early locoregional therapy to systemic treatment, indicating that the role of this strategy should be carefully considered within specific disease scenario.

Notably, although SABR-COMET supports the benefit of aggressive local therapy targeting metastatic lesions, the proportion of breast cancer patients included in this trial was limited. In contrast, the NRG-BR002 trial, specifically conducted in oligometastatic breast cancer, failed to demonstrate a survival benefit from metastasis-directed local therapy. Importantly, this study did not mandate the use of positron emission tomography-computed tomography (PET/CT) and lacked standardization of systemic therapy. Subgroup analyses revealed no survival advantage even among patients with a single metastatic lesion; moreover, a higher incidence of new metastatic lesions was observed in the local therapy group, and patients with triple-negative breast cancer (TNBC) exhibited poorer outcomes. Collectively, these findings underscore the necessity of integrating and maintaining effective systemic therapy, as well as the importance of standardized imaging and treatment strategies in future clinical trials evaluating oligometastatic breast cancer.

2. DEFINITION OF OLIGOMETASTASIS

2.1 Clinical and Imaging Criteria

Oligometastasis is commonly defined as the presence of up to five metastatic lesions, confined to defined anatomical regions and amenable to local treatment modalities. Hellman et al. initially proposed this definition and further analyzed its clinical applications and limitations. For instance, the ESTRO and EORTC criteria emphasize the role of clinical disease course and lesion number in defining the oligometastatic state.

2.2. Biological Basis

The rationale for local therapy in oligometastatic disease is based on the hypothesis that early intervention to reduce tumor burden may induce a state approaching cure, thereby improving prognosis. However, data from ovarian cancer studies have raised questions regarding this assumption. Specifically, in ovarian cancer, initiating treatment based solely on an increase in CA125 levels (approximately six months earlier on average) compared with treatment initiation after radiologic detection of disease on CT did not result in differences in clinical outcomes. Furthermore, although secondary cytoreductive surgery is commonly employed in ovarian cancer, its survival benefit has not been consistently demonstrated. These findings call into question the validity of applying local treatment strategies in oligometastatic breast cancer.

Differences in tumor biology across cancer types may significantly influence the effectiveness of local or locoregional interventions. Therefore, treatment strategies for oligometastatic disease should incorporate not only tumor burden but also molecular and biological characteristics. Future studies should integrate these aspects to develop novel therapeutic approaches tailored to the unique biology of oligometastatic disease.

Emerging evidence suggests that oligometastasis may represent a distinct biological entity. Mutations such as PIK3CA H1047R and overexpression of markers such as YAP/TAZ have been associated with oligometastatic breast cancer (OMBC) and may predict a more favorable response to local therapies.

3. TREATMENT STRATEGIES IN OLIGO-METASTASIS

3.1. Role of local therapies

In the management of oligometastatic disease, local treatment modalities-including stereotactic body radiation therapy (SBRT), surgical resection, and radiofrequency ablation (RFA)-play a pivotal role in achieving high rates of local control and optimizing survival outcomes when appropriately integrated with systemic therapy. SBRT is particularly effective for small lesions in the brain, lung, and liver, with excellent local control rates in selected patient populations. Proton therapy has shown promising results in liver metastases with minimal toxicity, while surgical resection remains the standard of care for lesions amenable to complete removal. However, in de novo stage IV breast cancer, the role of primary tumor resection remains controversial.

From a biological perspective, removal of the primary tumor has been hypothesized to confer immunomodulatory benefits, analogous to strategies previously applied in renal cell carcinoma. Conversely, an opposing hypothesis suggests that surgical intervention may promote disease progression through alterations in the immune microenvironment and the release of growth factors. Retrospective studies have yielded heterogeneous results and are subject to selection bias, while also failing to fully reflect advances in modern systemic therapies. Meta-analyses have suggested an improvement in 3-year survival in patients undergoing surgery, particularly in those with oligometastatic disease; however, a major limitation is the lack of comprehensive data on targeted therapies such as anti-HER2 agents.

Randomized clinical trials have reported conflicting findings. The study by Soran et al. demonstrated a long-term survival benefit, particularly in subgroups with ER/PR-positive, HER2-positive disease, or bone-only metastases, despite baseline imbalances between study arms. In contrast, trials such as those conducted by Badwe et al., POSYTIVE, and ECOG-ACRIN E2108 did not demonstrate an overall survival benefit from locoregional therapy, although improvements in local control were occasionally

observed. Notably, the BOMET MF14-01 study, which included patients with bone-only metastases, reported a significant improvement in 5-year survival in the local therapy group; however, its generalizability is limited by the absence of contemporary systemic therapies and imbalances between study cohorts.

Overall, there is currently no consensus regarding the indication for primary tumor surgery in metastatic breast cancer. The benefit appears to be more pronounced in patients with low metastatic burden, particularly those with oligometastatic or bone-only disease, and in the context of well-controlled systemic disease. Therefore, optimal management strategies should be based on careful patient selection, comprehensive assessment of tumor biology, and close integration with modern systemic therapies, rather than routine application of surgery.

3.2. Role of local therapies for metastatic lesions

The management of metastatic breast cancer (MBC) remains fundamentally based on systemic therapy, including chemotherapy, endocrine therapy, immunotherapy, and targeted agents, with a median overall survival (OS) ranging from 18 to 60 months depending on tumor subtype and disease burden. In the oligometastatic setting, prognosis appears more favorable, and the potential benefit of curative-intent strategies has been increasingly explored; however, current evidence remains inconsistent.

Real-world data in patients with HER2-positive disease and a single metastatic site have demonstrated that first-line treatment with trastuzumab plus pertuzumab significantly improves progression-free survival (PFS) ($p < 0.0001$) and overall survival (OS) ($p = 0.004$).

The phase II/III NRG-BR002 trial enrolled patients with ≤4 metastatic lesions (≤5 cm) who did not progress following systemic therapy and compared standard treatment (with palliative radiotherapy as needed) versus a comprehensive metastasis-directed approach using SBRT and/or surgery. The results did not demonstrate an improvement in PFS (23 months in the standard arm versus 19.5 months in the metastasis-directed therapy arm).

Local treatment modalities considered in curative-intent strategies include metastasectomy, SBRT, external beam radiotherapy (EBRT), and radiofrequency ablation (RFA). However, there remains a lack of predictive biomarkers and robust prospective data to guide patient selection. In summary, systemic therapy remains the cornerstone of treatment, while curative-intent approaches in oligometastatic disease should be individualized based on tumor biology, number and location of metastases, and the degree of systemic disease control.

4. ORGAN-SPECIFIC TREATMENT STRATEGIES IN OLIGOMETASTATIC DISEASE

4.1. Liver

The liver represents one of the most common sites of oligometastatic involvement, particularly in colorectal and breast cancer. In breast cancer, hepatic metastases-along with pulmonary and osseous metastases-are among the most frequently observed sites. The overall 5-year survival rate in this population ranges from approximately 4% to 12%, while 5-15% of patients present with isolated or liver-limited metastatic disease.

Although no prospective trials have definitively established the benefit of hepatic metastasectomy, retrospective studies suggest improved survival in selected patients, with 5-year survival rates exceeding 30% and median overall survival ranging from 25 to 70 months. Favorable prognostic factors include achievement of

microscopically negative margins (R0 resection), younger age, hormone receptor–positive or HER2-positive disease, and a favorable response to initial systemic therapy. A matched case–control study conducted in Europe demonstrated that the combination of systemic therapy (including trastuzumab in HER2-positive patients) and hepatic resection significantly improved overall survival compared with systemic therapy alone (82 vs. 31 months; HR 0.28; $p < 0.001$). However, the role of repeat hepatic resection remains insufficiently characterized. In patients who are not candidates for surgery due to comorbidities or unfavorable lesion location, alternative local modalities such as radiofrequency ablation (RFA) or microwave ablation (MWA) may be considered. Retrospective data suggest that laparoscopic RFA combined with surgery is associated with longer overall survival compared with systemic therapy alone (47 vs. 9 months; $p = 0.0001$).

Regarding radiotherapy, stereotactic body radiation therapy (SBRT) and proton beam therapy (PBT) represent minimally invasive options with high local control rates (>90%). A nationwide cohort study in Japan reported a 3-year local control rate of 100% with PBT in patients with breast cancer liver metastases. However, SBRT is less frequently utilized in the liver due to the risk of radiation-induced liver disease and limitations in treating larger lesions. Additionally, the role of liver transplantation is currently under investigation in highly selected patients with favorable tumor biology.

In summary, the management of liver metastases in the oligometastatic setting requires careful patient selection and prioritizes a multidisciplinary approach integrating systemic therapy with appropriate local treatment strategies.

4.2. Bone

Bone is the most common site of metastasis in breast cancer. Local treatment is typically indicated in the presence of spinal cord compression, pathological fractures, or pain. In the oligometastatic setting, curative-intent treatment may be considered in selected patients with a limited number of osseous lesions.

Retrospective data suggest that this subgroup of patients may achieve better symptom control and potentially improved survival outcomes. However, it should be noted that patients with bone metastases often have a more favorable prognosis and respond well to systemic therapy; moreover, surgical intervention for bone lesions may be associated with significant complication rates. Therefore, radiotherapy is generally the preferred modality.

In cases of bone-only oligometastases, high-dose stereotactic radiotherapy (HSRT/SBRT) has demonstrated substantial benefit, with reported 5-year and 10-year overall survival rates of 83% and 75%, respectively, compared with 31% and 17% in patients without bone-only disease ($p = 0.002$). For isolated sternal metastases, surgery or radiotherapy is recommended. A phase II study evaluating SBRT or intensity-modulated radiotherapy (IMRT) to all metastatic lesions (predominantly bone) reported 1-year and 2-year progression-free survival rates of 75% and 53%, respectively.

Historically, bone metastases have been primarily managed with radiotherapy due to its efficacy in pain relief and local control. SBRT is particularly effective in solitary bone metastases, achieving durable local control with low toxicity. However, distinguishing true oligometastatic bone disease from more widespread skeletal involvement remains challenging, necessitating careful imaging evaluation and biopsy when appropriate. While the role of SBRT in improving quality of life has been well established, its impact on overall survival requires further investigation.

4.3. Lung

Oligometastatic lung disease can be managed with either surgical resection or stereotactic body radiation therapy (SBRT), depending on patient characteristics and lesion features. Surgery is particularly valuable when histopathological confirmation is required to differentiate primary lung cancer from metastatic disease, which may occur in approximately 12-57% of surgically resected pulmonary lesions. Video-assisted thoracoscopic surgery (VATS) has improved procedural safety while reducing invasiveness.

Several studies have demonstrated improved progression-free survival (PFS) in patients undergoing pulmonary metastasectomy. A landmark study reported a 5-year survival rate of 38% and a median overall survival (OS) of 37 months following complete resection. A meta-analysis of 16 studies demonstrated a pooled 5-year survival rate of 46% after surgery. Favorable prognostic factors include a disease-free interval (DFI) >36 months, solitary metastasis, estrogen receptor (ER) positivity, small lesion size, and achievement of microscopically negative margins (R0). In contrast, DFI ≤3 months, multiple lesions, and ER-negative status are associated with poorer outcomes. However, perioperative morbidity and mortality should be carefully considered.

SBRT represents a noninvasive alternative with high rates of local control and low toxicity, although radiation-induced pneumonitis remains a potential risk. The phase II SABR-COMET trial, which included multiple tumor types (with approximately 50% of treated lesions located in the lung), demonstrated improved overall survival with SBRT compared with standard palliative care (median OS 50 vs. 28 months; HR 0.47). A meta-analysis of 10 studies involving 467 patients with oligometastatic breast cancer treated with SBRT reported 1-year and 2-year local control rates of 97% and 90%, respectively, with overall survival rates of 93% at 1 year and 81% at 2 years.

Currently, no randomized trials have directly compared surgery with SBRT in oligometastatic lung disease from breast cancer. Therefore, treatment selection should be individualized based on the number of lesions, disease-free interval, tumor biology, and patient performance status.

4.4. Brain (Without Extracranial Metastases)

Brain metastases represent a poor prognostic factor across multiple malignancies. In a subset of selected breast cancer patients, brain metastases may occur in the absence of extracranial disease. Although the underlying mechanisms remain unclear, one potential explanation is the limited penetration of certain systemic therapies across the central nervous system.

Local treatment should be considered for patients with isolated brain metastases. In cases of a solitary lesion, surgical resection may be preferred. However, other factors, such as patient performance status, must also be taken into account. In patients with multiple brain lesions, stereotactic radiosurgery (SRS) is generally recommended [24]. Whole-brain radiotherapy (WBRT) may be considered in cases where surgery or SRS is not feasible due to extensive intracranial disease. Several studies have shown that adjuvant WBRT following surgical resection improves local control but does not confer an overall survival benefit and is associated with neurocognitive toxicity. Following local therapy, there remains insufficient evidence regarding the continuation of systemic therapy or the optimal duration of treatment, if administered.

4.5. Lymph Nodes

Distant lymph node metastases, particularly contralateral axillary metastases (CAMs), may represent a subgroup of oligometastatic disease

with one of the highest potentials for curative treatment. Emerging evidence suggests that CAMs should be considered a "quasi-oligometastatic" entity, in which aggressive local treatment strategies may achieve durable remission.

In cases of CAMs without concomitant visceral metastases, surgical resection combined with systemic therapy may provide significant clinical benefit, with improvements observed in both progression-free survival (PFS) and overall survival (OS) in selected patients.

5. ONGOING CLINICAL TRIALS

Multiple phase III trials are currently underway worldwide to evaluate the impact of local therapies on clinical outcomes in patients with oligometastatic breast cancer (Table 1). Most of these studies use progression-free survival (PFS) as the primary endpoint; however, the JCOG2110 trial is notable as the only study employing overall survival (OS) as the primary endpoint. SBRT represents the principal intervention across these trials, while surgical approaches are generally reserved for cases in which SBRT is not feasible. Notably, several studies include triple-negative breast cancer (TNBC) as a predefined subgroup; however, based on findings from the NRG-BR002 trial, the benefit of local therapy in this population remains controversial. In contrast, ongoing and future trials focusing on estrogen receptor (ER)-positive or HER2-positive subtypes are anticipated to yield more promising results. The outcomes of these ongoing prospective trials are expected to clarify the indications and optimal integration of local therapies in the oligometastatic setting. Detailed analyses of these results will provide critical evidence to refine treatment strategies for this unique metastatic state.

6. CLINICAL IMPLICATIONS OF CTDNA AND LIQUID BIOPSY IN OLIGOMETASTATIC BREAST CANCER

Liquid biopsy, including the analysis of circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and exosomes, has emerged as a minimally invasive tool for real-time monitoring of tumor dynamics. ctDNA analysis may facilitate patient stratification, enabling treatment intensification with systemic therapy or early implementation of local interventions prior to radiologic disease progression. In parallel, molecular profiling of CTCs or exosomal RNA can identify emerging mechanisms of resistance and potential therapeutic targets. Integration of liquid biopsy into clinical practice holds promise for optimizing surveillance strategies and enhancing personalized disease management. At the molecular level, the presence of ctDNA following local therapy in early-stage breast cancer has been associated with a higher risk of recurrence. The median time to overt metastatic relapse is typically less than one year, suggesting that early detection of ctDNA positivity may allow identification of metastatic disease at a subclinical stage, when disease burden may still be limited. Accordingly, intensified imaging surveillance in ctDNA-positive patients may be beneficial, although further validation from prospective clinical trials is required. Conversely, in patients with oligometastatic breast cancer who have undergone curative-intent treatment, the role of adjuvant systemic therapy remains controversial. A key unresolved question is whether ctDNA positivity should serve as an indication for additional systemic therapy, which warrants further investigation in future studies.

Table 1. Ongoing Prospective Trials Evaluating the Prognostic Impact of Local Therapies in Oligometastatic Breast Cancer

NCT Number	Study Title	Conditions	Interventions	Primary Outcome Measures	Phases	Enrollment	Start Date
NCT04698252	Local Therapy for ER/PR-positive Oligometastatic Breast Cancer (LARA)	Breast Cancer	Radiotherapy/ surgery/ radiofrequency ablation	Two-year progression-free survival (PFS): The PFS is defined as the time from randomization until the date of progression or death. The 2-year PFS rate represents the probability of a patient being free of progression 2 years after randomization and will be estimated using the Kaplan–Meier method from the baseline to 2 years later.	PHASE 2	74	1 April 2021
NCT03808337	Investigating the Effectiveness of Stereotactic Body Radiotherapy (SBRT) in Addition to Standard of Care Treatment for Cancer That Has Spread Beyond the Original Site of Disease	Triple-Negative Breast Cancer/Non-Small-Cell Lung Cancer	SBRT/systemic therapy/standard of care	Progression-free survival: To determine whether stereotactic body radiotherapy administered to all sites of metastatic disease in patients with oligometastatic non-small-cell lung cancer or triple-negative breast cancer improves progression-free survival (PFS), defined as time from randomization to disease progression or death, compared to standard-of-care therapy alone, for up to 2 years.	PHASE 2	145	16 January 2019
NCT03808662	Randomized Study of Stereotactic Body Radiation Therapy (SBRT) in Patients With Oligoprogressive Metastatic Cancers of the Breast and Lung	Triple-Negative Breast Cancer/Non-Small-Cell Lung Cancer	SBRT/standard of care	Progression-free survival: To study if the addition of early SBRT to the treatment of extra-cranial oligoprogressive metastatic disease could prolong the PFS compared to treatment with no SBRT. The PFS is defined as the time from randomization to disease progression or death and measured for up to 52 weeks after the final participant is enrolled.	PHASE 2	107	16 January 2019
NCT06135714	Metastasis-directed Therapy for Oligometastases of Breast Cancer (JCOG2110: ORIGAMI)	Breast Cancer	Systemic therapy for 12 weeks after primary registration/radiation therapy (SBRT/conventional RT) and surgery/same systemic therapy after secondary registration	Overall survival after second registration over 5 years.	PHASE 3	340	8 November 2023
NCT02089100	Trial of Superiority of Stereotactic Body Radiation Therapy in Patients With Breast Cancer (STEREO-SEIN)	Breast Cancer	SBRT/systemic treatment	Progression-free survival (PFS), events: Local recurrence, distant progression of target metastases, any new metastasis, death from any cause. Definition of progression is based on RECIST1.1 criteria. Progression is assessed locally, in any metastasis present at time of randomization or in any newly diagnosed metastasis, with minimal follow-up of 3 years for all patients.	PHASE 3	280	1 February 2014
NCT04646564	Radiotherapy for Extracranial Oligometastatic Breast Cancer	Breast Cancer	Standard of care/ radiotherapy + standard of care	Progression-free survival: Time from randomization to disease progression at any site or death. Measured over 2 years.	PHASE 3	170	6 April 2021

7. CONCLUSION

Although metastatic breast cancer is traditionally considered an incurable disease, a subset of patients with a limited metastatic burden may achieve prolonged disease control when treated with an aggressive multimodal approach combining systemic therapy and definitive local interventions.

Significant advances in systemic treatment-including anti-HER2 therapies, CDK4/6 inhibitors, immunotherapy, and antibody-drug conjugates-together with improved early detection of metastatic disease, have contributed to improved survival outcomes and have expanded the potential for curative-intent strategies in oligometastatic breast cancer. However, the optimal timing for definitive local intervention remains unclear, and the lack of well-designed clinical trials continues to limit the establishment of standardized treatment strategies. In the current context, a rational approach involves a neoadjuvant-like strategy with initial systemic therapy, followed by definitive surgery and/or radiotherapy, and subsequent adjuvant systemic treatment. Although cure cannot be guaranteed, a proportion of patients may achieve durable remission, potentially lasting for many years or even lifelong. Therefore, further strategic clinical trials and a multidisciplinary, personalized treatment approach are essential to optimize long-term disease control in this unique patient population.

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TREATMENT OUTCOME OF NEOADJUVANT THERAPY WITH TCHP REGIMEN IN PATIENTS WITH HER2+ BREAST CANCER AT HANOI ONCOLOGY HOSPITAL

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ABSTRACT

Objective: To evaluate the efficacy of neoadjuvant treatment using the TCHP regimen in patients with HER2-positive breast cancer at Hanoi Oncology Hospital.

Materials and Methods: A combined retrospective and prospective cross-sectional descriptive study was conducted on patients with HER2-positive breast cancer treated with the TCHP regimen as neoadjuvant at Hanoi Oncology Hospital from January 2023 to September 2025.

Results: Among 36 enrolled patients, the average age was 48.6 years (range 30–70). There were 20 patients (55.6%) with stage II and 16 patients (44.4%) with stage III disease; 14 patients (38.9%) underwent clip placement before treatment. After 3 cycles, 7 patients (19.4%) achieved clinical complete response; after 6 cycles, this rate doubled to 14 patients (38.9%). The pathological complete response (pCR) rate was achieved in 24 patients (75%). Clinical complete response was a predictive factor for achieving pCR ($p < 0.05$), while no significant association was found between pCR and age, stage, histological grade, hormone receptor status, or Ki-67. No patients experienced disease progression during treatment. Most adverse events (AEs) were at grade 1–2. The most common grade 3–4 AE was neutropenia (3 patients, 8.3%). No grade 3–4 thrombocytopenia, hepatic, renal, or cardiac toxicities were observed. Two patients (5.6%) experienced grade 1 left ventricular ejection fraction reduction without requiring treatment delay.

Conclusion: The TCHP regimen demonstrates high efficacy with good tolerability and manageable, predictable AEs in patients with HER2+ breast cancer.

Keywords: HER2-positive breast cancer, neoadjuvant therapy, TCHP.

1. INTRODUCTION

Breast cancer is the most common cancer among women worldwide and the leading cause of cancer-related mortality in females.[1]whereas around one in nine men and one in 12 women die from it. Lung cancer was the most frequently diagnosed cancer in 2022, responsible for almost 2.5 million new cases, or one in eight cancers worldwide (12.4% of all cancers globally According to GLOBOCAN 2022, there were 24,563 new cases of breast cancer, with an age-standardized incidence rate of 46.1 per 100,000 population in Vietnam. HER2-positive breast cancer is often associated with poor prognosis, rapid progression, and early recurrence.

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Breast cancer treatment is a typical example of multimodal therapy combining local-regional approaches (surgery, radiotherapy) and systemic treatments (chemotherapy, endocrine therapy, targeted therapy, immunotherapy). Neoadjuvant chemotherapy is administered before surgery and has comparable survival outcomes to adjuvant chemotherapy. [2]Additionally, neoadjuvant therapy offers advantages such as downstaging inoperable tumors to operable status, increasing breast-conserving surgery rates, and enabling assessment of tumor response. In HER2-positive breast cancer, multiple studies have shown that achieving pathological complete response (pCR) is associated with improved disease-free survival (DFS) and overall survival (OS).[3] Therefore, pCR is an important prognostic factor and a key endpoint in evaluating treatment efficacy.

The TCHP regimen combines dual HER2-targeted therapy (trastuzumab and pertuzumab) with chemotherapy (docetaxel and carboplatin), administered every 3 weeks for 6 cycles before surgery. The TRYPHAENA trial demonstrated that TCHP achieved comparable efficacy to anthracycline-containing regimens, with a pCR rate of 66.2%. Patients achieving pCR had significantly improved DFS (HR = 0.27), while cardiac safety was favorable, with only 3.9% experiencing decreased left ventricular ejection fraction compared to 5.6% in anthracycline-containing regimens. [4] Despite its proven efficacy and widespread use, data on the TCHP regimen in Vietnam remain limited. Therefore, we conducted this study to evaluate the efficacy of this regimen in the neoadjuvant treatment of HER2-positive breast cancer.

2. MATERIALS AND METHODS

2.1. Study population

Patients with HER2-positive breast cancer treated with neoadjuvant TCHP at Hanoi Oncology Hospital from January 2023 to September 2025 were included.

Inclusion criteria

Histologically confirmed invasive breast carcinoma with HER2 positivity on immunohistochemistry; cases with HER2 (++) required confirmation by dual-ISH or FISH amplification;

Stage II–III disease: tumor ≥ 2 cm or node-positive;

Received neoadjuvant TCHP regimen;

ECOG performance status ≤ 2;

No contraindications to anti-HER2 therapy: severe cardiovascular diseases, LVEF < 50%;

Adequate hematologic and biochemical parameters;

Complete medical records available.

Exclusion criteria

Bilateral breast cancer;

Concurrent malignancies;

Severe comorbidities with high risk of mortality;

Non-compliance with treatment.

2.2. Methods

Study design: Retrospective–prospective descriptive study.

Study period: March 2024 to September 2025.

Sample size: Convenience sampling, all patients who satisfied the inclusion criteria and did not violate exclusion criteria were enrolled.

Data collection

Data collected from archived medical records (retrospective group) and inpatient records (prospective group).

Standardized medical report forms were used.

AEs were recorded and clinical response assessed after each cycle.

Response was evaluated after 3 and 6 cycles using clinical and imaging assessment, pCR was evaluated following the pathology protocol.

Response rate and selected factors's association with pCR response were calculated.

Treatment regimen:

Table 1: TCHP regimen

Drug	Dose	Administration
Pertuzumab	840 mg Cycle 1	In 250 mL sodium chloride 0.9% over 60 minutes
	420 mg Cycle 2 - 6	In 250 mL sodium chloride 0.9% over 30-60 minutes
Trastuzumab	8 mg/kg Cycle 1	In 250 mL sodium chloride 0.9% over 90 minutes
	6 mg/kg Cycle 2 - 6	In 250 mL sodium chloride 0.9% over 30 minutes
Docetaxel	75 mg/m^2	In 250 mL to 500 mL sodium chloride 0.9% over 60 minutes
Carboplatin	AUC 6	In 500 mL glucose 5% over 30-60 minutes

Study variables

- Patient characteristics: age, PS, menopausal status, tumor characteristics (stage, immunohistochemistry, Dual-ISH, histological type, histological grade)

- Treatment outcomes: response rate and adverse events.

+ Clinical response was evaluated according to RECIST 1.1 criteria after every 3 cycles.

+ Pathological response was assessed according to the Chevallier classification. Based on this classification, responses were categorized into two groups: pathological complete response (pCR) yp T0/Tis ypN0. and non–pathological complete response (non-pCR).

+ Adverse events were graded according to CTCAE version 5.0

- Management of treatment-related adverse events:

+ Prophylaxis of neutropenia using pegfilgrastim administered on day 2, at least 24 hours after completion of chemotherapy infusion.

+ Patients experiencing AEs were managed according to severity.

+ Management of cardiotoxicity related to trastuzumab and pertuzumab: if LVEF < 50%, treatment was discontinued and the patient was referred for cardiology evaluation.

Statistical analysis

Data were analyzed using SPSS version 20.0.

2.3. Research ethics

The study regimen was approved and issued in the national guidelines for diagnosis and treatment by the Ministry of Health. The study was conducted with the approval of Hanoi Oncology Hospital Ethics Committee. This was a descriptive study and did not interfere with the patient's treatment process. All patient-related information and clinical data were kept confidential. The study results were intended solely to improve treatment quality and quality of life, and not for any other purposes.

4. RESULTS

4.1. Patient characteristics

Table 2. Patient characteristics

Patient characteristics	(n=36)	(%)
Age(mean: 48.6)		
Reason for hospital admission	5	13.5
Self-detected breast lump	24	66.7
Self-detected lymph node	5	13.9
Self-detected breast lump and node	7	19.4
Menstrual status		
Postmenopausal	15	41.7
Premenopausal	21	58.3
cT		
cT1	1	2.8
cT2	24	66.7
cT3	4	11.1
cT4	7	19.4
cN		
cN0	10	27.8
cN1	15	41.7
cN2	7	19.4
cN3	4	11.1
Stage		
IIA	10	27.8
IIB	10	27.8
IIA	7	19.4
IIB	5	13.9
IIC	4	11.1
Clip placement		
Yes	14	38.9
No	22	61.6
Pathology		
NST	34	94.4
Micropapillary carcinoma	1	2.8
Papillary carcinoma	1	2.8
Grade		
2	31	86.1
3	5	13.9
HR		
Positive	18	50
Negatiive	18	50
Ki-67		
< 15%	6	16.7
15-35%	9	25
> 35%	21	58.3

HR: Hormone receptor, NST: invasive carcinoma of no special type.

A total of 36 patients were enrolled, including 10 patients in the retrospective group and 26 patients in the prospective group. The characteristics of the study population are presented in the above Table 2.

4.2. Treatment efficacy

Table 3. Response rate

Response		N	%
Clinical response			
3 cycles	CR	7	19.4
	PR	25	69.4
	SD	4	11.1
	PD	0	0
6 cycles	CR	14	38.9
	PR	19	52.8
	SD	3	8.3
	PD	0	0

Response		N	%
Planned for surgery		36	100
Surgical methods	MRM	24	75
	SSM	7	21.9
	Conservation	1	3.1
	Total	32	100
Pathology response			
Chevallier classification	Grade 1	17	53.1
	Grade 2	7	21.9
	Grade 3	5	15.6
	Grade 4	3	9.4
	Total	32	100
pCR	pCR	24	75
	Non pCR	8	25
	Total	32	100

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, MRM: modified radical mastectomy, SSM: skin-sparing mastectomy, pCR: pathology complete response (yp T0/Tis ypN0).

According to the above Table 3, clinical response was evaluated according to RECIST 1.1 criteria. The overall response rate was 88.9%. Four patients had stable disease, and no patients were reported to have disease progression during treatment. All 36 patients completed 6 cycles of neoadjuvant therapy and were planned for surgery. The majority underwent modified radical mastectomy (MRM), with only one patient undergoing breast-conserving surgery and seven patients undergoing skin-sparing mastectomy. Seventeen patients had no residual cancer in both the breast tumor and axillary lymph nodes (53.1%), while seven patients had residual carcinoma in situ (21.9%). The pCR rate (grade 1 and grade 2 according to Chevallier classification) was 75%.

Table 4. Response rate and correlated factors

Correlated factors	pCR	No pCR	p
Age(mean: 48.6)	50.5	42.6	0.109
cT			
cT1	0	1	
cT2	16	5	
			0.225
cT3	4	0	
cT4	4	2	
cN			
cN0	8	1	
cN1	7	7	0.041
cN2	6	0	
cN3	3	0	
Stage			
II	13	6	0.42
III	11	2	
Clinical response			
CR	14	0	
PR	10	5	0.001
SD	0	3	
Pathology			
NST	23	7	
			0.444
Other	1	1	
Grade			
2	19	8	
			0.296
3	5	0	
HR			
Positive	11	6	
			0.229
Negative	13	2	
Ki-67			

Correlated factors	pCR	No pCR	p
> 15%	3	3	0.346
15-35%	7	1	
> 35%	14	4	

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, MRM: modified radical mastectomy, SSM: skin-sparing mastectomy, pCR: pathology complete response (yp T0/Tis ypN0), HR: hormone receptor, NST: invasive carcinoma of no special type.

Table 4 showed that the pCR rate was associated with nodal metastasis status (p = 0.041), and clinical response was a predictor of pCR (p = 0.001). Meanwhile, we did not observe any statistically significant differences in pCR rates when analyzing associations with age, tumor stage, overall stage, tumor histology, histological grade, hormone receptor status, and Ki-67(p > 0.05).

Table 5. Treatment adverse events

Adverse Event (AE)	Grade 3, 4		Grade 1, 2	
	n = 36	%	n=36	%
Neutropenia	3	8.3	4	11.1
Febrile neutropenia	0	0		
Anemia	1	2.8	7	19.4
Thrombocytopenia	0	0	4	11.1
Nausia, vomiting	0	0	14	38.9
Increased serum creatinine	0	0	0	0
Increased AST	0	0	16	44.4
Increased ALT	0	0	17	47.2
Decreased LVEF	0	0	2	5.6

LEVF: left ventricular ejection fraction.

During treatment, most adverse events were at grade 1–2. The most common grade 3–4 AE was neutropenia. No grade 3–4 thrombocytopenia, hepatic, or renal toxicities were recorded. No patients developed heart failure or a decrease in left ventricular ejection fraction, leading to treatment delay or discontinuation. Two patients experienced grade 1 reduction in LEVF that did not require treatment delay.

5. DISCUSSION

Neoadjuvant chemotherapy was previously associated with concerns about delaying local treatment; if the disease progresses on neoadjuvant, patients could lose the chance of definitive treatment. However, breast cancer is considered a systemic disease, emphasizing the importance of systemic therapy. Numerous studies have demonstrated that neoadjuvant chemotherapy provides survival outcomes comparable to adjuvant therapy.[2] Recent evidences indicate that pCR is the most important endpoint, strongly associated with long-term outcomes such as OS and DFS.[3] It also allows treatment escalation or de-escalation strategies, particularly relevant in HER2-positive disease with the advancement of targeted therapies. The development of anti-HER2 therapies, starting with trastuzumab followed by pertuzumab, has demonstrated an improvement in pCR rates when dual HER2 blockade is combined. The NeoSphere study showed that the pCR rate increased from 29% to 46% with the combination of dual HER2 blockade and chemotherapy.[5] The combination of non-anthracycline chemotherapy with trastuzumab and pertuzumab helps reduce AEs without compromising pCR rates in the neoadjuvant setting.[6]

In our study, 24 patients achieved pCR (53.1% group 1 and 21.9% group 2 according to the Chevallier classification), accounting for 75%. This is a relatively high pCR rate compared with other studies such as the THP regimen in the NeoSphere study, where the pCR rate was 45.8%. [5] This difference may be explained by the fact that our regimen used a combination of two chemotherapeutic agents rather than docetaxel alone com-

bined with anti-HER2 therapy. When compared with the landmark studies using the same TCHP regimen, namely TRAIN-2 and TRYPHAENA, where the pCR rates were 68% and 66%, respectively, our response rate was also higher. Furthermore, when compared with anthracycline-based regimens, which have traditionally been considered the backbone of breast cancer treatment, the pCR rate of the TCHP regimen is not inferior, and may even be somewhat higher, as shown in the results of these two studies.[4], [6] When compared with real-world data from Kim et al. in South Korea (2022) using neoadjuvant TCHP, our pCR rate was also higher (75% vs. 64%).[7] Compared with a domestic study by Phung Thi Huyen (2021), which evaluated AC-THP and TCHP in 20 patients with neoadjuvant breast cancer and reported a pCR rate of 80%, our result was slightly lower.[8] This difference may be attributed to heterogeneity in study populations (high proportion of cT2, stage II, HR-negative status, treatment regimens, sample size, disease stage, and pathological and molecular characteristics). Therefore, further studies with larger sample sizes are needed.

Many studies have attempted to identify predictive factors for pCR. The TECHNO study showed no difference in pCR rates according to age (<40 vs. ≥40), histological type, histological grade, tumor stage, nodal stage, and hormone receptor status.[9] However, the GeparQuattro study demonstrated a significantly different pCR rate in the hormone receptor-negative group (43.5%) compared with the hormone receptor-positive group (23.4%), with $p < 0.001$.[10] In our analysis, while evaluating pCR according to age, tumor stage (T), nodal stage (N), overall stage, histological type, histological grade, hormone receptor status, and Ki-67, we did not observe any association between these factors and pCR, which is consistent with the TECHNO study. The pCR rate in our study was higher in patients who achieved clinical complete response (100% vs. 66.7%, $p < 0.05$). This finding is similar to that reported by Hang D.N (2022), where a higher pCR rate was observed in patients achieving clinical complete response ($p < 0.001$).[11]

Our study also showed that the TCHP regimen was well tolerated. The most common grade 3–4 adverse events were neutropenia and anemia, with rates of 8.3% and 2.8%, respectively. These rates were significantly lower compared with the same regimen used in the TRYPHAENA study, where the rate of grade 3–4 neutropenia was 46%, and even higher in the TRAIN-2 study at 54%. [4], [5] This may be explained by the routine use of prophylactic G-CSF in all patients, as the TCHP regimen carries a high risk of neutropenia and is included in national guidelines. The higher rate of neutropenia in the TRAIN-2 study may also be due to the use of 9 cycles of TCHP instead of 6 cycles. This may be one of the reasons why 6 cycles of TCHP are recommended as the standard regimen, as 9 cycles do not improve efficacy but increase AEs. Cardiotoxicity is always a concern when using anti-HER2 therapies; however, in our study, no cases of severe cardiac events or treatment delay/discontinuation due to cardiac toxicity were observed. Overall, the TCHP regimen demonstrated good tolerability, both in terms of hematologic and non-hematologic AEs.

6. CONCLUSION

The TCHP regimen demonstrated high efficacy with a high pCR rate (75%) and good tolerability, with manageable AEs.

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PRELIMINARY RESULTS OF TOTAL NEOADJUVANT THERAPY IN STAGE II-III RECTAL CANCER: REAL-WORLD DATA FROM K HOSPITAL

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ABSTRACT

Background: Total Neoadjuvant Therapy (TNT) has recently emerged as a promising approach in the management of locally advanced rectal cancer. However, real-world evidence on its effectiveness and safety in Vietnam remains limited.

Methods: We retrospectively analyzed 148 patients with stage II–III rectal cancer of the middle or lower rectum treated with TNT at K Hospital. TNT regimens included chemotherapy combined with either short-course or long-course chemoradiation therapy. Surgery was performed 4–8 weeks after completion of TNT. Treatment outcomes, pathological response, sphincter preservation, and adverse events were assessed.

Results: The mean age was 57.2 years, with a male-to-female ratio of 1.96:1. Tumor downstaging was achieved in 68.9% of patients with a pathological complete response (pCR) rate of 25.7% and sphincter preservation rate of 71.6%. Peripheral neuropathy and elevated AST were the most common adverse events. Grade 3–4 toxicities most frequently included neutropenia (8.1%) and diarrhea (4.1%). Multivariate analysis revealed that earlier tumor stage and the use of triplet chemotherapy regimens were significantly associated with higher pCR rates.

Conclusions: Total neoadjuvant therapy (TNT) was well tolerated in this cohort and was associated with favorable pathological response in patients with stage II–III rectal cancer. Further prospective studies are warranted to confirm these findings and optimize treatment strategies in the Vietnamese setting.

Keywords: Rectal cancer; Total neoadjuvant therapy (TNT); pathological complete response (pCR).

1. INTRODUCTION

Rectal cancer is one of the most common malignancies of the gastrointestinal tract. According to GLOBOCAN 2022, there are approximately 784,139 new cases and 365,852 deaths from rectal cancer worldwide each year[1]. In Vietnam, colorectal cancer ranks fourth in incidence and fifth in cancer-related mortality[1].

Over recent decades, significant advances in treatment have contributed to improved prognosis for patients with rectal cancer. Notably, these include total mesorectal excision (TME), preoperative concurrent chemoradiotherapy, and more recently, Total Neoadjuvant Therapy (TNT) has emerged as an alternative to the standard preoperative chemoradiotherapy regimen, aiming to achieve tumor downstaging, increase sphincter

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preservation rates, reduce distant metastasis and recurrence, prolong survival, and improve patients' quality of life.

The efficacy of TNT has been demonstrated in phase III randomized controlled trials such as RAPIDO[2] and PRODIGE-23[3], which reported higher pathological complete response (pCR) rates, improved disease-free survival, and acceptable toxicity profiles. Consequently, TNT is increasingly recognized as a global treatment paradigm. However, most large-scale studies have been conducted in Western populations, which may not fully reflect the clinical characteristics of Asian patients in general and Vietnamese patients in particular.

In Vietnam, TNT has been implemented in several oncology centers, including K Hospital. Preliminary studies have reported pCR rates ranging from 19.4% to 33.3%[4–7] and high rates of sphincter preservation, with treatment-related toxicities generally limited to mild-to-moderate severity. Nevertheless, these studies are limited by small sample sizes and often evaluate only a single TNT sequence, without comparing different TNT strategies in real-world clinical practice in Vietnam.

Based on this context, we conducted this study to evaluate the efficacy and toxicity of various TNT regimens at K Hospital during the period 2021–2025, and to analyze factors associated with pathological complete response as well as selected treatment-related toxicities.

2. MATERIALS AND METHODS

2.1. Subjects

A total of 148 patients with stage II–III mid and low rectal cancer who received Total Neoadjuvant Therapy (TNT) at K Hospital between January 2021 and May 2025 were included in this study.

Inclusion Criteria

- Patients diagnosed with mid to low-rectal cancer with histopathological confirmation of adenocarcinoma based on endoscopic biopsy.

- Tumors staged as stage II or III (cT3-4 and/or cN+ M0) according to the UICC/AJCC 8th edition (2017).

- Availability of complete medical records.

Exclusion Criteria:

- Prior treatment for rectal cancer.

- Presence of other malignancies within the past 5 years.

- Previous pelvic radiotherapy or chemotherapy.

- Pregnant or breastfeeding women.

- Patients with severe acute or chronic comorbid conditions.

2.2. Study Methods

- Study design: Retrospective observational study.

- Sample size and sampling method: Total sampling.

- Study setting and period: K Hospital, from January 2021 to May 2025.

2.3. Study Procedure

Step 1: Patient selection and pretreatment evaluation.

Step 2: Treatment according to Total Neoadjuvant Therapy (TNT) protocols:

1. Short-course radiotherapy → consolidation chemotherapy → surgery

2. Long-course chemoradiotherapy→ consolidation chemotherapy → surgery

3. Induction chemotherapy → long-course chemoradiotherapy → surgery

In this real-world cohort, the selection and sequencing of Total Neoadjuvant Therapy were not protocol-mandated and were based on multidisciplinary team discussions, physician experience and patient- and disease-related factors.

- Radiotherapy:

+ Target volume delineation: Defined according to the 2016 international consensus guidelines

+ Radiation dose: Long-course chemoradiotherapy: Total dose of 50.4 Gy delivered in 28 fractions, with concurrent Capecitabine 825 mg/m² administered twice daily on radiotherapy days (5 days/week); Short-course radiotherapy: Total dose of 25 Gy delivered in 5 fractions.

- Chemotherapy: Consolidation/induction chemotherapy regimens included mFOLFIRINOX, mFOLFOX6, or CAPEOX administered over 12-16 weeks.

Step 3: Monitoring and recording all treatment-related adverse events during and after therapy.

Step 4: Assessment of clinical and paraclinical response before surgery.

Step 5: Surgery is performed 4-8 weeks after completion of neoadjuvant treatment.

Step 6: Postoperative evaluation and consideration of adjuvant therapy.

Step 7: Postoperative follow-up.

Treatment completion was defined as the receipt of all planned radiotherapy dose and all planned cycles of chemotherapy without premature discontinuation.

**** Study Variables and Outcomes:***

- Patient characteristics (age, gender, tumor stage).

- Treatment response (pathological complete response [pCR], resection margin status, downstaging rate).

- Treatment-related toxicities.

**** Research Instruments and Data Collection Methods:***

- Medical records of all eligible rectal cancer patients meeting inclusion and exclusion criteria were collected, organized by patient, and chronologically.

- Patient data were extracted from medical records using a standardized data collection form (case report form).

**** Statistical Analysis:***

Data were analyzed using SPSS version 26.

Baseline characteristics between treatment groups were compared using the chi-square test or Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney U test for continuous variables, as appropriate. The primary endpoint was pathological complete response (pCR). Factors associated with pCR were initially evaluated using univariable logistic regression analysis. Multivariable logistic regression was then performed to identify independent factors associated with pCR. Variables included in the multivariable model were selected a priori based on clinical relevance, including treatment strategy and key tumor characteristics. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). A two-sided p-value < 0.05 was considered statistically significant.

2.4. Ethical Considerations

The study protocol was approved by the Institutional Review Board of K Hospital on April 22, 2025. All collected data were kept confidential and used solely for research purposes.

3. RESULTS

A total of 148 patients with stage II–III rectal cancer who received Total Neoadjuvant Therapy (TNT) at three facilities of K Hospital between January 2021 and May 2025 were included in this study.

The mean age of the study population was 57.2 ± 11.4 years, with a male-to-female ratio of 1.96:1. Overall, the majority of patients presented with cT3–T4 disease (94.4%), and 85.1% had clinically suspected nodal metastases.

Three TNT regimens were implemented at K Hospital. The most commonly used regimen was

long-course concurrent chemoradiotherapy followed by consolidation chemotherapy (60.8%), followed by induction chemotherapy combined with long-course chemoradiotherapy (22.9%), and short-course radiotherapy followed by consolidation chemotherapy (18.2%).

The most frequently utilized radiotherapy technique was three-dimensional conformal radiotherapy (3D-CRT) (66.2%), while intensity-modulated radiotherapy/volumetric modulated arc therapy (IMRT/VMAT) accounted for 33.1%.

Table 1: Baseline Characteristics of the Study Patients

Characteristics		n (%)
Age		57.2±11.4
Gender	Female	50 (33.8%)
	Male	98 (66.2%)
Stage T	cT2	8 (5.4%)
	cT3	114 (77.0)
	cT4	26 (17.6)
Stage N	cN0	22 (14.9)
	cN1	56 (37.8)
	cN2	70 (47.3)
MRF	(+)	48 (32.4)
	(-)	96 (64.9)
	Missing	4 (2.7)
EMVI	(+)	31 (20.9)
	(-)	113 (76.4)
	Missing	4 (2.7)
Position Tumor	Middle rectum	61 (41.2)
	Lower rectum	87 (58.8)
Treatment Regimens	Induction CT + LCRT	31 (21.0)
	LCRT + Consolidation CT	90 (60.8)
	SCRT + Consolidation CT	27 (18.2)
Chemotherapy regimens	mFOLFIRINOX	29 (19.6)
	mFOLFOX6/ XELOX	119 (80.4)
Radiotherapy techniques	3D	98 (66.2)
	IMRT	27 (18.2)
	VMAT	22 (14.9)
	Missing	1 (0.7)
Treatment completion	Radiationtherapy Completed	148 (100)
	Incompleted	0 (0)
	Chemotherapy Completed	115 (77.7)
	Incompleted	33 (22.3)

Among the study population, the majority of patients achieved R0 resection (98.6%). In addition, the sphincter preservation rate was 71.6%. Following treatment, tumor downstaging was observed in 68.9% of patients, and 25.7% achieved a pathological complete response (pCR).

Table 2: Response Evaluation

Characteristics		n (%)
Interval between treatment completion and surgery		43±14 days
Resection margin status	R0	146 (98.6)
	R1	1 (0.7)
	R2	1 (0.7)
Sphincter preservation	Yes	106 (71.6)
	No	42 (28.4)
ypT	ypT0	39 (26.3)
	ypT1	8 (5.4)
	ypT2	43 (29.1)
	ypT3	49 (33.1)
	ypT4	9 (6.1)

Characteristics		n (%)
ypN	ypN0	120 (81.1)
	ypN1	26 (17.6)
	ypN2	2 (1.3)
pCR	Complete response	38 (25.7)
	Incomplete response	110 (74.3)
Tumor downstaging	Yes	102 (68.9)
	No	46 (31.1)
Nodal downstaging	Yes	135 (91.2)
	No	13 (8.8)

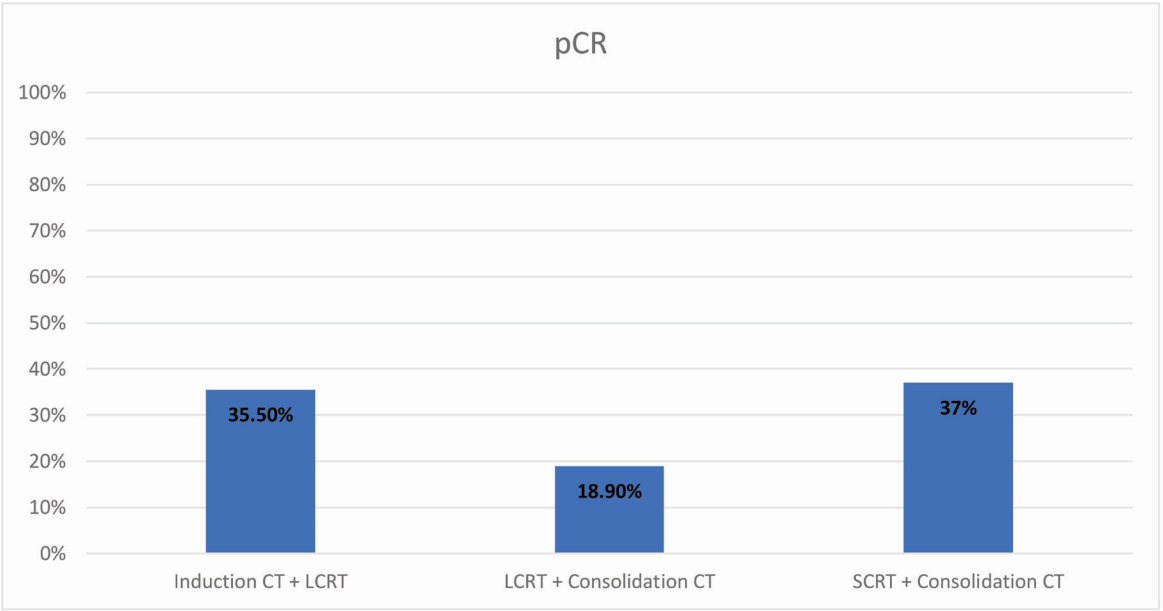

Chart 1: Pathological complete response (pCR) rates among the three Total Neoadjuvant Therapy (TNT) regimens

Analysis of Factors Associated with Pathological Complete Response (pCR): Multivariable logistic regression analysis demonstrated that:

- The mFOLFIRINOX regimen was associated with a 2.8-fold increase in the likelihood of achieving pathological complete response (pCR) compared to doublet chemotherapy regimens (OR = 2.795; p = 0.033).

- Patients with cT2–3 tumors had a 4.7-fold higher likelihood of achieving pCR compared to those with cT4 tumors (OR = 0.213; p = 0.048).

The use of triplet chemotherapy and tumor stage were identified as independent predictive factors associated with pathological complete response.

Table 3: Treatment-Related Adverse Events

Treatment-Related Adverse Events		Grade 1-2 (%)	Grade 3 (%)	Grade 4 (%)
Hematologic toxicities	Anemia	38.5	0.7	
	Leukopenia	50.0	2.0	0.7
	Neutropenia	41.9	6.1	2.0
	Thrombocytopenia	59.4	2.7	0.7
Hepatic and renal toxicities	Elevated AST	70.3	2.0	0
	Elevated ALT	56.7	1.4	0
	Elevated urea	4.7	0	0
	Elevated creatinine	3.4	0	0
Clinical toxicities	Diarrhea	43.3	4.1	0
	Proctitis	21.0	0.7	0
	Cystitis	9.0	0	0
	Peripheral neuropathy	87.0	2.7	0
	Nausea	37.2	0.7	0
	Vomiting	13.5	0	0

Analysis of Factors Associated with Treatment Toxicity:

Neutropenia: Univariate logistic regression analysis showed that the use of the mFOLFIRINOX regimen was associated with a 4.75-fold increased risk of neutropenia compared with other regimens (OR = 4.750; p = 0.020).

Diarrhea: When stratified by radiotherapy technique, the short-course radiotherapy group had a significantly higher rate of severe diarrhea (Grade 3-4) compared to the long-course radiotherapy group (18.5% vs. 0.8%; p = 0.001).

4. DISCUSSION

Total Neoadjuvant Therapy (TNT) has recently emerged as a novel treatment strategy for locally advanced rectal cancer. Phase III randomized controlled trials, such as RAPIDO[2] and PRODIGE-23[3], have demonstrated that TNT increases pathological complete response (pCR) rates and reduces the risk of distant metastasis, thereby influencing treatment guidelines worldwide, including in Vietnam. In Vietnam, TNT has been implemented in recent years across multiple oncology centers. Preliminary studies suggest that TNT is a feasible, effective, and safe approach for Vietnamese patients.

Our study included 148 patients with a mean age of 57 years and a male-to-female ratio of approximately 2:1. The epidemiological characteristics of this cohort are generally consistent with both domestic and international reports on rectal cancer, with most patients aged between 50 and 70 years and a higher prevalence in males[8, 9]. Regarding disease characteristics, a substantial proportion of patients presented with high-risk features: cT4 accounted for 17.6%, cN2 for 47.3%, 32.4% had suspected mesorectal fascia (MRF) involvement, and 20.9% had suspected vascular invasion. These rates are higher than those reported in some studies, such as PRODIGE-23[3], which documented 21% MRF involvement and 26% N2 disease. This discrepancy may be explained by the initial

implementation phase, during which TNT was preferentially applied to high-risk patients to ensure cautious translation from Western clinical trials into Vietnamese practice.

At K Hospital, the most commonly used TNT sequence was long-course chemoradiotherapy followed by consolidation chemotherapy (60.8%), predominantly using doublet chemotherapy regimens. This choice reflects the favorable tolerability profile of doublet regimens in Vietnamese patients. Additionally, long-course chemoradiotherapy remains more routinely utilized than short-course radiotherapy due to greater clinical experience at the institution.

The study results demonstrated an R0 resection rate of 98.6%, with 71.6% of patients achieving sphincter preservation. Tumor downstaging occurred in 68.9% of patients, and the pCR rate was 25.7%. These findings are comparable to large international trials such as PRODIGE-23[3] and RAPIDO[2] (pCR ~28%, R0 rate 90–95%). The pCR rate in our study is also consistent with domestic reports, such as Nguyen Van Dang[6] (2025) reporting 21.2% and Nguyen Hai Hoang[4] reporting 23.6%.

Notably, patients receiving induction chemotherapy followed by long-course chemoradiotherapy achieved a significantly higher pCR rate (35.5%) compared to those receiving consolidation chemotherapy (18.9%) ($p < 0.05$). One key explanation for this difference lies in the chemotherapy regimens used. In the induction group, up to 84% of patients received triplet chemotherapy (based on the PRODIGE-23 protocol), whereas only 5% in the consolidation group received such regimens ($p < 0.05$). Multivariable logistic regression confirmed that the use of triplet chemotherapy was an independent predictor of pCR, increasing the likelihood by 2.8-fold compared to doublet regimens ($p = 0.033$). This suggests that higher chemotherapy intensity, rather than TNT sequencing alone, plays a crucial role in improving treatment outcomes.

Additionally, the pCR rate in the short-course radiotherapy plus consolidation chemotherapy group was 37.0%, higher than that in the long-course chemoradiotherapy plus consolidation group (18.9%) ($p < 0.05$). However, this difference is largely attributable to baseline patient characteristics. Specifically, the long-course group had a significantly higher proportion of cT4 tumors (22.2%) compared to the short-course group (0%) ($p = 0.007$). This observation aligns with evolving clinical practice at K Hospital following updated 5-year results from the RAPIDO trial[10], which suggested superior local control with long-course chemoradiotherapy, particularly in patients at high risk of local recurrence. Logistic regression analysis in our study further confirmed tumor stage as an independent predictor of pCR, with cT2–3 tumors having a 4.7-fold higher likelihood of achieving pCR compared to cT4 tumors ($p = 0.048$). Therefore, differences in pCR between radiotherapy strategies in this study should primarily be interpreted as reflecting patient selection rather than intrinsic treatment efficacy.

Regarding toxicity, peripheral neuropathy and elevated AST were the most common adverse events, occurring in 89.7% and 72.3% of patients, respectively. However, these were predominantly low-grade and did not lead to treatment interruption. Grade 3–4 toxicities were mainly neutropenia (8.1%) and diarrhea (4.1%). The use of triplet chemotherapy increased the risk of grade 3–4 neutropenia by 4.8-fold compared to doublet regimens ($p = 0.02$); However, these events were manageable with granulocyte colony-stimulating factor (G-CSF) prophylaxis in subsequent cycles. Two patients (6.9%) required modification of chemotherapy due to toxicity.

In terms of gastrointestinal toxicity, the short-course radiotherapy group exhibited a higher rate

of diarrhea compared to the long-course group. This may be related to the fact that 85.2% of patients in the short-course group were treated using three-dimensional conformal radiotherapy (3D-CRT), as well as the higher dose per fraction and larger irradiated volumes, which may increase acute toxicity. Other adverse events were mostly grade 1-2 and showed no significant differences among the three TNT regimens.

Clinical T stage and chemotherapy regimen were significantly associated with pCR, consistent with findings from other international studies. Additional factors such as incomplete chemotherapy cycles, interval between radiotherapy and surgery, carcinoembryonic antigen (CEA) levels, and tumor length may also influence pCR rates, although further data are required to confirm these associations.

This study has several limitations. First, its retrospective design introduces potential information and selection biases. Second, the sample sizes of the short-course radiotherapy and induction chemotherapy groups were relatively small. Therefore, prospective, multicenter studies with larger sample sizes are needed to validate and expand upon these findings in the future.

5. CONCLUSION

This cohort study shows that Total Neoadjuvant Therapy (TNT) was associated with favorable rates of pathological complete response (pCR), R0 resection, and sphincter preservation in patients with locally advanced rectal cancer. Higher clinical T stage (cT) and the use of triplet chemotherapy (versus doublet) were associated with differences in pCR rates.

These findings further support the role of TNT in the management of rectal cancer in Vietnam and suggest that individualized selection of treatment sequence and chemotherapy regimen is essential to optimize efficacy while minimizing toxicity. However, due to the retrospective design and limited sample size, particularly in the short-course radiotherapy and induction chemotherapy groups, prospective, multicenter studies with larger cohorts are warranted to validate these results and strengthen the evidence base for clinical practice.

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EARLY OUTCOMES OF LAPAROSCOPIC RECTAL SEGMENTAL RESECTION WITH PRIMARY ANASTOMOSIS IN THE TREATMENT OF RECTAL CANCER AT VIET TIEP FRIENDSHIP HOSPITAL

Tran Quang Hung*, Tran Quang Hoc

SUMMARY

Objective: Describe the clinical and paraclinical characteristics of patients who underwent laparoscopic anterior resection with immediate anastomosis for rectal cancer at Viet Tiep Friendship Hospital from January 2023 to September 2025. Evaluate the early outcomes of laparoscopic anterior resection with immediate anastomosis in this patient cohort.

Patient and methods: A retrospective and prospective descriptive study of 39 patients diagnosed with rectal cancer who underwent laparoscopic anterior resection with immediate anastomosis at Viet Tiep Friendship Hospital.

Results: The male-to-female ratio was 1.17:1. The mean age was 67.38 ± 9.81 years. The prevalence of comorbidities was 48.7%. Clinical symptoms included mucus–bloody stool in 71.8% of patients, lower abdominal and perineal pain in 100%, and altered bowel habits in 53.8%. Colonoscopy revealed tumor location in the upper rectum (>10 cm) in 12.8%, mid rectum (>5 cm) in 61.5%, and lower rectum (≤5 cm) in 25.7%. Computed tomography (CT) detected rectal tumors in 97.4% of cases. The mean operative time was 193.2 ± 38.43 minutes. Low anterior resection accounted for 82.1%, anterior resection for 5.1%, and ultra-low anterior resection for 12.8%. The mean number of harvested lymph nodes was 6.3 ± 3.9. Postoperative complications occurred in 15.4% of patients. The mean distal resection margin was 3.09 ± 1.06 cm. The mean postoperative hospital stay was 11.13±2.61 days. Postoperative pathological staging showed stage I in 23.1%, stage II in 43.6%, and stage III in 33.3%. Overall outcomes were good in 84.6% of cases and moderate in 15.4%.

Keywords: Rectal cancer.

1. INTRODUCTION

Rectal cancer is a common malignancy, ranking fourth in incidence and fifth in cancer-related mortality in Vietnam. According to GLOBOCAN 2022, among 180,480 newly diagnosed cancer cases in Vietnam, colorectal cancer accounts for 9.3%, corresponding to 16,835 cases. The management of rectal cancer requires a multimodal approach, including surgery, radiotherapy, chemotherapy, and targeted therapy, among which surgical intervention plays a pivotal role, particularly in curative treatment. In the 1970s–1980s, advances in surgical technology, including the development of modern stapling and anastomotic devices, were increasingly applied

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in rectal cancer surgery. These innovations significantly improved the feasibility of low and ultra-low anterior resection in the confined pelvic space, thereby reducing the need for permanent colostomy and shortening operative time. In recent years, Viet Tiep Friendship Hospital has routinely implemented laparoscopic rectal segmental resection with primary anastomosis in the treatment of rectal cancer, achieving favorable clinical outcomes and demonstrating satisfactory surgical proficiency.

2. PATIENT AND METHOD

A total of 39 patients diagnosed with rectal cancer who underwent laparoscopic rectal segmental resection with primary anastomosis at Viet Tiep Friendship Hospital from January 2023 to September 2025 were included in this study. Data were collected using a pre-designed medical record form. Statistical analysis was performed using SPSS software version 22.0, applying standard methods of medical statistics.

3. RESULTS

3.1. Clinical characteristics

General characteristics

Age: The mean age was 69.03±6.64 years (range: 60–83 years). The male-to-female ratio was 1.17:1.

One patient had a history of prior abdominal surgery. Comorbid medical conditions were present in 53.8% of patients.

3.2. Clinical presentation

3.2.1. Reason for hospital admission

Table 1. Reasons for Hospital Admission (n=39)

Reasons for Hospital Admission	Number of patients (n=39)	Percentage%
Mucus-bloody stool	26	66.7
Hypogastric pain	25	64.1
Defecation disorders	3	7.7

3.2.2. Duration of Disease Progression

02 patients (5.1%) had a prolonged disease course before presenting to the hospital, with the longest duration being approximately 1 year. The majority of patients (66.7%) presented within less than 1 month after the onset of symptoms.

3.2.3. Functional Symptoms

Table 2. Clinical Functional Symptoms (n=39)

Symptom	Number of patients (n=39)	Percentage%
Mucus-bloody stool	28	71.8
Change in stool shape (thin, flattened)	2	5.1
Hypogastric and perineal pain	39	100
Defecation disorders	21	53.8
Constipation	7	17.9
Vomiting	2	5.1

3.2.4. Systemic symptoms

Systemic manifestations in patients with rectal cancer were generally mild. Anemia was observed in 12.8% of cases.

3.2.5. Physical examination findings

Digital rectal examination is an essential procedure in patients with rectal cancer. In this study, a palpable tumor was detected in 46.2% of patients, and blood on the examining glove was observed in 41% of cases.

** Characteristics of Tumors on Digital Rectal Examination*

Table 3. Characteristics of Tumors on Digital Rectal Examination (n=18)

Characteristics	Number of patients (n=18)	Percentage %
Tumor location from anal verge (AV)		
Low rectum (3-5 cm)	6	33.3
Mid rectum (>5 cm)	12	66.7
Tumor mobility		
Good mobility	5	27.8
Limited mobility	13	72.2

4.3. Paraclinical Characteristics

4.3.1. Endoscopic Characteristics of Tumors

A total of 22/39 patients underwent complete colonoscopy. Synchronous colorectal polyps were identified in 36.4% of these cases.

Table 4. Endoscopic Tumor Characteristics (n=39)

Characteristics	Number of patients (n=39)	Percentage (%)
Tumor location from anal verge (AV)		
Upper rectum (11-15 cm)	9	23.1
Mid rectum (6-10 cm)	24	61.5
Lower rectum (3-5 cm)	6	15.4
Circumferential involvement		
< 1/2 circumference	12	30.8
1/2 - 3/4 circumference	12	30.8
> 3/4 circumference	15	38.4
Macroscopic appearance		
Exophytic (polypoid)	1	2.6
Ulcerative	1	2.6
Mixed (ulcerative + exophytic)	37	94.8
Complete colonoscopy		
Yes	22	56.4
No	17	43.6
Total	39	100

4.3.2. CEA Levels and Hematological Parameters

- Among the 39 patients, 26 underwent carcinoembryonic antigen (CEA) testing. Elevated CEA levels (>5 ng/mL) were observed in 46.2% of cases, with the highest recorded value being 55.46 ng/mL.

- Most patients had normal red blood cell counts (82.1%) and hemoglobin levels (71.8%). The lowest recorded hemoglobin concentration was 88 g/L.

4.3.3. Diagnostic Imaging Results

** Abdominal and Pelvic CT Scan Results*

Table 5. Abdominal and Pelvic CT Findings (n = 39)

CT results	Number of patients (n=39)	Percentage (%)
Rectal tumor detected	38	97.4
Suspected regional lymph node metastasis	24	61.5
Suspected distant metastasis	0	0

** CT-based T Staging*

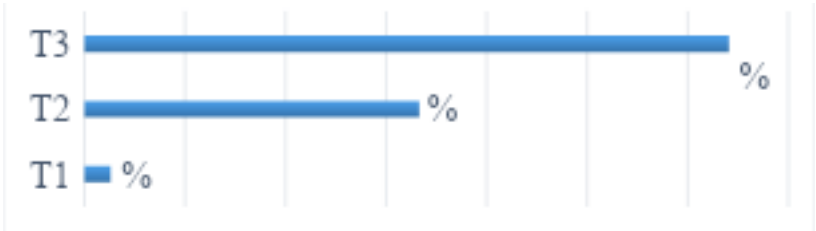

Chart 1. CT-based T staging (n = 39)

** Pelvic MRI Findings*

Table 6. Pelvic MRI Findings (n=10)

MRI findings	Number of patients (n=10)	Percentage %
Rectal tumor detected	10	100
Suspected regional lymph node metastasis	2	20
Suspected distant metastasis	0	0

4.3.4. Preoperative Clinical Staging

Table 7. Preoperative Disease Stage (n=39)

Preoperative stage	Number of patients (n=39)	Percentage %
Stage I	1	2.6
Stage II	18	46.2
Stage III	20	51.2

5. SURGICAL OUTCOME

5.1. Intraoperative Results

5.1.1. Operative time

The mean operative time was 193.2±38.43 minutes. The shortest operative time was 120 minutes, while the longest was 280 minutes.

5.1.2. Association between Operative Time and Gender

Table 8. Relationship between Operative Time and Gender (n=39)

	Gender	Number of patients (n=39)	Mean operative time (minutes)	p
Operative time	Female	18	190±36.8	0.636
	Male	21	196±40.5	

5.1.3. Intraoperative Pathological Stage

Table 9. Intraoperative Disease Stage (n=39)

Intraoperative stage	Number of patients (n=39)	Percentage %
Stage II	13	33.3
Stage III	26	66.7
Total	**39**	**100**

5.1.4. Surgical Approach

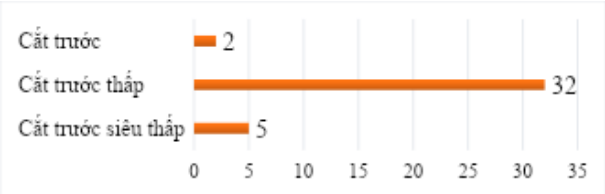

Chart 2. Characteristics of Surgical Procedures (n=39)

5.1.5. Number of Harvested Lymph Nodes

The mean number of harvested lymph nodes was 6.3 ± 3.9 (range: 1–15 nodes). In the subgroup with ≥12 harvested lymph nodes, the rate of lymph node positivity was 50%, which was higher than that observed in the group with <12 harvested lymph nodes (31.4%).

5.2. Postoperative Outcomes

5.2.1. Postoperative Recovery

The mean duration of postoperative analgesic use was 2.69 ± 1.36 days. The mean time to first flatus was 3.48 ± 1.17 days. The mean postoperative hospital stay was 11.13 ± 2.61 days. The mean time to removal of the anal drainage tube was 5.3 ± 2.85 days, ranging from 2 to 17 days.

5.2.2. Postoperative Complications

Table 10. Characteristics of Postoperative Complications (n=39)

Early Postoperative Complications (within the first month)	Number of patients (n=39)	Percentage %
Localized anastomotic leakage (no reoperation required)	0	0
Anastomotic bleeding	1	2.6
Subileus	3	7.7
Surgical site infection	2	5.1
No complications	33	84.6

5.2.3. Classification of Postoperative Complications

Table 11. Classification of Postoperative Complications (n=6)

Complication grade	Number of patients (n=6)	Percentage %
Grade I	2	33.3
Grade II	4	66.7
Total	6	100

5.2.4. Histopathological Characteristics After Surgery

- All cases (100%) were diagnosed as adenocarcinoma on histopathological examination.

- The majority of tumors were moderately differentiated (94.9%), and no well-differentiated tumors were identified.

** Tumor Invasion Depth*

Table 12. Tumor Invasion Depth (n=39)

pT stage	Number of patients (n=39)	Percentage %
pT2	9	23.1
pT3	13	33.3
pT4	17	43.6
Total	39	100

5.2.5. Postoperative Pathological Stage

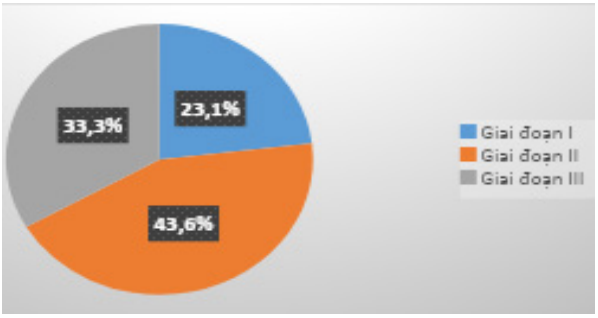

Chart 3. Postoperative Pathological Stage (n=39)

5.2.6. Surgical Resection Margin

The mean distal resection margin was 3.09 ± 1.06 cm, ranging from 1.5 cm to 5 cm. All cases achieved a negative distal margin (R0 resection), with no residual tumor cells detected at the resection margin.

6. DISCUSSION

6.1. General characteristics

Age: The mean age in our study was 69.03 ± 6.64 years (range: 60–83 years). This result was slightly higher compared with the study by Nguyễn Quang Huy (2023) at Hospital 115, which included 51 patients with a mean age of 63 years [60], and the study by Cao Minh Tiệp (2022) conducted at Military Hospital 103 and K Hospital, which reported a mean age of 58.88 ± 12.1 years in 88 patients.

The male-to-female ratio in our study was 1.17:1, with 54% male and 46% female patients (Figure 3.2), indicating a higher prevalence of rectal cancer in males. This finding is consistent with Lê Quốc Tuấn, who reported a male-to-female ratio of 1.15:1, and with the meta-analysis by Akagi Y et al., which included 14 studies on sphincter-preserving surgery for low rectal cancer and demonstrated a male predominance ranging from 1.3 to 2.5.

Regarding medical history, one patient had a previous history of abdominal surgery, and 53.8% of patients presented with comorbidities. This proportion of comorbid conditions was higher than that reported by Cao Minh Tiệp (2022), who documented 26 patients with associated diseases, including hypertension in 11.3%, diabetes mellitus in 2.3%, and multiple comorbidities in 5.7%.

6.2. Clinical Characteristics

6.2.1. Reason for hospital admission

In our study (n = 39), as shown in Table 1, the main reasons for hospital admission were hypogastric pain in 25/39 patients (64.1%), mucus-bloody stool in 26/39 patients (66.7%), and defecation disorders in 3/39 patients (7.7%). These findings are consistent with the study by Lê Quốc Tuấn (2020), in which mucus-bloody stool accounted for 89.3% of admission reasons, and the study by Phạm Cẩm Phương (2013), which also reported mucus-bloody stool as the predominant presenting symptom in 90.9% of patients.

6.2.2. Duration of disease progression

Two patients (5.1%) had a prolonged symptomatic period before hospital admission, with the longest duration being approximately 1 year. The majority of patients (66.7%) presented within less than 1 month after symptom onset. Our results indicate earlier hospital presentation compared with other studies. Lê Quốc Tuấn

(2020) reported a mean duration of 4.1 months, while Phạm Văn Bình reported a mean interval from symptom onset to hospital admission of 3.8 ± 1.2 months, with 75.6% of patients presenting within 6 months.

6.2.3. Functional symptoms

In our study, the most common symptoms included hypogastric pain (100%), mucus-bloody stool (71.8%), defecation disorders (53.8%), vomiting (5.1%), change in stool shape (5.1%), and constipation (17.9%). These findings are consistent with previous studies. Cao Minh Tiệp (2022) reported mucus-bloody stool in 81.8%, constipation in 20.5%, and vomiting in 1.1% among 88 rectal cancer patients. Mai Đức Hùng reported mucus-bloody stool in 72.5% of 138 patients, while Trần Anh Cường (2017) reported rectal bleeding in 93.1%, abdominal pain in 81.9%, changes in bowel habits in 75.9%, and increased stool frequency in 70.7% of patients.

6.2.4. Systemic symptoms

Systemic manifestations in rectal cancer patients were generally mild. Anemia was observed in 12.8% of cases.

6.2.5. Physical examination findings

Digital rectal examination is a mandatory clinical procedure in patients with rectal cancer. In our study, a palpable tumor was detected in 46.2% of patients, while blood on the examining glove was observed in 41% of cases. These results were higher than those reported by Cao Minh Tiệp, who found palpable tumors in 29.5% and blood on glove in 31.8% of 88 patients, but lower than those reported by Lê Quốc Tuấn, who identified palpable tumors in 78.6% and blood on glove in 92.9% of cases, likely due to differences in tumor location and patient selection criteria across studies.

6.3. Paraclinical Characteristics

6.3.1. Endoscopic tumor characteristics

Among 39 patients, 22 underwent complete colonoscopy. Synchronous colorectal polyps were detected in 36.4% of cases. These findings are generally consistent with previous studies reporting the presence of associated colorectal lesions in patients with rectal cancer. Mai Đức Hùng (2012), in a study of 138 cases (84.8% mid-rectal cancer), reported a mean tumor size of 9.28 ± 2.61 cm. Other authors such as Mai Đình Điểu also reported tumor distribution across lower, middle, and upper rectum at rates of 43.8%, 40.4%, and 15.8%, respectively, reflecting variability in patient selection and tumor location across studies.

6.3.2. CEA levels and hematological parameters

- Among 39 patients, 26 underwent CEA testing, of whom 46.2% had elevated CEA levels (>5 ng/mL), with a maximum value of 55.46 ng/mL.

- Most patients had normal red blood cell counts and hemoglobin levels, accounting for 82.1% and 71.8%, respectively. The lowest recorded hemoglobin level was 88 g/L, indicating that anemia was present but not common in the study population.

6.3.3. Diagnostic Imaging Results

All 39 patients underwent abdominal and pelvic CT scans, with rectal tumors detected in 97.4% of cases. This demonstrates that CT remains an important first-line imaging modality for detecting primary rectal tumors, particularly in provincial hospitals or centers without MRI availability. One case was not detected on CT due to an early-stage lesion with ulcerative morphology and minimal wall thickening. Our detection rate was higher than that reported by Lê

Quốc Tuấn (55.4%) and comparable to Nguyễn Tuấn Cảnh (2023), who reported a detection rate of 97.1% (34/35 patients).

6.3.4. Preoperative Staging

Based on Table 11, most patients were classified preoperatively as stage II (46.2%) and stage III (51.2%), while stage I accounted for only 2.6%. Preoperative staging was based on clinical examination, endoscopic findings, tumor location, and CT and/or pelvic MRI results. Similar to other studies relying on MRI-based staging, such as that by Nguyễn Tô Hoài et al. at Military Hospital 108, stage III disease was also predominant (87.1%), followed by stage II (12.9%), highlighting the high proportion of locally advanced disease in rectal cancer patients at diagnosis.

7. SURGICAL RESULTS

7.1. Intraoperative outcomes

7.1.1. Operative time

The mean operative time was 193.2±38.43 minutes, ranging from 120 to 280 minutes. This result was higher than that reported by Nguyễn Quang Huy (2023) at Hospital 115 (mean 241.84 ± 65.66 minutes in 51 patients), lower than Lê Quốc Tuấn (2020), who reported a mean operative time of 113.4 ± 16.1 minutes (range: 90–160 minutes), and comparable to Nguyễn Tuấn Cảnh (2023), who reported a mean operative time of 210.06 ± 35 minutes (range: 150–290 minutes).

7.1.2. Association between operative time and gender

According to Table 12, the mean operative time was 190 ± 36.8 minutes in females (n=18) and 196 ± 40.5 minutes in males (n=21), with no statistically significant difference between the two groups ($p = 0.636 > 0.05$). This may be explained by the nearly balanced sex distribution (male/female ratio 1.17/1), as well as tumor location and pelvic anatomy. Although male patients generally have a narrower pelvis, which may increase surgical difficulty and operative time, in our study the difference was not significant. This finding is consistent with Cao Minh Tiệp (2022), who also reported no significant difference in operative time between males and females (157.9 vs 145.8 minutes, $p = 0.175$).

7.1.3. Surgical procedures

In our study, 82.1% of patients underwent low anterior resection (LAR), 12.8% underwent ultra-low anterior resection (ULAR), and 5.1% underwent standard anterior resection (AR). The proportion of standard anterior resection was relatively low compared with other studies, as surgeons tended to prefer sphincter-preserving low anterior resection even for higher rectal tumors to ensure adequate resection margins and reduce local recurrence risk. Consequently, the rate of low anterior resection (84.6%) was higher than that reported by other authors. For example, Nguyễn Tô Hoài (2023) reported LAR in 74.3% of 70 patients undergoing total mesorectal excision, while Cao Minh Tiệp (2022) reported rates of AR, LAR, and ULAR at 34.1%, 52.3%, and 13.6%, respectively.

7.1.4. Number of harvested lymph nodes

The mean number of harvested lymph nodes was 6.3 ± 3.9 (range: 1–15 nodes). In the subgroup with ≥12 harvested lymph nodes, the rate of lymph node positivity was 50%, higher than that observed in the group with <12 nodes (31.4%). Our results were higher than those reported by Nguyễn Quang Huy (2023), who found a mean of 4.50±4.26 nodes, but lower than Lê Quốc Tuấn (2020), who reported a mean of 11.1±4.9 nodes (range: 3–24 nodes).

7.2. Postoperative Outcomes

7.2.1. Postoperative recovery

The mean duration of postoperative analgesic use was 2.69±1.36 days. The mean time to first flatus was 3.48±1.17 days. The mean postoperative hospital stay was 11.13±2.61 days. The mean time to removal of the anal drainage tube was 5.3 ± 2.85 days, ranging from 2 to 17 days.

7.2.2. Postoperative complications

Among 39 patients, the overall rate of early postoperative complications (within 30 days) was 15.4%, including anastomotic bleeding in 1/39 cases (2.6%), subileus in 3/39 cases (7.7%), and surgical site infection in 2/39 cases (5.1%). No cases of anastomotic leakage were recorded in our study. This outcome was more favorable compared with Lê Quốc Tuấn, who reported 1/56 cases (1.8%) of anastomotic leakage; however, the leakage was localized, managed conservatively, and healed without reoperation. Nguyễn Quang Huy (2023) reported a 5.9% rate of early postoperative complications in 51 patients, including 2 cases (3.9%) of anastomotic leakage requiring surgical intervention. Similarly, Trịnh Đức Hoàng (2021) reported 1 case of anastomotic leakage (1.3%) and 6 cases of surgical site infection among 76 patients.

7.2.3. Histopathological characteristics

All tumors (100%) were adenocarcinomas. The majority were moderately differentiated (94.9%), with no well-differentiated tumors identified. These findings are consistent with Nguyễn Tuấn Cảnh (2023), who reported 82.8% moderately differentiated tumors, 14.3% poorly differentiated, and 2.9% well differentiated, and higher than those reported by Cao Minh Tiệp (2022), where adenocarcinoma accounted for 86.4% and moderate differentiation was predominant (71.1%).

** Tumor invasion depth*

Postoperative pathological staging showed pT2 in 23.1%, pT3 in 33.3%, and pT4 in 43.6%, meaning approximately 77% of patients had T3–T4 disease. In comparison, preoperative CT assessment showed T3 in 64.1%, T2 in 33.3%, and T1 in 2.6%. The discrepancy between imaging and pathological staging is due to the limited sensitivity and specificity of CT in assessing rectal wall invasion compared with MRI.

7.2.4. Postoperative stage

Postoperative staging showed stage I in 23.1%, stage II in 43.6%, and stage III in 33.3%, with no stage 0 or stage IV cases according to AJCC 2018 criteria [14]. These results were more favorable compared with Trương Vĩnh Quý, who reported 71.2% stage I–II and 28.8% stage III–IV in 52 patients, and Cao Minh Tiệp, who reported 53.7% stage I–II and 46.3% stage III–IV in 88 patients.

7.2.5. Surgical resection margin

The mean distal resection margin was 3.09 ± 1.06 cm, ranging from 1.5 cm to 5 cm. All cases achieved a negative distal margin (R0 resection), with no residual tumor cells detected at the resection margin. This result was lower than that reported by Cao Minh Tiệp, who found a mean distal margin of 4.438 ± 2.06 cm (minimum 1.5 cm), with 100% negative margins on pathological examination. Similarly, Mai Đức Hùng reported distal resection margins ranging from 2 cm to 9 cm, with a mean of 4.59 ± 1.44 cm in laparoscopic low anterior resection for rectal cancer. Nguyễn Hoàng Bắc also reported a mean distal margin of 4.19 ± 1.6 cm (range: 2–10 cm).

7.2.6. Treatment outcomes

Overall, good outcomes were achieved in 84.6% of patients, while 15.4% had moderate outcomes. All patients were discharged in stable

condition. These results were comparable to Cao Minh Tiệp (2022), who reported 83.0% good outcomes, 15.9% moderate outcomes, and 1.1% poor outcomes, and similar to Mai Đức Hùng (2014), who reported 89.9% good outcomes, 10.1% moderate outcomes, and no poor outcomes.

8. CONCLUSION

8.1. Clinical and paracinical characteristics of patients with rectal cancer undergoing laparoscopic anterior resection with primary anastomosis

- The study included patients with a mean age of 67.38 ± 9.81 years (range: 45–86 years), with a male-to-female ratio of 1.17:1.

- The main reasons for hospital admission were abdominal pain (64.1%), mucus-bloody stool (66.7%), and defecation disorders (7.7%).

- The most common clinical manifestations included mucus-bloody stool (71.8%), hypogastric and perineal pain (100%), changes in stool form (5.1%), defecation disorders (53.8%), and constipation (17.9%).

- On digital rectal examination, a palpable tumor was detected in 46.2% of patients, and 27.8% of tumors showed good mobility.

- Colonoscopy findings showed tumor distribution mainly in the mid rectum (>5 cm) in 61.5% of cases, followed by upper rectum (>10 cm) in 12.8% and lower rectum (≤5 cm) in 25.7%. The majority of tumors (94.8%) were mixed ulcerative–polypoid in morphology, while pure ulcerative and polypoid types accounted for 2.6% each. Complete colonoscopy was achieved in 56.4% of patients, and synchronous colorectal polyps were present in 36.4%.

- CT imaging detected rectal tumors in 97.4% of cases.

- Preoperative staging showed that most patients were in stage III (51.2%), followed by stage II (46.2%), and stage I (2.6%).

8.2. Results of laparoscopic anterior resection with primary anastomosis

- The mean operative time was 193.2 ± 38.43 minutes (range: 120–280 minutes).

- The surgical procedures included low anterior resection in 82.1% of patients, standard anterior resection in 5.1%, and ultra-low anterior resection in 12.8%. The mean number of harvested lymph nodes was 6.3 ± 3.9 nodes.

- The mean duration of postoperative analgesic use was 2.69 ± 1.36 days (range: 1–7 days). The mean time to first flatus was 3.48 ± 1.17 days (range: 2–6 days). The mean time to removal of the anal drainage tube was 5.3 ± 2.85 days (range: 2–17 days).

- The mean distal resection margin was 3.09 ± 1.06 cm (range: 1.5–5 cm), and all cases achieved negative distal margins (R0 resection), with no residual tumor cells detected.

- All tumors were adenocarcinomas (100%), with the majority being moderately differentiated (94.9%).

- The mean distal resection margin was 3.09 ± 1.06 cm (range: 1.5–5 cm), and 100% of cases achieved negative distal margins with no residual tumor cells detected.

- Postoperative staging showed stage I in 23.1% of patients, stage II in 43.6%, and stage III in 33.3%.

- Overall outcomes were classified as good in 84.6% and moderate in 15.4% of patients. All patients were discharged in stable condition.

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SURGICAL SITE INFECTIONS IN GASTROINTESTINAL SURGERY AT DANANG ONCOLOGY HOSPITAL

Nguyen Thi Thanh Duyen

ABSTRACT

Background: Surgical site infection (SSI) is a significant postoperative complication, especially in gastrointestinal (GI) surgery in low- and middle-income countries. This study aimed to determine the incidence of SSI and identify its associated risk factors among patients undergoing GI surgery at Da Nang Oncology Hospital.

Methods: A prospective, descriptive analytical study was conducted on 309 patients undergoing GI surgery from January to September 2024. Data on patient demographics, preoperative clinical status, and intraoperative factors were collected. SSI was defined according to the CDC/NHSN criteria and followed for 30 days postoperatively. Statistical significance was set at $p < 0.05$.

Results: The overall incidence of SSI was 12.9% (40/309), with all cases classified as superficial incisional SSIs. Gram-negative bacteria were the predominant pathogens (93.75%), with *Escherichia coli* (50.0%) and *Klebsiella pneumoniae* (28.1%) being most frequent. The SSI rate was significantly higher in contaminated surgeries (50.0%) compared to clean-contaminated procedures (8.7%). Univariate analysis identified significant risk factors ($p < 0.05$) including: comorbidities (16.2%), preoperative hospital stay >7 days (16.1%), ASA score ≥ III (24.5%), history of GI surgery (52.5%), emergency surgery (39.6%), contaminated wound class (46.9%), operative time >120 minutes (16.8%), NNIS risk index ≥3 (48.3%), and open surgical approach (16.0%). All patients achieved complete clinical resolution following treatment.

Conclusions: SSI remains a prevalent challenge in gastrointestinal oncology surgery. The predominance of Gram-negative pathogens and the identification of modifiable risk factors, such as operative duration and preoperative stay, underscore the need for enhanced perioperative infection control protocols and a shift towards minimally invasive techniques to improve patient safety.

Keywords: Surgical site infection, gastrointestinal surgery, risk factors, Escherichia coli, oncology.

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1. INTRODUCTION

Ensuring surgical safety remains a formidable global challenge, particularly in low- and middle-income countries (LMICs) where healthcare resources are often constrained. Despite substantial advancements in surgical methodology, perioperative technology, and the adoption of minimally invasive techniques, surgical site infection (SSI) persists as a prevalent and significant postoperative complication (1,8). SSIs are inherently linked to extended hospitalizations, escalated healthcare expenditures, and detrimental clinical outcomes (2,6).

Within the Vietnamese context, reported SSI rates fluctuate between 5% and 10%, representing a substantial contribution to the overall burden of disease and the necessity for prolonged antimicrobial therapy (11,13). Patients undergoing gastrointestinal procedures face a disproportionately high risk of SSI. This susceptibility is primarily attributed to the deliberate intraoperative entry into the gastrointestinal tract—a region characterized by a high endogenous microbial load—and the fact that most of these procedures are classified as either clean-contaminated or contaminated according to global standards, such as those defined by the Centers for Disease Control and Prevention (CDC) (6).

While established clinical guidelines from the Ministry of Health and international bodies offer effective preventive measures (4,5,6), their adherence in routine practice remains suboptimal. Systematic surveillance of SSI is therefore essential to generate the empirical evidence required for targeted interventions, ultimately enhancing surgical quality and patient safety. Consequently, the present study was conducted to determine the incidence of SSI and delineate its associated risk factors among patients undergoing gastrointestinal surgery at Da Nang Oncology Hospital...

2. MATERIALS AND METHODS

2.1. Study Population and Setting

This study enrolled patients who underwent gastrointestinal surgery at Da Nang Oncology Hospital between January and September 2024.

Inclusion criteria:

Eligible participants were required to meet the following criteria:

- Underwent either elective or emergency gastrointestinal surgery at the study site during the specified period.

- Received surgical intervention via either an open or laparoscopic approach.

- Provided informed consent for study participation and possessed comprehensive medical records for data extraction.

Exclusion criteria:

- Patients who had undergone gastrointestinal surgery at another facility and were subsequently transferred to Da Nang Oncology Hospital for postoperative management or secondary procedures.

- Patients who were not postoperatively managed at the study hospital.

- Patients who did not complete the mandatory 30-day postoperative follow-up period, which is essential for the definitive diagnosis of surgical site infections (SSIs).(5)

Sample size and sampling method:

The minimum required sample size was calculated using the formula for estimating a single population proportion:

$$\mathbf{N} = \mathbf{Z}^{\mathbf{2}}_{\mathbf{1-\frac{\alpha}{2}}} \frac{\mathbf{p(1-p)}}{\mathbf{d^2}}$$

In which:

- N is the required sample size for the study.

- α is the level of significance (α = 0.05).

- Z = 1.96

- p = 0.238 based on a previous study in oncologic digestive surgery (Brazil, 2010).

- The margin of error, set at 0.05.

- Design effect:1.0

The minimum required sample size for the study is N = 279.

2.2. Study Design and Data Collection

A prospective, cross-sectional descriptive, and analytical study was conducted. The following key variable groups were systematically collected:

Demographic Data: Age, sex, height, weight, and Body Mass Index (BMI).

Preoperative Status: American Society of Anesthesiologists (ASA) physical status, presence of comorbidities, and surgical history.

Intraoperative Variables: Surgical urgency (elective vs. emergency), wound classification (clean, clean-contaminated, contaminated, or dirty), surgical approach (laparoscopic vs. open), type of incision, targeted organ, and operative duration.

SSI Characteristics: Surgical site infections were identified and classified based on the Centers for Disease Control and Prevention (CDC/NHSN) criteria. An SSI must occur within 30 days of the operative procedure and involve only the skin and subcutaneous tissue of the incision (Superficial Incisional SSI), deeper soft tissues such as fascia and muscle layers (Deep Incisional SSI), or any part of the anatomy opened or manipulated during the procedure (Organ/Space SSI). Diagnosis was confirmed by the presence of at least one of the following:

- Purulent drainage from the incision or a drain placed through a stab wound.

- Organisms isolated from an aseptically obtained culture of fluid or tissue.

- At least one symptom of infection (e.g., pain, localized swelling, redness, or heat) and the incision is deliberately opened by a surgeon, unless the culture is negative.

Diagnosis of SSI by the attending surgeon or attending physician. (5,6)

Clinical Outcomes: Prophylactic and therapeutic antibiotic regimens, and final clinical status (recovery, discharge, transfer, or mortality).

2.3. Statistical analysis

Data were analyzed using IBM SPSS Statistics version 20.0.

2.4. Ethical Considerations

The study protocol was reviewed and formally approved by the Ethics Committee) of Da Nang Oncology Hospital. The study was conducted in strict accordance with the ethical principles of the Declaration of Helsinki.

All eligible participants were provided with comprehensive information regarding the study's objectives, procedures, and potential benefits. Written informed consent was obtained from each patient (or their legal guardian) prior to enrollment. Participants were informed of their right to withdraw from the study at any time without any impact on the quality of their medical care. To ensure patient confidentiality, all data were anonymized and coded; personal identifiers were removed during data processing and analysis. The collected information was used solely for research purposes.

3. RESULTS

3.1. General characteristics of the study population

Table 1. Baseline Characteristics of the Study Population (n = 309)

Characteristics	Number of patients (n = 309)	Percentage %
Age Group (years)		
19 - 39	32	10.4
40 - 59	110	35.6
≥ 60	167	54.0
Mean age ± SD (Min;Max)	59.37 ± 13.58 (24; 93)	
Gender		
Male	205	66.3
Female	104	33.7
***BMI* (kg/m^2)**		
Underweight (< 18.5)	76	24.6
Normal weight (18.5 ≤ 23)	198	64.1
Overweight (23 - 27.5)	34	11.0
Obese (≥ 27.5)	1	0.3
Comorbidities		
Present	204	66.0
Absent	105	34.0
Surgical History		
No prior surgery	238	77.0
Prior surgery (Total)	71	23.0
- Prior gastrointestinal surgery (n=71)	40	56.3
- Other surgical procedures (n=71)	31	43.7
ASA Physical Status		
Class I	6	1.9
Class II	193	62.5
Class III	110	35.6
Type of Admission		
Emergency surgery	53	17.2

Characteristics	Number of patients (n = 309)	Percentage %
Elective surgery	256	82.8
Surgical wound classification		
Clean-contaminated	277	89.6
Contaminated	32	10.4
Surgical approach		
Open surgery	187	60.5
Laparoscopic surgery	60	19.4
Combined (Laparoscopic converted to Open)	62	20.1
Operative Time (minutes)		
≤ 120	119	38.5
> 120	190	61.5
Organ Operated		
Esophageal	26	8.4
Gastroduodenal	83	26.9
Small bowel	26	8.4
Colonic	55	17.8
Rectal	66	21.4
Hepatopancreatobiliary (HPB)	45	14.6
Multi-organ procedures	8	2.6
NNIS risk index		
1 point	188	60.8
2 points	92	29.8
3 points	29	9.4
Length of Stay (Mean ± SD)		
Preoperative stay (days)	9.9 ± 6.57	
Total hospital stay (days)	19.06 ± 9.22	
Postoperative wound status		
Normal healing	270	87.4

Characteristics	Number of patients (n = 309)	Percentage %
Swelling, warmth, redness, pain, and purulent discharge from the skin and subcutaneous tissue	39	12.6
NNIS risk index		
1 point	188	60.8
2 points	92	29.8
3 points	29	9.4
**Note: 100% (n=309) of patients received prophylactic antibiotics*		

The mean age of the study population was 59.37 ± 13.58 years. The majority of patients had comorbidities (66.0%). Among those with a surgical history, 56.3% had undergone prior gastrointestinal procedures. Regarding physical status, 35.6% were classified as ASA score ≥ III. Most patients underwent elective surgery (82.8%), and the vast majority of procedures were clean-contaminated (89.6%).

Gastroduodenal procedures accounted for the largest proportion (26.9%), followed by rectal (21.4%) and colonic surgeries (17.8%), whereas multi-organ procedures were uncommon (2.6%). Open surgery was the predominant approach (60.5%), while laparoscopic and combined approaches accounted for the remainder.

In terms of surgical risk, 60.8% of patients had an NNIS risk index of 1, while 9.4% reached a score of 3. The operative time exceeded 120 minutes in 61.5% of cases. The mean preoperative hospital stay was 9.9 ± 6.57 days, with an overall mean length of hospital stay of 19.06 ± 9.22 days.

3.2. Surgical site infection rate in gastrointestinal surgery

3.2.1. Severity of surgical site infection

Table 2. Incidence and Severity of Surgical Site Infection (n = 309)

Characteristics	Frequency (n)	Percentage %
Incidence of SSI (N=309)		
Present	40	12.9
Absent	269	87.1
Timing of SSI Diagnosis		
Inpatient	40	100.0
Post-discharge	0	0.0
Classification of SSI		
Superficial incisional	40	100.0
Deep incisional	0	0.0
Organ/space	0	0.0

The overall incidence of surgical site infection (SSI) was 12.9%. Regarding severity, all cases (100%) were classified as superficial incisional SSIs.

3.2.2. SSI rate according to type of surgery and operated organ

Characteristics	Total Patients (n = 309)	SSI Cases (n = 40)	SSI Rate %
Wound Classification			
Clean-contaminated	277	24	8.7
Contaminated	32	16	50.0
Operated organ			
Esophagus	26	4	15.4
Gastroduodenal	83	7	8.4
Small bowel	26	5	19.2
Colonic	55	8	14.5
Rectal	66	12	18.2
Hepatopancreatobiliary (HPB)	45	3	6.7
Multivisceral (≥ 2 organs)	8	1	12.5
*Note: Clean and Dirty wounds were not observed in this study population.			

The incidence of SSI was significantly associated with wound classification. Specifically, contaminated procedures exhibited a substantially higher infection rate (50.0%) compared to clean-contaminated procedures (8.7%). Regarding the anatomical site, the highest infection rates were observed in small bowel (19.2%) and rectal surgeries (18.2%). In contrast, hepatobiliary and pancreatic procedures showed the lowest infection rate at 6.7%. Multivisceral and esophageal surgeries had SSI rates of 12.5% and 15.4%, respectively.

3.2.3. Causes of surgical site infection (SSI)

Table 4. Microbiological Culture Results from SSI Cases (n = 40)

Specimen Type	Number of specimens	Pathogen-Positive Cultures (n)	Positivity Rate (%)
Pus, wound discharge	40	32	80.0

A total of 40 specimens, consisting of pus and wound exudates from SSI cases, were submitted for microbiological culture. The culture positivity rate was 80.0% (n = 32), while the remaining 20% yielded no identifiable growth, possibly due to prior antibiotic administration or fastidious organisms.

Table 5. Distribution of Isolated Pathogens (n = 32)

Pathogen characteristics	Frequency (n)	Percentage (%)
Number of isolates per specimen		
Single pathogen	32	100
Polymicrobial (≥2 pathogens)	0	0.0
Bacterial Classification		
Gram-negative bacteria	30	93.75
Gram-positive bacteria	2	6.25
Identified Species		
Escherichia coli	16	50
Pseudomonas aeruginosa	2	6.25
Klebsiella pneumoniae	9	28.1
Proteus mirabilis	3	9.4
Enterococcus spp	2	6.25

Monotherapy was observed in all culture-positive cases, with no polymicrobial infections recorded. Gram-negative bacilli predominated the microbial profile, accounting for 93.75% of the total isolates. Among these, *Escherichia coli* was the most prevalent pathogen (50.0%), followed by *Klebsiella pneumoniae* (28.1%). Gram-positive bacteria, specifically *Enterococcus* spp., represented a small fraction of the cases (6.25%).

3.2.4. Factors associated with surgical site infection in gastrointestinal surgery

Table 6. Factors Associated with Surgical Site Infection (n = 309)

Charateristics	SSI (n=40)	No SSI (n=269)	Total (n=309)	p-value
Age Groups (years)				0.585
19-39	3 (9.4%)	29 (90.6%)	32	
40-59	17 (15.5%)	93 (84.5%)	110	
≥ 60	20 (12%)	147 (88%)	167	
Gender				0.868
Male	27 (13.2%)	178 (86.8%)	205	
Female	13 (12.5%)	91 (87.5%)	104	
Nutritional Status (BMI)				0.978
Malnutrition	10 (13.2%)	66 (86.8%)	76	
Normal weight	26 (13.1%)	172 (86.9%)	198	
Overweight	4 (11.8%)	30 (88.2%)	34	

Charateristics	SSI (n=40)	No SSI (n=269)	Total (n=309)	p-value
Obese	0 (0.0%)	1 (100.0%)	1	
Comorbidities				0.018*
Absent	7 (6.7%)	98 (93.3%)	105	
Present	33 (16.2%)	171 (83.8%)	204	
Preoperative hospital stay				0.035*
≤ 7 days	11 (8.5%)	118 (91.5%)	129	
> 7 days	29 (16.1%)	151 (83.9%)	180	
ASA Physical Status				< 0.001*
< III	13 (6.5%)	186 (93.5%)	199	
≥ III	27 (24.5%)	83 (75.5%)	110	
Surgical History				
No history of surgery	26 (10.9%)	212 (89.1%)	238	0.065
History of GI surgery	21 (52.5%)	19 (47.5%)	40	< 0.001*
Type of Admission				< 0.001*
Elective	19 (7.4%)	237 (92.6%)	256	
Emergency	21 (39.6%)	32 (60.4%)	53	
Wound Classification				< 0.001*
Clean-contaminated	25 (9.0%)	252 (91.0%)	277	
Contaminated	15 (46.9%)	17 (53.1%)	32	
Operative time				0.014*
≤ 120 mins	8 (6.7)	111 (93.3)	119	
> 120 mins	32 (16.8)	158 (83.2)	190	
NNIS Risk Index				< 0.001*
NNIS < 3 points	26 (9.3)	254 (90.7)	280	
NNIS ≥ 3 points	14 (48.3)	15 (51.7)	29	
Surgical Site				0.036*
Esophageal Procedures	4 (15.4%)	22 (84.6%)	26	
Gastroduodenal surgery	7 (8.4%)	76 (91.6%)	83	
Small bowel surgery	5 (19.2%)	21 (80.8%)	26	
Colonic surgery	8 (14.5%)	47 (85.5%)	55	
Rectal surgery	12(18.2%)	54 (81.8%)	66	

Charateristics	SSI (n=40)	No SSI (n=269)	Total (n=309)	p-value
Hepatopancreatobiliary (HPB)	3 (6.7%)	42 (93.3%)	45	
Surgical Approach				0.039*
Laparoscopic	2 (3.33)	58 (96.7)	60	
Open	30 (16)	157 (84)	187	
Combined (Laparoscopic/Open)	8 (12.9)	54 (87.1)	62	
**Statistically significant (p < 0.05)*				

The incidence of surgical site infection (SSI) was significantly higher in patients with comorbidities compared to those without (16.2% vs. 6.7%, (p = 0.018). Similarly, a prolonged preoperative hospital stay of more than 7 days was associated with an increased SSI rate compared to a stay of ≤7 days (16.1% vs. 8.5%, (p = 0.035).

Regarding physical status and surgical history, patients with an ASA score ≥III exhibited a substantially higher SSI incidence than those with an ASA score < III (24.5% vs. 6.5%, (p < 0.001). Notably, a history of prior gastrointestinal surgery emerged as a strong predictor of infection, with an incidence rate of 52.5% (p < 0.001).

The NNIS risk index also showed a significant correlation with outcomes; the SSI rate was markedly higher in patients with an NNIS score ≥3 compared to those with a score < 3 (48.3% vs. 9.3%, (p < 0.001). Furthermore, significant associations were observed between SSI and the type of surgery (emergency vs. elective), operative duration (> 120 minutes), and the surgical approach, with all variables reaching statistical significance (p < 0.05).

3.2.5. Treatment outcomes of surgical site infection (SSI)

Table 7. Clinical Outcomes of Patients with SSI (n = 40)

Outcome Category	Number of patients	Percentage %
Successful SSI Resolution	40	100.0
Hospital Transfer	0	0
Discharge Against Medical Advice (DAMA)	0	0
Mortality	0	0
Total	40	100.0

Regarding the clinical outcomes of postoperative complications, complete resolution of surgical site infections was achieved in 100.0% (n = 40) of the affected cases.

4. DISCUSSION

4. 1. General characteristics of the Study Population

The demographic profile of the cohort revealed a predominance of elderly patients, with 54% aged ≥60 years (mean age: 59.37 ± 13.58 years). This distribution is consistent with the study by Hegde et al. (1), which also identified older age as a significant factor in the surgical population. A male preponderance (66.3%) was observed, aligning with findings by Tran Que Son

(2) and Zhiwei Wang (3), reflecting established epidemiological patterns in gastrointestinal diseases.

Regarding nutritional status, the prevalence of obesity was remarkably low (0.3%), whereas undernutrition affected 24.6% of the population. This high rate of malnutrition is typical in oncological patients and corresponds with results reported by Tran Que Son (2). A significant proportion of patients presented with comorbidities (66%) and a history of prior surgery (23%), both of which are recognized factors that elevate the risk of surgical site infection (SSI). Preoperative physical status was primarily classified as ASA II (62.5%) and ASA III (35.6%); notably, higher ASA scores were identified as a critical risk factor, echoing the conclusions of both Zhiwei Wang (3) and Hegde et al. (1).

Most procedures were elective (82.8%), a higher rate than those reported in other domestic oncology settings (11,12), likely due to the specialized nature of the oncology hospital. In accordance with guidelines from the Ministry of Health and the CDC (4,5,6), the majority of cases involved clean-contaminated wounds (89.6%). Although 61.5% of surgeries exceeded 120 minutes—a known risk factor also highlighted in Hegde et al.'s analysis (1)—the mean preoperative hospital stay (9.9 days) and overall stay (19.06 days) were relatively prolonged, potentially increasing patient exposure to nosocomial pathogens. Notably, the overall SSI rate in this study (12.9%) was significantly lower than the 24% incidence reported by Hegde et al. (1), a variance that may be attributed to differences in sample size, surgical complexity, and the specific perioperative protocols employed.

4. 2. Surgical site infection (SSI) rate in gastrointestinal surgery

In this study of 309 patients, the SSI incidence was 12.9%. While this rate is lower than those reported in international literature, such as the 24% observed by Hegde et al. (1) and rates in other global cohorts (8,9), it is higher than the 7.5% reported domestically by Tran Que Son (2). Nevertheless, the incidence remains within the globally reported range of 5–30%. Interestingly, all SSI cases (100%) in this cohort were classified as superficial, with no deep or organ/space infections identified. This deviates from studies by Nguyen Thi Bich Ngoc (12) and other domestic authors (11,13), who documented all three classifications of SSI. This discrepancy may reflect rigorous postoperative wound care and effective infection control protocols at the study site.

The SSI rate for clean-contaminated procedures (8.7%) aligned with the Ministry of Health's benchmarks of 5–10% (4,5). Conversely, contaminated procedures exhibited a markedly higher infection rate (50%), predominantly in cases of intestinal obstruction or hollow viscus perforation, a finding consistent with the high risk associated with contaminated surgical fields (1,6). Anatomically, the highest SSI rates occurred in small bowel (19.2%) and rectal surgeries (18.2%), whereas the lowest was observed in hepatobiliary and pancreatic procedures (6.7%), aligning with established surgical site risk profiles (3,8).

4.3. Causes of surgical site infection in gastrointestinal surgery

Bacterial cultures were positive in 80% of SSI specimens, showing a stark predominance of Gram-negative organisms (93.75%). Escherichia coli was the most frequently isolated pathogen (50%), followed by Klebsiella pneumoniae (28.1%). Notably, all identified infections in this cohort were monomicrobial.

The 80% culture positivity rate in this study is significantly higher than the 47% reported by

Siddiqui et al. (7). However, both studies show a consensus on the microbial profile, with E. coli being the primary driver of SSIs in gastrointestinal surgery, accounting for 50% in this study compared to 36.4% in the reference study (7). The high prevalence of Gram-negative bacilli reinforces the theory that SSIs in gastrointestinal procedures primarily originate from endogenous enteric flora (1,8).

Cases with negative cultures in this study (20%) may be attributed to preoperative antibiotic administration or the presence of fastidious organisms. Furthermore, as the diagnostic focus was limited to aerobic cultures, the role of anaerobic pathogens—which are common in the gut—may be underestimated (6,7). These findings highlight the necessity of targeted antibiotic prophylaxis and the potential for developing local antibiograms to manage Enterobacteriaceae-related infections effectively (5).

4.4. Factors associated with surgical site infection in gastrointestinal surgery

The present study identified several clinical and operative variables significantly associated with the development of surgical site infection (SSI). Statistically significant factors included the presence of comorbidities, a preoperative hospital stay exceeding 7 days, an impaired preoperative physical status (ASA ≥ III), and emergency surgical intervention. Furthermore, contaminated wound classification, the specific organ operated upon (notably small bowel and rectal procedures), prolonged operative duration, an NNIS risk index ≥ 3, and the open surgical approach were also confirmed as critical predictors.

Specifically, our results echo those of Tran Que Son (2) and Zhiwei Wang (3), who reported significant correlations between ASA scores, wound classification, and SSI incidence. Similarly, the impact of extended operative time and emergency procedures in elevating infection risks aligns with findings by Hegde et al. (1) and domestic reports (11). Regarding the duration of hospitalization, our findings are consistent with established literature identifying prolonged preoperative stays as a significant risk factor, potentially due to increased exposure to nosocomial pathogens (12,13). Additionally, the correlation between a high NNIS risk index and increased SSI susceptibility supports the conclusions drawn by the CDC and other surveillance studies (6,12).

Conversely, demographic and anthropometric factors such as age, sex, and BMI did not show statistically significant associations with SSI. These observations are in agreement with studies conducted by Tran Que Son (2) and other regional analyses (10). Although some literature identifies obesity as a risk factor, this association was not replicated in our cohort, likely due to the exceptionally low prevalence of obesity (0.3%) within the study population. Furthermore, while the universal administration of prophylactic antibiotics (100%) adhered strictly to clinical guidelines (4,5), this uniformity precluded an objective evaluation of its efficacy as a comparative risk factor. In summary, the risk of SSI is primarily driven by the patient's preoperative clinical status, procedural complexity, and the duration of hospital exposure, reinforcing the need for targeted perioperative management in high-risk groups (1,8).

4.5. Treatment outcomes

Regarding clinical outcomes, complete resolution of surgical site infections was achieved in 100% of the affected cases, with all patients subsequently discharged in stable condition. There were no recorded instances of persistent infection, inter-hospital transfers, or procedure-related mortality within this cohort. These results align with the findings of Pham Van Tan (14)

and Nguyen Thi Bich Ngoc (12), reflecting a high degree of therapeutic efficacy in managing postoperative complications.

The favorable prognosis observed in this study can be attributed to early detection through systematic surveillance and the application of standardized wound care protocols as recommended by the Ministry of Health (4,5). In summary, although the occurrence of SSI is inherently associated with prolonged hospitalization, the implementation of effective clinical management and evidence-based nursing interventions resulted in successful recovery for all patients. These findings reinforce the importance of maintaining rigorous infection control standards to mitigate the clinical impact of SSIs in oncology-focused surgical settings (6,11).

5. CONCLUSION

In this study of 309 patients undergoing gastrointestinal surgery at Da Nang Oncology Hospital in 2024, the incidence of surgical site infection (SSI) was 12.9%. Microbiological analysis revealed a high culture positivity rate of 80%, with a marked predominance of Gram-negative bacteria (93.75%). *Escherichia coli* was the most prevalent pathogen (50%), followed by *Klebsiella pneumoniae* (28.1%), *Proteus mirabilis* (9.4%), *Pseudomonas aeruginosa*, and *Enterococcus* spp. (6.25% each). Notably, all identified infections were monomicrobial.

Several critical risk factors were significantly associated with an increased SSI incidence, including the presence of comorbidities, a preoperative stay exceeding 7 days, ASA score ≥III, a history of gastrointestinal surgery, and emergency procedures. Additionally, contaminated wound classification, small bowel surgery, operative duration > 120 minutes, and an NNIS risk index ≥ 3 were identified as major predictors of infection.

Regarding therapeutic outcomes, 100% of patients with SSI achieved complete resolution and were discharged in stable condition, with a mean hospital stay of 19.06 ± 9.22 days. In summary, while SSI in gastrointestinal surgery is frequently caused by endogenous Gram-negative flora and influenced by multiple perioperative factors, effective clinical management ensures a favorable prognosis and high recovery rates.

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COMBINATION OF TACE AND TKIs IN THE TREATMENT OF HEPATOCELLULAR CARCINOMA: FROM THEORY TO CLINICAL PRACTICE

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ABSTRACT

Background: Over recent decades, hepatocellular carcinoma (HCC) has remained one of the Major challenges in oncology, particularly in countries with a high prevalence of viral hepatitis, such as Vietnam. Intermediate-stage HCC according to the Barcelona Clinic Liver Cancer (BCLC-B) classification represents a heterogeneous population in terms of tumor burden and baseline liver function. Transarterial chemoembolization (TACE) is currently considered the standard treatment for this stage. However, not all patients are suitable candidates for TACE, and repeated TACE alone may lead to deterioration of liver function. The advent of tyrosine kinase inhibitors (TKIs) has ushered in a new era of systemic therapy for HCC, initially in advanced-stage disease, and subsequently explored in combination with TACE in earlier-stage settings to exploit the potential synergy between locoregional tumor control and inhibition of angiogenesis.

Objective: To review and analyze the available evidence regarding the efficacy and emerging trends of combining TACE with tyrosine kinase inhibitors in the treatment of HCC.

Methods: A narrative review of expert consensus statements, clinical studies, and treatment guidelines from the AASLD, EASL, and BCLC was conducted. Relevant literature was retrieved from PubMed, Google Scholar, ScienceDirect, and domestic Vietnamese medical journals.

Results: Recent evidence suggests that the combination of TACE and TKIs may improve tumor control and prolong progression-free survival in patients who are no longer suitable for TACE monotherapy, particularly when patient selection and treatment timing are optimized.

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Conclusion: The combination of TACE and TKIs is increasingly regarded as a critical transitional strategy between locoregional and systemic therapies in the management of HCC. This approach highlights the need for further research to identify patients most likely to benefit, optimize treatment sequencing, and assess long-term efficacy and safety. In Vietnam, this combined modality is being progressively adopted in clinical practice.

Keywords: Hepatocellular carcinoma, transarterial chemoembolization (TACE), tyrosine kinase inhibitors (TKIs), combination therapy.

1. INTRODUCTION

Hepatocellular carcinoma (HCC) has remained a major global cancer burden for decades. According to GLOBOCAN 2022, HCC ranks sixth in incidence and third in cancer-related mortality worldwide. The disease burden is particularly high in the Asia–Pacific region, with Vietnam being one of the most affected countries, ranking second in incidence and first in mortality in both sexes [1].

In Vietnam, HCC is strongly associated with the high prevalence of chronic hepatitis B and C infections, as well as alcohol-related liver disease and other causes of cirrhosis. Most patients are diagnosed with HCC on a background of cirrhosis, which significantly limits the feasibility of curative treatment options such as surgical resection or liver transplantation. In addition, the majority of cases are detected at intermediate or advanced stages, making treatment strategies more complex and resulting in poor overall prognosis.

Patients with intermediate-stage HCC (BCLC stage B) are primarily treated with transarterial chemoembolization (TACE). However, TACE monotherapy has several limitations, particularly in large tumors, multifocal disease, or cases requiring repeated procedures. Moreover, repeated TACE may induce tumor recurrence and progression through upregulation of angiogenic factors. Although systemic therapy has become the standard of care for advanced-stage disease (BCLC stage C), outcomes remain unsatisfactory due to poor prognosis and limited treatment response in this stage [2].

Given the limitations of single-modality therapy, combination strategies involving TACE and systemic treatment have been increasingly investigated worldwide, particularly combinations with tyrosine kinase inhibitors (TKIs). This approach is based on a synergistic mechanism, whereby TACE provides local tumor control while TKIs inhibit angiogenesis and suppress microscopic tumor progression.

Objective of the review: This narrative review aims to summarize and critically analyze the existing evidence on the therapeutic efficacy and current trends in the application of combined TACE and TKI-based therapy in the treatment of hepatocellular carcinoma (HCC).

2. LITERATURE REVIEW

This narrative review was synthesized from expert consensus documents, clinical trials, and treatment guidelines issued by major international societies such as AASLD, EASL, JSH, and the Barcelona Clinic Liver Cancer (BCLC) staging system. Relevant literature was searched in PubMed, Google Scholar, ScienceDirect, and peer-reviewed medical journals covering the period from 2008 to 2025.

The search strategy used key terms and their synonyms combined with Boolean operators (AND/OR), including: “Hepatocellular carcinoma,” “HCC,” “transarterial chemoembolization,” “TACE,” “tyrosine kinase

inhibitor," "TKIs," "sorafenib," "lenvatinib," "combination," "concurrent," and "sequential."

Eligible studies included phase II–III clinical trials, meta-analyses, systematic reviews, and clinical practice guidelines. Studies with small sample sizes, single case reports, or those not directly related to the topic were excluded. After the screening process, a total of 19 articles were included in the final analysis and synthesis of this review.

3. HISTORICAL ROLE OF TACE IN THE TREATMENT OF HCC

3.1. Biological basis and principles of TACE

The vascular supply of tumors varies depending on their degree of malignancy. During hepatocarcinogenesis, the arterial blood supply initially decreases and then abnormally increases [3]. In contrast, the portal venous blood supply progressively decreases and eventually disappears in moderately or poorly differentiated HCC [4]. Based on this vascular shift, intra-arterial delivery of embolic agents into the main tumor-feeding artery can induce ischemia, leading to tumor necrosis.

3.2. Position of TACE within staging systems

Within current staging systems, TACE plays a central role as the standard treatment for patients with intermediate-stage HCC. In addition, TACE is also flexibly applied across different stages depending on therapeutic intent. In early-stage disease (BCLC A), TACE may be used as a bridging therapy or for downstaging in patients who are not initially eligible for curative treatments such as resection or liver transplantation. TACE may also be considered in carefully selected patients with advanced-stage disease who have limited macrovascular invasion, no extrahepatic spread, and preserved liver function, particularly when combined with systemic therapy [5–8].

3.3. Limitations of TACE monotherapy

The efficacy of TACE as a standalone treatment remains limited. Tumor recurrence rates after TACE are high, often necessitating repeated procedures. Repeated TACE sessions may lead to progressive deterioration of liver function and reduced tumor response, thereby negatively affecting long-term patient prognosis [9].

In addition, TACE induces significant changes in the tumor microenvironment. The ischemic conditions triggered by embolization activate hypoxia-inducible factors such as HIF-1α, which in turn upregulate angiogenic mediators including VEGF and PDGF. This neovascularization contributes to tumor recurrence, progression, and metastatic potential, highlighting the biological limitations of TACE when used as monotherapy [10].

4. EMERGENCE OF TKIS AND EXPANSION OF SYSTEMIC THERAPY IN HCC

4.1. Mechanisms of TKIs in HCC

Tyrosine kinase inhibitors (TKIs) exert their anti-tumor effects by inhibiting tumor cell proliferation, suppressing angiogenesis, and promoting widespread apoptosis of cancer cells. These effects are mediated through the blockade of multiple signaling pathways, including VEGF, PDGF, and FGF receptors, as well as intracellular cascades such as Raf-1 and B-Raf [11]. In addition, TKIs modulate the tumor immune microenvironment by reducing immunosuppressive cell populations, including myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and regulatory T cells (Tregs), while enhancing the activity of cytotoxic CD8+ T cells [1]. Based on these mechanisms, the combination of TACE and TKIs is expected to produce a synergistic effect, improving tumor control and overall therapeutic outcomes in HCC.

4.2. TKIs in advanced HCC treatment

The introduction of tyrosine kinase inhibitors (TKIs) represented a breakthrough in the management of advanced-stage hepatocellular carcinoma (HCC). Sorafenib was the first agent to demonstrate a survival benefit, extending median overall survival (OS) from 7.9 months to 10.7 months [2]. Subsequently, lenvatinib showed superiority in improving progression-free survival and overall response rate compared with sorafenib in clinical trials [1,3]. However, TKI monotherapy remains limited in clinical efficacy. Although it improves overall survival, response rates are relatively low, and treatment-related toxicities may affect adherence and long-term treatment continuity [5,6].

5. SCIENTIFIC RATIONALE FOR TACE + TKI COMBINATION STRATEGY

5.1. Biological synergy

The rationale for combining TACE and TKIs is based on two complementary mechanisms: (i) TACE induces rapid tumor shrinkage but subsequently leads to increased expression of pro-angiogenic factors, and (ii) TKIs counteract this effect by inhibiting VEGF, PDGF, and FGF receptor signaling pathways, thereby suppressing tumor angiogenesis and growth [4]. These two modalities therefore exhibit both independent antitumor effects and a synergistic biological interaction when used in combination.

5.2. Combination strategies

5.2.1. Sequential strategy (TACE → TKIs)

In this approach, TACE is performed first to achieve local tumor control, followed by the initiation of TKI therapy when residual disease persists or when tumor progression is observed. This strategy is consistent with conventional clinical practice, allowing clinicians to evaluate the response to TACE before transitioning to systemic therapy. However, delayed initiation of TKIs may result in missing the post-TACE angiogenic surge window. In addition, liver function may deteriorate after repeated TACE sessions, potentially limiting the eligibility for subsequent TKI therapy [5].

5.2.2. Concurrent strategy (TACE combined with TKIs)

This approach involves administering TKIs during the peri-TACE period to suppress early angiogenic activation induced by TACE. TKIs are typically initiated before TACE and continued for a short duration around the procedure. This strategy provides enhanced tumor control based on the biological synergy between the two modalities.

5.2.3. "On-demand" TACE on a TKI backbone

In this strategy, TKIs are maintained continuously throughout treatment, while TACE is performed only when intrahepatic lesions show progression. This approach reduces unnecessary repeated TACE sessions and helps preserve liver function. It has gained increasing attention in the context of personalized treatment strategies for HCC.

6. CLINICAL EVIDENCE OF TACE + TKIS WORLDWIDE

6.1. Early-phase trials and inconsistent results

Initial clinical trials did not demonstrate a clear survival benefit of the combined TACE and TKI strategy. In the SPACE study, TACE was performed on a fixed schedule rather than based on tumor response, which may have limited treatment optimization. Similarly, the TACE-2 trial did not optimize the timing of TKI administration; delayed initiation and treatment interruption around the TACE procedure

potentially reduced anti-angiogenic efficacy and overall tumor control. In addition, these studies mainly used conventional response assessment criteria (RECIST), which do not adequately capture the therapeutic effects of TACE, thereby potentially underestimating the true benefit of combination therapy.

6.2. Recent studies and analyses

Table 1: Studies evaluating TACE combined with TKIs

TACE-2 Phase 2, randomized August 2017	N= 313	PFS DEB-TACE + Sorafenib vs DEB-TACE + placebo	Sorafenib + DEB-TACE did not improve progression-free survival (PFS) compared with TACE alone in European patients with intermediate-stage hepatocellular carcinoma (HCC)
SPACE Phase 3, randomized May 2016	N= 307	TTP DEB-TACE + Sorafenib vs DEB-TACE + placebo	DEB-TACE + sorafenib did not show a clinically meaningful improvement in time to progression (TTP) compared with DEB-TACE monotherapy
TACTICS Phase 2, RCT, randomized December 2019	N= 156	PFS, OS Sorafenib + TACE vs TACE unresectable HCC	PFS was significantly improved in the sorafenib + TACE group (25.2 vs. 13.5 months; p = 0.006). Overall survival (OS) did not show a statistically significant improvement (36.2 vs. 30.8 months), although an absolute gain of 5.4 months was observed.
TACTICS-L (Lenvatinib) Phase 2, Single-arm study 2023	N= 62	PFS, OS, ORR LEN-TACE	Significant improvements in both PFS and OS were reported in patients with unresectable disease. Median TACE-specific PFS was 25.9 months (RECICL), and median OS was 40.1 months. Best overall response rate (ORR) reached 88.7% (90% CI: 79.8-95.6).

Recent evidence suggests that optimizing treatment strategies by using a TKI backbone combined with on-demand or early sequential TACE may improve progression-free survival (PFS), time to progression (TTP), and objective response rate (ORR). In the TACTICS trial evaluating the combination of TACE and sorafenib, a marked improvement in PFS was observed (25.2 months vs. 13.5 months), along with a significant prolongation of TTP (26.7 months vs. 16.4 months). However, overall survival (OS) was not fully analyzed due to only 73.6% OS events being reached, and ORR data were also reported [15]. In the single-arm TACTICS-L study by the same group, which replaced sorafenib with lenvatinib due to its stronger anti-VEGFR activity, encouraging results were also reported. Median OS reached 40.1 months (data cut-off April 2024), while median PFS was 28 months. The ORR at 4 weeks was 79%, with a best ORR of 88.7%.

The selection of appropriate patients, the timing of selective or on-demand TACE based on tumor response, and the optimal timing of

TKI administration are key determinants for maximizing the biological synergism between the two treatment modalities. Careful patient selection with preserved liver function, including Child–Pugh A status, absence of macrovascular invasion or extrahepatic metastasis, and ECOG performance status 0–1, is essential to minimize the risk of post-TACE hepatic decompensation and to maintain effective dosing of TKIs. Selective or on-demand TACE, rather than a fixed-schedule approach, may reduce irreversible liver injury and allow prolonged continuation of TKI therapy. TKIs initiated 2–3 weeks prior to the first TACE procedure may help normalize tumor vasculature and enhance TACE efficacy. Continued TKI administration after TACE is important to counteract hypoxia-induced angiogenesis, thereby contributing to prolonged progression-free survival (PFS) [15]. In addition, PFS assessment using RECICL criteria, rather than mRECIST, is considered more appropriate in intermediate-stage disease, as mRECIST may underestimate treatment benefit and lead to premature stage migration.

6.3. Position of TACE + TKIs in current guidelines

Despite encouraging results from several studies, the combination of TACE and TKIs has not yet been formally incorporated into major international guidelines such as BCLC or EASL, primarily due to the lack of consistent evidence demonstrating an overall survival (OS) benefit [5,7]. The AASLD guidelines also emphasize that although progression-free survival (PFS) improvement has been observed in some trials, the OS benefit remains unclear. In addition, the heterogeneity of patients with intermediate-stage HCC makes it challenging to standardize indications for this combination strategy [6].

7. CLINICAL PRACTICE OF TACE + TKIS IN VIETNAM

7.1. Characteristics of HCC patients in Vietnam

In Vietnam, hepatocellular carcinoma (HCC) remains a major challenge in oncology, ranking second in incidence and first in mortality in both sexes according to GLOBOCAN 2022. The epidemiological profile of HCC patients in Vietnam is characterized by a high prevalence of viral hepatitis-related liver disease and late-stage diagnosis. According to a study by Trần Ngọc Ánh at Hanoi Medical University Hospital, hepatitis B virus infection is the most common risk factor for HCC, accounting for 73% of cases, followed by hepatitis C at 19%. Most patients are diagnosed at intermediate and advanced stages, accounting for 34% and 37%, respectively [6].

7.2. Real-world application of TACE + TKIs in Vietnam

In clinical practice in Vietnam, the combination of TACE and TKIs is applied in a flexible and individualized manner. As most patients are diagnosed at non-curative stages, TACE remains the most used locoregional treatment modality. When there is evidence of poor response to TACE or a high risk of tumor recurrence, early initiation of TKIs instead of repeated TACE sessions is often considered to reduce the risk of liver function deterioration, and this strategy is increasingly adopted in many treatment centers.

Given the current limitations of immunotherapy in Vietnam, including high costs and limited insurance coverage, the implementation of combination strategies has not yet been standardized. Therefore, treatment decisions are largely individualized, depending on clinical experience, hepatic functional reserve, tumor burden, and the patient's financial capacity.

7.3. Factors influencing treatment decisions

Treatment cost remains a major barrier, particularly as TKIs are not yet fully covered by health insurance. According to Circular No. 20/2022/TT-BYT, sorafenib is reimbursed at 50% for the treatment of hepatocellular carcinoma (HCC) in national special-grade, grade I, and grade II hospitals. However, when compared with newer systemic agents or immunotherapy, which are not covered by insurance, TKIs remain more accessible and are therefore more commonly selected in combination with TACE in many clinical settings.

The experience of the treatment center plays a crucial role in determining therapeutic outcomes. Variations in resources and clinical expertise across institutions may lead to differences in implementation and results of combination therapy. In centers with limited manpower and monitoring facilities, treatment decisions may be more conservative or primarily based on individual clinical judgment.

The decision to initiate combination therapy also depends on the ability to monitor and manage treatment-related toxicities. TKIs are associated with adverse effects such as hypertension, hand–foot skin reaction, and other toxicities that require close monitoring and timely dose adjustment. In centers with adequate follow-up systems and multidisciplinary collaboration, this strategy can be implemented more safely and effectively.

8. PATIENT SELECTION AND TREATMENT MANAGEMENT

Patient selection is based on multidisciplinary tumor board decisions and is typically indicated for intermediate-stage HCC patients who are likely to be TACE-refractory or unsuitable for TACE, as well as for selected advanced-stage patients with disease confined to both liver lobes and preserved liver function (Child–Pugh A) [7]. The definition of "unsuitable for TACE" follows the criteria proposed by the Japanese Society of Hepatology [8], including:

- High likelihood of TACE refractoriness: tumors beyond the "up-to-7" criteria.

- High risk of post-TACE hepatic decompensation, particularly in bilobar disease and patients with mALBI grade 2b.

- Poor or absent response to TACE, including multinodular diffuse disease, infiltrative type, nodular lesions with extranodular growth, disseminated lesions, or sarcomatoid transformation following TACE.

Transition from TACE monotherapy to TACE + TKIs and treatment management considerations

The combination strategy may increase toxicity due to overlapping effects between TACE-induced hepatic ischemia and the systemic adverse events of TKIs. Management of adverse events is therefore based on dose reduction or temporary interruption of TKI therapy when necessary. In the TACTICS-L study, 79% of patients required temporary interruption of TKIs and 80.2% required dose reduction, indicating a high incidence of treatment-related adverse events; however, toxicity management did not compromise overall treatment efficacy [9]. Liver function should be closely monitored using Child–Pugh classification and ALBI score. Treatment should be discontinued in cases of unacceptable toxicity or radiological disease progression.

9. CONCLUSION

Currently, in real-world clinical practice in Vietnam, there remains a lack of robust local data regarding the efficacy and safety of the TACE plus TKIs combination strategy. Differences in epidemiology, tumor burden, healthcare

infrastructure, follow-up capacity, and financial accessibility may significantly influence treatment outcomes compared with international study populations. Therefore, real-world evidence studies are essential to identify which subgroups of Vietnamese patients derive the greatest benefit and to help standardize treatment protocols.

The combination of TACE and TKIs represents an important transitional strategy between locoregional and systemic therapy in the management of intermediate-stage HCC or advanced-stage disease confined to the liver. In Vietnam, where most patients are diagnosed at non-curative stages and access to immunotherapy remains limited, TACE combined with TKIs is a feasible and appropriate treatment option. However, further real-world data are needed to determine the optimal patient population and to refine treatment strategies tailored to the specific resource constraints in Vietnam.

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HEPATOCELLULAR CARCINOMA MIMICKING FOCAL NODULAR HYPERPLASIA: A CASE REPORT AND LITERATURE REVIEW

Pham The Anh*, Truong Manh Cuong, Vu Duc Trung, Trinh Huy Phuong

ABSTRACT

Focal nodular hyperplasia (FNH) is the second most common benign hepatic lesion, characterized by a central fibrous scar with radiating septa. It is typically asymptomatic and often discovered incidentally. Several reports in the literature have described misdiagnoses of FNH as fibrolamellar variant of hepatocellular carcinoma (HCC), and rare cases of HCC arising in the background of FNH have also been documented.

We report the case of a 64-year-old male patient accidentally found to have hepatitis B and a left hepatic mass measuring 88 mm which was done core biopsy showing FNH while contrast-enhanced computed tomography favored a diagnosis of HCC over FNH. A resection of hepatic segments III and IV was performed, along with cholecystectomy. Postoperative histopathological examination demonstrated moderately differentiated HCC.

Keywords: Focal nodular hyperplasia, Hepatocellular carcinoma.

I. INTRODUCTION

Focal nodular hyperplasia (FNH) accounts for approximately 8% of all primary liver tumors and is the second most common benign hepatic lesion after hemangioma. It is more frequently observed in women (80–95% of cases), typically between 30 and 40 years of age. FNH is considered a hyperplastic response to increased local blood flow rather than a true neoplastic process. Various vascular abnormalities, including capillary telangiectasia, arteriovenous malformations, and anomalous venous drainage, are thought to be associated with its development.[1]

Histopathologically, FNH is characterized by hyperplasia of hepatocytes with normal morphology. A central fibrous scar with radiating fibrous septa is typically present, containing large, anomalous feeding arteries and their branches. Ductular proliferation is a characteristic feature along the fibrous septa.[2] The central fibrous area consists of dense connective tissue with numerous thick-walled abnormal arteries. Ductular proliferation is accompanied by inflammatory cell infiltrates within and at the periphery of the fibrous septa. Kupffer cells are also present within FNH lesions.[1]

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Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver. Although FNH is generally considered a benign lesion with no malignant potential, rare cases of HCC arising in association with FNH have been reported in the literature. Differentiating between FNH and HCC (particularly in atypical cases or when HCC develops within FNH) with risks of sampling error in needle biopsies can pose a significant diagnostic challenge. This discrepancy underscores the critical importance of accurately distinguishing between benign and malignant hepatic lesions in order to develop an optimal treatment strategy for the patient. Authors report a case of HCC mimicking FNH and provide a brief review of the literature, highlighting the clinical and pathological characteristics of this entity.

2. CASE PRESENTATION

A 64-year-old male with a history of hypertension under medical management was found to have a liver mass 2 months before admission. A liver biopsy performed at a provincial hospital revealed histopathological findings consistent with FNH, characterized by trabecular structures composed of 1–2 layers of hepatocytes interspersed with thin-walled sinusoidal spaces. Tumor cells exhibited small, uniform nuclei with mild hyperchromasia, inconspicuous or absent nucleoli, and clear to eosinophilic cytoplasm, with focal fatty change.

The patient was admitted with right upper quadrant abdominal pain, without fever, jaundice, or weight loss. On physical examination, the patient had a moderate general condition (BMI: 19.84 kg/m^2), heart rate of 80 beats per minute, and blood pressure of 120/70 mmHg. No peripheral lymphadenopathy was detected. The abdomen was soft and non-distended, with no palpable masses; the liver and spleen were not enlarged.

Contrast-enhanced computed tomography (CT) of the abdomen revealed a hypodense lesion involving segments III and IV of the liver, measuring 65 × 88 mm, with pathognomic features. Internal fibrous bands were noted. The lesion demonstrated intense arterial enhancement followed by washout, favoring a diagnosis of hepatocellular carcinoma over FNH.

Serum tumor marker alpha-fetoprotein (AFP) was within the normal range (2.84 ng/mL). The patient tested positive for HBsAg. Other laboratory investigations, including complete blood count, coagulation profile, biochemistry, microbiology, and immunological tests, were within normal limits.

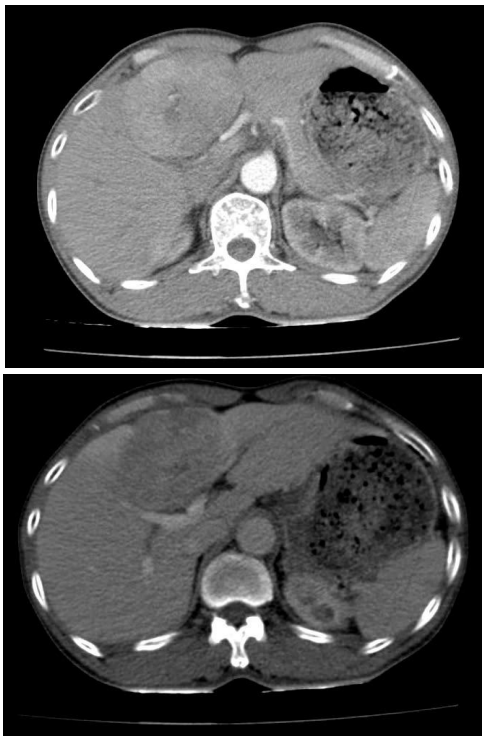

Figure 1. CT scan: Subsegmental mass III and IV measuring 65 × 88 mm, showing arterial phase enhancement and venous washout, with well-defined margins and a distinct capsule, indicative of HCC lesion.

The patient was initially diagnosed with focal nodular hyperplasia (FNH) involving hepatic segments III and IV and underwent surgery on February 7, 2025. Intraoperative exploration revealed a dry abdominal cavity, smooth peritoneal surfaces, and a non-cirrhotic liver. A multilobulated mass measuring approximately 8 cm in diameter was identified in segment IV and partially in segment III, protruding from the liver parenchyma.

A resection of hepatic segments III and IV was performed, along with cholecystectomy. Postoperative histopathological examination demonstrated a tumor composed of maligant hepatocytes with increased nuclear-to-cytoplasmic ratio, pleomorphic nuclei, prominent nucleoli, and occasional mitotic figures. The tumor cells were arranged in trabecular, nested, and pseudoglandular patterns. The tumor was divided into small lobules separated by thick fibrous septa. No vascular invasion was identified. The final diagnosis was moderately differentiated hepatocellular carcinoma (HCC).

The postoperative course was uneventful, and the patient was discharged after 10 days with a final diagnosis of HCC involving segments III and IV. At the 1-month postoperative follow-up, no abnormalities were detected.

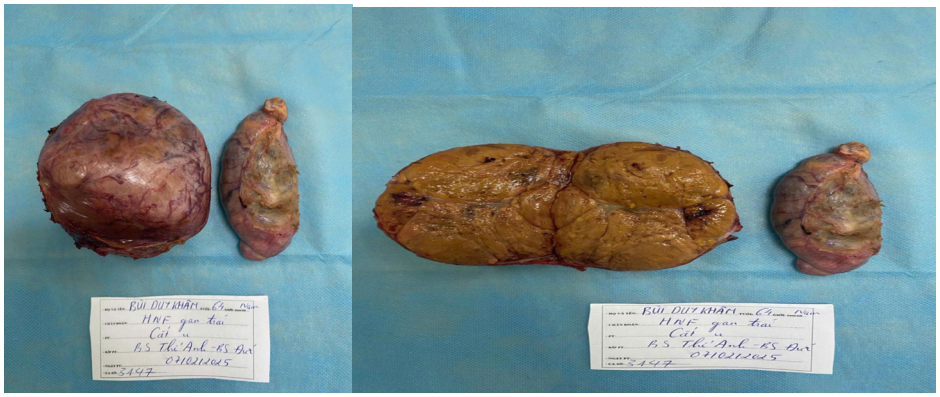

Figure 2a, b. Gross (macroscopic) appearance of the resected lesion.

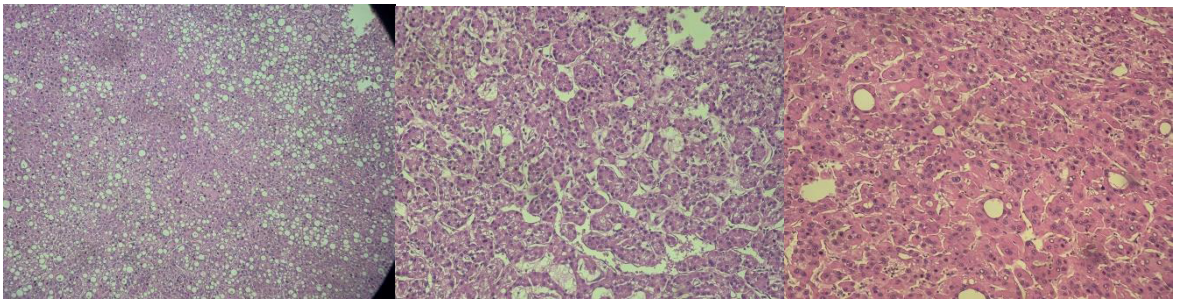

Figure 3a, b, c. Histopathological features of the resected lesion.

3. DISCUSSION

Our case study describes a 64-year-old male who was initially diagnosed with focal nodular hyperplasia (FNH) based on preoperative biopsy; however, postoperative histopathological examination revealed hepatocellular carcinoma (HCC). This discrepancy underscores the critical

importance of accurately distinguishing between benign and malignant hepatic lesions in order to develop an optimal treatment strategy for the patient.

3.1. Differentiation of lesions using imaging diagnostics

Abdominal CT scans revealed a lesion with arterial phase hyperenhancement and venous phase washout, imaging features that are more suggestive of hepatocellular carcinoma (HCC) than focal nodular hyperplasia (FNH). The radiological-pathological discordance between imaging findings and the initial biopsy result raised concerns about a sampling error regarding the limitation of initial 1-2 layers hepatocyte biospy in a huge mass, and consequently led to the indication for surgery. This case highlights the critical role of imaging in differentiating hepatic lesions with similar clinical and histological characteristics.

On non-contrast CT, FNH typically appears hypoattenuating or isoattenuating relative to the surrounding liver parenchyma; however, it may appear hyperattenuating in the setting of hepatic steatosis. A central scar, a characteristic feature, is observed in approximately 60% of lesions larger than 3 cm, although its absence may complicate the diagnosis. During the arterial phase, FNH typically demonstrates intense and homogeneous enhancement, occasionally with prominent central feeding arteries. In the portal venous phase, the lesion becomes slightly hyperattenuating or isoattenuating relative to the liver, making detection more challenging; the central scar remains hypoattenuating and may demonstrate delayed enhancement in approximately 80% of cases.

However, atypical imaging features of FNH are relatively common, occurring in 10–50% of cases, including the presence of a pseudocapsule due to compression of adjacent liver parenchyma—a feature also frequently observed in HCC.[2] A study by Kitao A et al. demonstrated that arterial phase hyperenhancement with early washout on CT, combined with a low apparent diffusion coefficient (ADC) on MRI, are important factors in differentiating HCC from FNH.[3] The degree of arterial enhancement on CT is generally higher in FNH than in HCC, reflecting differences in pathophysiology: HCC arises from neoangiogenesis driven by hypoxia, whereas FNH results from localized vascular hyperplasia and increased blood flow.[3]

Venous drainage patterns also play an important role in differentiation. FNH typically drains via small hepatic veins associated with the central scar, whereas HCC tends to compress and obliterate hepatic veins, resulting in predominant drainage through the portal venous system. The classic CT imaging feature of HCC is arterial phase hyperenhancement with washout in the delayed phase, observed in up to 96% of lesions exhibiting T1 hyperintensity on MRI. In contrast, FNH demonstrates arterial phase hyperenhancement without delayed washout in approximately 78% of cases, consistent with previous reports.[3]

On magnetic resonance imaging (MRI), FNH typically appears iso- to mildly hypointense on T1-weighted sequences and iso- to mildly hyperintense on T2-weighted sequences. The central scar is hypointense on T1-weighted images and hyperintense on T2-weighted images. Following gadolinium administration, FNH demonstrates strong arterial phase enhancement, and the central scar may exhibit delayed enhancement. When hepatocyte-specific contrast agents such as gadoxetate disodium (Eovist/ Primovist) are used, FNH typically shows uptake and retention in the hepatobiliary phase, appearing iso- or slightly hyperintense relative to the surrounding liver parenchyma, while the central scar remains hypointense in this phase.

Typical HCC appears iso- to mildly hypointense on T1-weighted imaging and moderately hyperintense on T2-weighted imaging, although these features may vary depending on histological components such as fat, necrosis, or hemorrhage. In the hepatobiliary phase, HCC typically appears hypointense relative to the surrounding liver due to reduced uptake of contrast agents.

Contrast-enhanced ultrasound (CEUS) and microvascular imaging techniques have also been applied in differentiating atypical HCC from FNH. Although FNH may demonstrate rapid arterial enhancement similar to HCC, microvascular imaging can help identify distinguishing features such as a spoke-wheel arterial pattern in FNH and disorganized vascular architecture in HCC.

Table 1: Comparison of imaging characteristics of FNH and HCC

Imaging Characteristics		FNH	HCC
Computed tomography (CT)	Central scar	Commonly present	Usually absent
	Arterial phase enhancement	Intense and homogeneous	Intense, may be heterogeneous
	Venous phase washout	Typically absent	Typically present
	Capsule	Usually absent; may have a pseudocapsule (atypical)	Usually present
Magnetic resonance imaging (MRI)	Hepatobiliary phase enhancement	Isointense or slightly hyperintense	Hypointense
	T1-weighted signal	Isointense to mildly hypointense	Variable
	T2-weighted signal	Isointense to mildly hypointense	Variable
	Capsule	Usually absent; may have a pseudocapsule (atypical)	Usually present
Contrast-enhanced ultrasound (CEUS)	Spoke-wheel vascular pattern	Commonly present	Typically absent

3.2. Role of Histopathology in Diagnosis

Although the initial biopsy suggested focal nodular hyperplasia (FNH), the imaging findings on contrast-enhanced computed tomography (CT) were not consistent with this diagnosis. This discordance highlights the inherent limitations of needle biopsy in the evaluation of focal liver lesions. Some tumors may exhibit mixed histological features, and although rare, the development of hepatocellular carcinoma (HCC) within the background of FNH has been reported in the literature.[4] In the present case, the large tumor size (8 cm) raises the possibility that the initial biopsy sampled a region with histopathological features consistent with FNH, while other areas harbored HCC.

Histologically, FNH is characterized by a nodular architecture composed of benign hepatocytes arranged in trabeculae one to two cells thick. Abnormally thick-walled arteries are typically

present within the central scar. Ductular reaction can be highlighted by immunohistochemical staining for cytokeratin 7 (CK7) and cytokeratin 19 (CK19) at the interface between fibrous septa and hepatocellular nodules. Although the central fibrous area may contain radiating fibrous septa resembling portal tracts, true portal tracts are absent. Inflammatory infiltrates, either lymphocytic or mixed, may be observed. Immunohistochemical staining for glutamine synthetase (GS) demonstrates broad, interconnected bands of hepatocytes forming a characteristic "map-like" pattern.[5]

HCC can be distinguished from FNH by the presence of cytological atypia, thickened trabeculae (>2 cells thick), and loss of the reticulin framework. Diffuse GS staining observed in HCC may occasionally be mistaken for the map-like pattern seen in FNH, particularly in needle biopsy specimens. Fibrolamellar hepatocellular carcinoma (FL-HCC) is characterized by large polygonal tumor cells with abundant eosinophilic cytoplasm, prominent nuclei, and dense lamellar fibrosis, and is associated with the DnaJ homolog subfamily B member 1 (DNAJB1) gene fusion.[5]

Table 2: Key histopathological characteristics to differentiate FNH from HCC

Histopathological characteristics	FNH	HCC
Hepatocyte arrangement	Nodular; trabeculae 1-2 cells thick	Variable; typically trabeculae >2 cells thick
Cytological atypia	Absent	Present, variable degree
Reticulin framework	Preserved	Reduced or lost
Bile ductules	Proliferation within fibrous septa	May be present or absent
Central scar	Present, containing abnormal vessels	Usually absent
Vascular invasion	Absent	May be present
Glutamine Synthetase (GS) staining patterns	"Map-like" pattern	Typically diffuse staining or negative

3.3. Role of Alpha-Fetoprotein (AFP)

The patient's alpha-fetoprotein (AFP) level was 2.84 ng/mL, which is within the normal range. AFP is a commonly used biomarker for the diagnosis and monitoring of hepatocellular carcinoma (HCC). However, this case highlights the limitations of relying on AFP to exclude HCC.

In previously reported cases of HCC arising in focal nodular hyperplasia (FNH), tumor markers, including AFP, have remained within normal limits.[4] This suggests that HCC—even in tumors of considerable size, as in our case—may present with normal AFP levels. Serum AFP remains the most widely used biomarker for HCC screening, early detection, treatment response assessment, and prognostication. Nevertheless, not all HCCs secrete AFP, and elevated AFP levels may also be observed in patients with cirrhosis or hepatitis.

A systematic review reported a sensitivity of 41–65% and a specificity of 80–94% for AFP at a diagnostic cutoff of ≥20 ng/mL for HCC. A large multicenter study demonstrated an AFP positivity rate (cutoff >11 ng/mL) of 46% across all HCC cases and 23.4% in tumors smaller than 2 cm.

Another large multicenter analysis showed that AFP levels <20 ng/mL were observed in 52% of patients with tumors smaller than 3 cm, 53.5% of patients with stage I disease (TNM classification), 48% of those with Okuda stage I, and even among patients with advanced disease (41.5% in TNM stage IV and 28% in Okuda stage III). These findings indicate that nearly half of HCC patients may have AFP-negative disease, particularly in early-stage tumors and small lesions.[6]

3.4. Association between Hepatitis B Virus Infection and HCC

Hepatitis B virus (HBV) infection is a major risk factor for the development of hepatocellular carcinoma (HCC), particularly in Southeast Asia, where HBV prevalence remains high. A 2023 meta-analysis reported an HCC prevalence of up to 45.8% among HBV-infected individuals in Southeast Asia, with a rate of 22.4% in Vietnam.[7] Several studies have demonstrated that patients with high HBV viral load remain at increased risk of developing HCC, even in the inactive phase of infection (HBeAg-negative).[8]

In the present case, in addition to the typical imaging features of HCC on contrast-enhanced computed tomography (CT), the presence of positive hepatitis B surface antigen (HBsAg) further supported our decision to proceed with surgical resection.

3.5. Literature Review

A previously reported case described HCC arising in the background of FNH in an 86-year-old woman. In that case, imaging findings on abdominal CT were typical of HCC, tumor markers were not elevated, and preoperative biopsy suggested HCC. However, the initial postoperative histopathological diagnosis was FNH. Subsequent additional sampling revealed two nodules with marked cytological atypia, thickened trabeculae, and loss of the reticulin framework, leading to a final diagnosis of HCC.[4] This case raises the possibility that HCC may arise within or adjacent to areas resembling FNH, emphasizing the importance of adequate and representative tissue sampling.

Another report described a patient with multiple hepatic nodules, in whom biopsy revealed HCC in one region of the liver and FNH in another.[9] It is also important to note that FNH may be misdiagnosed as HCC. One case described a 48-year-old woman initially diagnosed with well-differentiated HCC based on CT imaging and biopsy; however, postoperative histopathology confirmed benign FNH.[10]

The discrepancy between the initial histopathological findings and CT imaging in this case highlights the need for a multidisciplinary approach involving clinicians, radiologists, and pathologists in the diagnosis and management of hepatic tumors. International guidelines for HCC management also emphasize the importance of multidisciplinary evaluation.

4. CONCLUSION

HCC mimicking FNH is a rare clinical entity. The diagnosis of HCC may be missed due to limitations of needle biopsy, atypical imaging enhancement patterns, and non-elevated tumor markers. Therefore, a multidisciplinary approach is essential to improve diagnostic accuracy and to guide appropriate treatment strategies for patients.

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ANALYSIS OF PROGNOSTIC FACTORS FOR SURVIVAL IN PATIENTS WITH METASTATIC PANCREATIC CANCER RECEIVING FIRST-LINE mFOLFIRINOX AT K HOSPITAL

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ABSTRACT

Objective: Evaluation of prognostic factors associated with survival outcomes in patients with metastatic pancreatic cancer receiving first-line mFOLFIRINOX.

Methods: A retrospective and prospective study on 36 patients diagnosed with metastatic pancreatic cancer at K Hospital were treated with the first-line mFOLFIRINOX regimen. The primary endpoints were overall survival (OS) and progression-free survival (PFS), with analyses of factors associated with OS and PFS. Secondary endpoints included response rate, treatment-related toxicity, and the rate of treatment interruption.

Results: The median follow-up was 15.6 months (95% CI, 3.8–27.3). The median progression-free survival was 6.7 months, and the median overall survival was 12.5 months. In univariate analysis, age <60 and ECOG performance status (PS) 0 were associated with prolonged progression-free survival (PFS) and overall survival (OS). ECOG PS 0 was identified as an independent prognostic factor for overall survival. The overall response rate (ORR) was 30.6 %, disease control rate (DCR) was 66.6%. Grade 3 or 4 toxicities were mainly hematologic, including neutropenia in 33.4% of patients and thrombocytopenia in 2.8%

Conclusion: The mFOLFIRINOX regimen demonstrated treatment efficacy. ECOG PS 0 was identified as favorable prognostic factors associated with prolonged survival in patients with metastatic pancreatic cancer.

Keyword: Pancreatic cancer, mFOLFIRINOX, chemotherapy, metastatic, prognostic factors.

1. INTRODUCTION

Pancreatic adenocarcinoma arises from the epithelial cells of the pancreatic tissue [1]. It ranks as the 12th most common cancer worldwide, with 495,773 new cases (2.6%) diagnosed annually. Pancreatic cancer is also the 7th leading cause of cancer-related mortality globally, accounting for 466,003 deaths (4.7%) [2].

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Surgical resection remains the only potentially curative treatment. However, most patients are diagnosed at an advanced stage, and only 15–20% are eligible for surgery. Systemic chemotherapy is the mainstay of treatment for patients with metastatic pancreatic cancer. The phase III PRODIGE 4/ACCORD 11 trial by Thierry Conroy et al. demonstrated that FOLFIRINOX significantly improved overall survival, progression-free survival, and quality of life compared with Gemcitabine, and has since become the standard first-line treatment for metastatic pancreatic cancer. However, high rates of neutropenia and febrile neutropenia were reported (45.7% and 5.4%, respectively) [3]a four-drug combination chemotherapy regimen was associated with objective responses in more than 30% of patients and increased survival by more than 4 months, as compared with standard gemcitabine. Pancreatic adenocarcinoma was the fourth leading cause of death from cancer in the United States in 2010,1 and it carries a grim prognosis: the 5-year survival rate is 6% in Europe and the United States.1,2 Gemcitabine became the reference regimen for advanced pancreatic cancer after a randomized trial showed significant improvement in the median overall survival as compared with fluorouracil administered as an intravenous bolus (5.6 vs. 4.4 months, P=0.002.

Dose reductions of Irinotecan and Fluorouracil bolus have been shown to reduce toxicity while maintaining efficacy, as demonstrated in a study by Masato Ozaka et al. (2018), evaluating modified FOLFIRINOX (mFOLFIRINOX) in patients with metastatic pancreatic cancer [4].

In Vietnam, the mFOLFIRINOX regimen has been increasingly adopted as a first-line treatment for metastatic pancreatic cancer due to its demonstrated efficacy. However, this is an intensive regimen associated with considerable toxicity, requiring patients to have good performance status and treatment tolerance. Therefore, appropriate patient selection—identifying those who can tolerate and truly benefit from this regimen—is of significant clinical importance. Based on this rationale, this study was conducted to evaluate factors associated with survival outcomes in patients with metastatic pancreatic cancer receiving first-line treatment with the mFOLFIRINOX regimen.

2. METHODS

2.1. Subjects

Patients with metastatic pancreatic cancer who received first-line treatment with the modified FOLFIRINOX (mFOLFIRINOX) regimen at K Hospital between January 2019 and June 2025.

Inclusion criteria: Patients were eligible if they met the following criteria: histologically confirmed metastatic pancreatic adenocarcinoma; age ≥18 years; ECOG 0–1; adequate hepatic, renal, and hematologic function; at least one measurable lesion according to RECIST 1.1; and receipt of at least four cycles of mFOLFIRINOX.

Exclusion criteria: Patients were excluded if they had received prior chemotherapy or radiotherapy; had grade ≥2 peripheral neuropathy; had a history of other malignancies; or had severe medical or surgical comorbidities associated with a high risk of early mortality.

2.2. Methods

Study design: This was a retrospective–prospective descriptive study. Patients treated between January 2019 – March 2025 were identified retrospectively, while those treated between April 2025 -June 2025 were enrolled prospectively. The final follow-up and study cut-off date was November 1,2025.

Sample size and sampling method: Consecutive sampling was applied, including all eligible patients (convenience sampling).

Treatment protocol: Patients received the mFOLFIRINOX regimen every 2 weeks, consisting of Oxaliplatin 85 mg/m² administered as a 120-minute intravenous infusion on day 1; Leucovorin 400 mg/m² administered intravenously over 120 minutes on day 1; Irinotecan 150 mg/m² administered intravenously over 90 minutes; and Fluorouracil administered as a continuous

intravenous infusion over 46 hours on days 1–2. Prophylactic granulocyte colony-stimulating factor (G-CSF) (PegGrafeel) was administered following chemotherapy to prevent neutropenia.

Treatment could be delayed by at least 7 days beyond the scheduled cycle under the following conditions: (1) any adverse event of grade ≥3; (2) persistent grade 2 toxicity over two consecutive assessments despite supportive care; or (3) first occurrence of grade 2 toxicity in patients aged ≥70 years.

Assessment of treatment efficacy and toxicity: Tumor response was evaluated every four cycles according to RECIST 1.1[5]. Overall survival (OS) was defined as the time from initiation of chemotherapy to death from any cause. Progression-free survival (PFS) was defined as the time from initiation of chemotherapy to disease progression or death. Adverse events were recorded and graded according to CTCAE v5.0. Treatment interruption was defined as discontinuation of therapy for at least one full chemotherapy cycle (≥14 days) between two treatment courses.

Data analysis: Data was collected and analyzed using SPSS version 26.0. Survival outcomes (OS and PFS) were estimated using the Kaplan–Meier method and compared between groups using the log-rank test. Factors associated with survival were evaluated using Cox proportional hazards regression models. Clinical and paraclinical variables were first assessed in univariate analysis; variables with statistical significance ($p < 0.05$) or clinical relevance were included in multivariate analysis to identify independent prognostic factors. Results were reported as hazard ratios (HRs) with 95% confidence intervals (CIs).

3. RESULTS

3.1. Patient characteristics

Between January 2019 and June 2025, a total of 36 patients were included in this ambispective cohort, comprising 31 retrospective and 5 prospective cases. The median follow-up time was 15.6 months (95% CI, 3.8–27.3). A total of 25 patients (69.4%) had an ECOG performance status of 0. The primary tumor was most commonly located in the head of the pancreas (58.3%). 8 patients presented with biliary obstruction prior to treatment. The most common metastatic site was the liver (66.7%), followed by the peritoneum and lymph nodes (each 22.2%), while lung and other sites were less frequent. Elevated carbohydrate antigen 19-9 (CA19-9) levels >1000 U/mL were observed in 33.3% of patients. Detailed patient characteristics are summarized in Table 1.

Table 1: Patient Characteristics

Table 1 Demographic and baseline characteristics of patients		
Characteristics	N = 36	
	No. of patients	%
Median age at diagnosis in years (range)	57 (27-74)	
Sex		
Male	22	61.1
Female	14	38.9
ECOG performance status		
0	25	69.4
1	11	30.6
Pancreatic tumor location		
Head	21	58.3
Body	6	16.7
Tail	9	25
Intervention for biliary obstruction		
Biliary stent	3	8.3
Percutaneous transhepatic biliary drainage	3	8.3
Operative biliary-enteric bypass	2	5.6
No	28	77.8
No. of metastatic sites involved		
1	29	80.6
2	5	13.9
3	2	5.6

Table 1 Demographic and baseline characteristics of patients		
Prior surgery		
No	29	80.6
Yes	7	19.4
CA19-9 (U/ml)		
Median (range)	258.25 (0.8-47430)	
<37 U/ml	13	36.1
37≤1000 U/ml	11	30.6
≥1000 U/ml	12	33.3
*ECOG, Eastern Cooperative Oncology Group; CA19-9, Carbohydrate antigen 19-9		

3.2. Treatment adherence

The median number of treatment cycles was 9 (range, 4–34), with 20 patients (55.6%) receiving more than 8 cycles. Dose reductions were required in 5 patients during treatment. Treatment interruption occurred in 14 patients (38.9%), of whom 7 were switched to a 3-week cycle after experiencing grade 2 toxicity for three consecutive cycles.

Neutropenia was the most common cause of treatment interruption. 2 patients discontinued treatment due to toxicity. Among the 29 patients who experienced disease progression on first-line therapy, 25 (86.2%) received second-line treatment, with gemcitabine-based regimens being the most commonly used (Total 27 patients).

3.3. Treatment outcomes

Table 2: Treatment response according to RECIST 1.1

Treatment response	N=36	
	n	%
Complete response (CR)	0	0
Partial response (PR)	11	30.6
Stable disease (SD)	13	36.1
Progressive disease (PD)	12	33.3
Overall response rate (ORR)	11	30.6
Disease control rate (DCR)	24	66.7
*ORR = CR + PR, DCR = CR + PR +SD		

Comment: The rates of partial response, stable disease, and progressive disease were 30.6%, 36.1%, and 33.3%, respectively. The overall response rate (ORR) was 30.6%, and the disease control rate (DCR) was 66.7%.

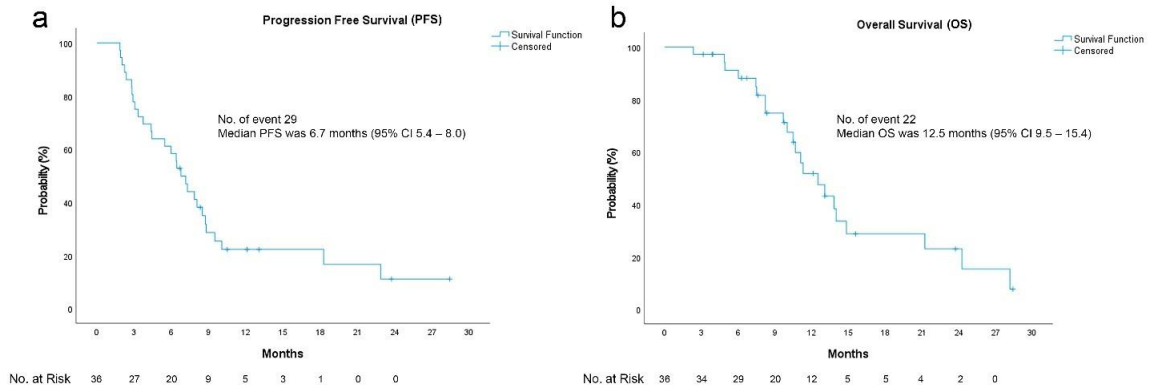

Figure 1. Kaplan-Meier curves for progression-free survival (PFS) (a) and overall survival (OS) (b).

Comment: The median follow-up was 15.6 months (95% CI, 3.8–27.3). Disease progression was observed in 29 patients, and 22 patients had died at the time of analysis. The median progres-

sion-free survival (PFS) was 6.7 months (95% CI, 5.4–8.0), and the median overall survival (OS) was 12.5 months.

3.4. Treatment-related toxicity

Table 3: Treatment-related adverse events according to CTCAE v5.0

N=36		Grade 1/2		Grade 3/4	
		n	%	n	%
Hematologic	Anemia	19	52.7	2	5.6
	Febrile neutropenia			0	0.0
	Neutropenia	11	30.6	12	33.4
	Thrombocytopenia	17	42.2	1	2.8
Non-hematologic	Increased liver enzymes	21	58.3	2	5.6
	Bilirubin	0	0.0	3	8.4
	Diarrhea	10	27.8	2	5.6
	Fatigue	17	47.3	1	2.8
	Vomiting	24	66.6	3	8.4
	Peripheral neuropathy	13	36.1	2	5.6

Comment: Most adverse events were grade 1–2. Grade 3–4 toxicities were predominantly hematologic, including neutropenia (33.4%), thrombocytopenia (2.8%), and anemia (5.6%), with no cases of febrile neutropenia observed during treatment. Non-hematologic grade 3–4 toxicities included elevated liver enzymes (5.6%), hyperbilirubinemia (8.3%), diarrhea (5.6%), fatigue (2.8%), and peripheral neuropathy (5.6%).

3.5. Prognostic factor analysis for survival

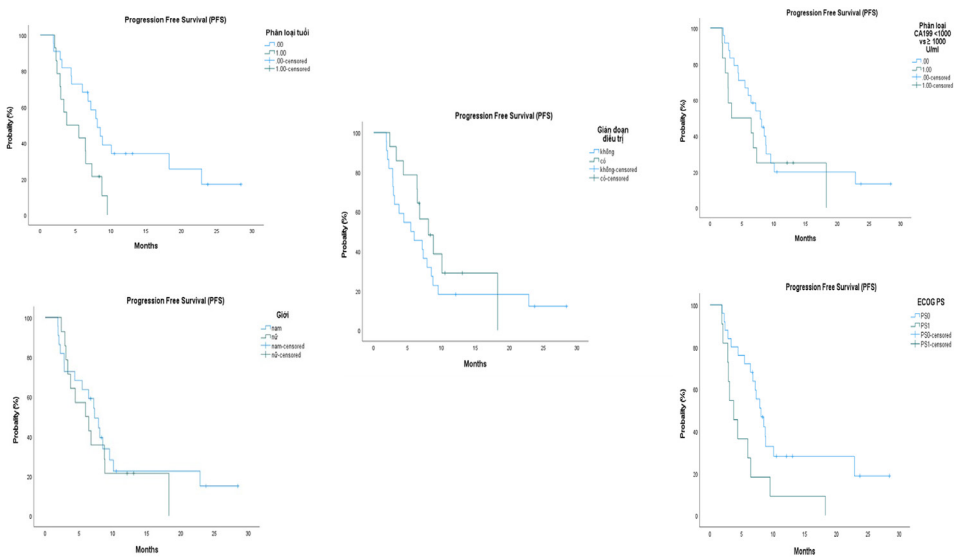

Figure 2. Kaplan–Meier estimates of progression-free survival (PFS) according to prognostic factors

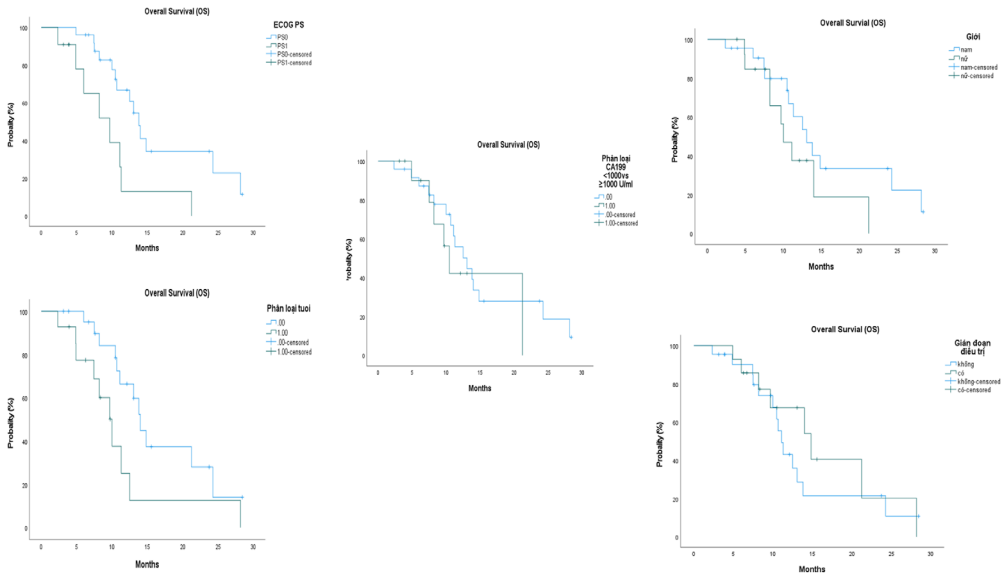

Figure 3. Kaplan–Meier curves of overall survival (OS) stratified by prognostic factors

Table 4. Univariate and multivariate analyses of factors associated with progression-free survival (PFS)

Variables	HR (95%CI), Univariable Cox	p	HR (95%CI) Multivariable Cox	p
Age < 60 vs ≥60	0.37 (0.17-0.83)	0.015	0.45 (0.19-1.03)	0.058
Male vs Female	0.81 (0.38-1.71)	0.577	-	-
ECOG PS 0 vs 1	0.3 (0.18-0.84)	0.017	0.51(0.23-1.18)	0.116
CA19-9 <1000 U/ml	0.67 (0.31-1.47)	0.325	0.75 (0.34-1.67)	0.48
TI Yes or No	0.68 (0.31-1.48)	0.335	-	-
Multivariable Cox regression model				0.016
* ECOG PS, Eastern Cooperative Oncology Group Performance Status; TI, Treatment interruption; HR, Hazard ratio; CI, Confidence interval				

Comment: Univariate analysis using the Cox regression demonstrated that age <60 years and ECOG performance status (PS) 0 were associated with prolonged progression-free survival (PFS) ($p < 0.05$). The multivariable Cox regression model was statistically significant, indicating the prognostic value of the combined variables. However, in the multivariable analysis, no individual variable reached statistical significance. Age <60 years showed a trend toward longer PFS ($p = 0.058$).

Table 5. Univariate and multivariable analyses of factors associated with overall survival (OS)

Variables	HR (95%CI), Univariable Cox	p	HR (95%CI) Multivariable Cox	p
Age < 60 vs ≥60	0.39 (0.16-0.94)	0.036	0.43 (0.17-1.08)	0.073
Male vs Female	0.54 (0.22-1.33)	0.186	-	-

ECOG PS 0 vs 1	0.31 (0.12-0.78)	0.012	0.36 (0.13-0.98)	0.047
CA19-9 <1000 U/ml	0.71 (0.28 -1.88)	0.49	0.85 (0.29-2.46)	0.773
TI Yes or No	0.72 (0.30-1.74)	0.469	-	-
Multivariable Cox regression model				0.015
* ECOG PS, Eastern Cooperative Oncology Group Performance Status; TI, Treatment interruption; HR, Hazard ratio; CI, Confidence interval				

Comment: In the univariate Cox regression, the patient group with age <60 years and ECOG performance status (PS) 0 were associated with prolonged overall survival (OS. In the multivariable Cox regression analysis, only ECOG PS 0 remained an independent prognostic factor for OS (HR 0.36; 95% CI, 0.13–0.98; p = 0.047).

4. DISCUSSION

In this study, the mFOLFIRINOX regimen demonstrated treatment efficacy in patients with metastatic pancreatic cancer in Vietnam, with median progression-free survival (PFS) and overall survival (OS) of 6.7 months (95% CI, 5.4–8.0) and 12.5 months (95% CI, 9.5–15.4), respectively. The median PFS was comparable to that reported in the phase III PRODIGE 4/ ACCORD 11 trial (6.7 vs 6.4 months; 95% CI, 5.5–7.2), while the median OS in our study showed a trend toward improvement (12.5 vs 11.1 months; 95% CI, 9.0–13.1)[6].

Compared with the study by Masato Ozaka et al. conducted in an Asian population, both PFS and OS in our study were slightly longer (6.7 vs 5.5 months [95% CI, 4.1–6.7] and 12.5 vs 11.2 months, respectively) [4]. Although these differences are modest, they may still be clinically meaningful in the context of the poor prognosis associated with pancreatic cancer.

Variations in survival outcomes across studies may be related to differences in treatment strategies and supportive care. In our study, all patients received prophylactic peg filgrastim from the initiation of treatment. In addition, a flexible treatment strategy was applied, including treatment delays or interruptions in response to toxicity, with patients allowed an additional 7-day delay beyond the standard cycle when necessary. These measures may have contributed to improved treatment tolerance and prolonged exposure to triplet chemotherapy.

In subgroup analysis, median OS tended to be longer in patients with treatment interruption compared with those without (14.1 months [95% CI, 8.5–21.1] vs 11.1 months [95% CI, 9.9–12.3]).

Univariate analyses identified age <60 years and ECOG performance status (PS) 0 as factors associated with prolonged survival, with consistent findings across log-rank testing and univariate Cox regression. This consistency strengthens the reliability of these results and supports their prognostic significance. In multivariable analysis, ECOG PS 0 was identified as an independent prognostic factor for overall survival, consistent with previous studies demonstrating the prognostic importance of performance status in pancreatic cancer [7-9].

Although other individual variables did not reach statistical significance, the overall multivariable Cox model remained significant ($p < 0.05$), suggesting that clinical factors—including age, ECOG PS, and biological markers—may have a cumulative effect on prognosis rather than acting independently. In clinical practice, younger age (<60 years) and good performance status (ECOG 0) reflect better overall patient condition and fewer comorbidities, which may enhance tolerance to intensive chemotherapy

regimens. Combined with a flexible treatment strategy, these factors may contribute to improved survival outcomes.

The toxicity profile of mFOLFIRINOX in this study was generally consistent with previous reports, with an acceptable rate of grade 3–4 neutropenia and no cases of febrile neutropenia observed. Compared with the PRODIGE 4/ ACCORD 11 trial and other Asian studies[4, 6], the incidence of hematologic toxicity appeared lower, possibly due to routine use of G-CSF prophylaxis and adaptive treatment modifications. However, the overall toxicity burden remains considerable, underscoring the importance of appropriate patient selection in clinical practice.

This study has several limitations. The single-center ambispective design may introduce selection bias and limit the generalizability of the findings. The relatively small sample size reduces the statistical power of multivariable analyses. Additionally, some potentially relevant factors, such as comorbidities and quality of life, were not fully assessed. Differences in patient accrual periods may also introduce temporal bias in treatment practices.

5. CONCLUSION

The mFOLFIRINOX regimen demonstrated clinical efficacy in patients with metastatic pancreatic cancer. Good performance status (ECOG PS 0) was identified as favorable prognostic factors associated with improved survival outcomes.

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EVALUATION OF NUTRITIONAL STATUS IMPROVEMENT IN CANCER PATIENTS UNDERGOING PERCUTANEOUS ENDOSCOPIC GASTROSTOMY (PEG)

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ABSTRACT

Objectives: Assessing the degree of improvement in nutritional status in cancer patients undergoing endoscopic gastrostomy (PEG).

Subjects and methods: A prospective longitudinal study was conducted, in 62 cancer patients who underwent percutaneous endoscopic gastrostomy.

Results: Pre-PEG, the mean BMI of the study cohort was 19.1 ± 2.3 kg/m²; the prevalence of underweight based on BMI was 38.7%, and 69.4% were malnourished according to SGA. Anemia was present in 32.3% of patients, and 22.6% had hypoalbuminemia. At 1 month post-PEG, body weight and BMI were largely unchanged; the prevalence of BMI-defined malnutrition decreased slightly, while SGA-defined malnutrition remained unchanged, with a shift toward a higher proportion of mild malnutrition and lower proportions of moderate and severe malnutrition. At 3 months post-PEG, mean body weight increased by 1.3 kg and mean BMI by 0.5 kg/m². The prevalence of BMI-defined malnutrition decreased from 38.7% to 27.4%, and SGA-defined malnutrition from 69.4% to 37.1%. Anemia increased from 32.3% to 58.1% at 3 months, whereas the prevalence of hypoalbuminemia decreased from 22.6% to 16.1%.

Conclusions: PEG in cancer patients helps maintain nutritional status during treatment at 1 month and improves nutritional status at 3 months.

Keywords: Percutaneous endoscopic gastrostomy (PEG), nutritional status in cancer patients.

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1. INTRODUCTION

Malnutrition is a common problem among cancer patients, with reported prevalence ranging from 20% to 70%. It has a direct impact on quality of life, increases the risk of treatment interruption, leads to higher complication rates, and may ultimately contribute to mortality [1]. Among nutritional support strategies, enteral nutrition is considered the first-line approach due to its ability to provide adequate nutritional intake, maintain intestinal mucosal integrity, and reduce complication rates compared with other methods [2,3].

However, in cancer patients, enteral feeding is often challenging due to tumor-related obstruction of the gastrointestinal tract, resulting in dysphagia in patients with head and neck cancers, esophageal cancer, and others. In addition, treatment-related toxicities such as radiotherapy-induced mucositis and mucosal burns, particularly in head and neck cancer patients, further impair swallowing function, despite preserved gastrointestinal absorptive capacity. In such cases, nasogastric tube placement or percutaneous endoscopic gastrostomy (PEG) is indicated to ensure adequate nutritional support.

Percutaneous endoscopic gastrostomy (PEG), first introduced in 1980, has become a widely used technique for long-term enteral nutritional support. Compared with nasogastric tube feeding, PEG is better tolerated, more suitable for prolonged use, associated with improved nutritional delivery, and generally has fewer complications [4].

Although numerous studies have evaluated PEG outcomes worldwide and in Vietnam, the impact of PEG on nutritional improvement in cancer patients remains insufficiently explored. Therefore, this study was conducted at Da Nang Oncology Hospital with the aim of:

- Describing the clinical characteristics of cancer patients undergoing PEG placement.

- Evaluating the improvement in nutritional status following PEG in cancer patients.

2. MATERIALS AND METHODS

2.1. Study population

The study population included cancer patients who underwent percutaneous endoscopic gastrostomy (PEG) at Da Nang Oncology Hospital from January 2024 to December 2024.

2.2. Inclusion criteria

Diagnosed with malignancy in clinical departments of the hospital.

Underwent percutaneous endoscopic gastrostomy (PEG).

Had complete follow-up data for at least 3 months after PEG placement.

2.3. Exclusion criteria

Complete esophageal obstruction preventing endoscopic access to the stomach, Gastrointestinal conditions causing gastric outlet obstruction.

Incomplete or missing medical records relevant to the study variables.

2.4. Study design and methods

Study design: A prospective longitudinal study was conducted.

Sample size and sampling method

A convenience sampling method was used. A total of 62 patients who met the inclusion criteria were enrolled during the study period.

Study materials

Medical records.

A medical weighing scale with an integrated height-measuring device.

The Subjective Global Assessment (SGA) tool for nutritional assessment.

Study procedures

Before percutaneous endoscopic gastrostomy (PEG) placement: clinical examination, laboratory and paraclinical investigations, measurement of body weight and height, BMI calculation, and nutritional status assessment using SGA.

Patients underwent percutaneous endoscopic gastrostomy in the endoscopy room; after the procedure, they were transferred back to the ward and received nutritional counseling within 24 hours.

After 1 month, body weight, BMI, and nutritional status according to SGA were reassessed.

After 3 months, body weight, BMI, and nutritional status according to SGA were reassessed; hemoglobin concentration and serum albumin level were recorded.

3. RESULTS

General characteristics of study participants.

Table 1. General characteristics

Characteristics		n (62)	Percentage %
Age range	< 40 years old	3	4,8
	40 – 59 years old	33	53,2
	≥ 60 years old	26	42,0
	Mean	57,7 ± 10,7 years old	
Gender	Male	50	80,6
	Female	12	19,4
Primary diagnosis	Head and neck cancer	49	79,0
	Esophageal cancer	11	17,8
	Other diagnoses	2	3,2
Stage	Stage I – II	6	9,7
	Stage III -IV	56	90,3
Treatment modalities	Chemotherapy	3	4,8
	Chemoradiotherapy	50	80,6
	Radiotherapy	7	11,3
	Palliative care	2	3,2

Comment: The mean age of the study population was 57.7±10.7 years, indicating a predominance of middle-aged and elderly patients. The male-to-female ratio was 4:1. Head and neck cancers accounted for 79% of cases, while esophageal cancer accounted for 17.8%. The majority of patients were diagnosed at an advanced stage (90.3%). Regarding treatment modalities, 80.6% of patients received concurrent chemoradiotherapy, while 11.3% underwent radiotherapy alone.

Improvement in nutritional status.

Table 2. Nutritional status before PEG placement

Characteristics		n (62)	Percentage %
Nutritional status according to BMI	Mean	19,1 ± 2,3 kg/m²	
	≥ 18,5kg/m²	38	61.3
	< 18,5kg/m²	24	38.7
Nutritional status according to SGA classification	SGA A	19	30.6
	SGA B	24	38.8
	SGA C	19	30.6
Hemoglobin (Hb) level	Normal	42	67.7
	Anemia	20	32.3
Serum albumin level	Normal	48	77.4
	Reduced	14	22.6

Comment: The mean BMI before PEG placement was 19.1 ± 2.3 kg/m², which was within the normal range. Malnutrition defined by BMI accounted for 38.7% of patients, while malnutrition assessed by SGA was higher at 69.4%. Additionally, 32.3% of patients had anemia, and 22.6% had hypoalbuminemia prior to PEG placement.

Table 3. Improvement in nutritional status according to body weight and BMI

Variables	Before PEG(0)	After 1 month(1)	After 3 months(2)	p(1-0)	p(2-0)
Weight	49,5 ± 7,7	49,7 ± 7,3	50,8 ± 7,2	0,488	< 0,001
BMI	19,1 ± 2,3	19,2 ± 2,2	19,6 ± 2,1	0,461	< 0,001

Comment: After 1 month of PEG placement, there was no significant change in body weight or BMI. However, after 3 months, both body weight and BMI showed a statistically significant increase in the study population.

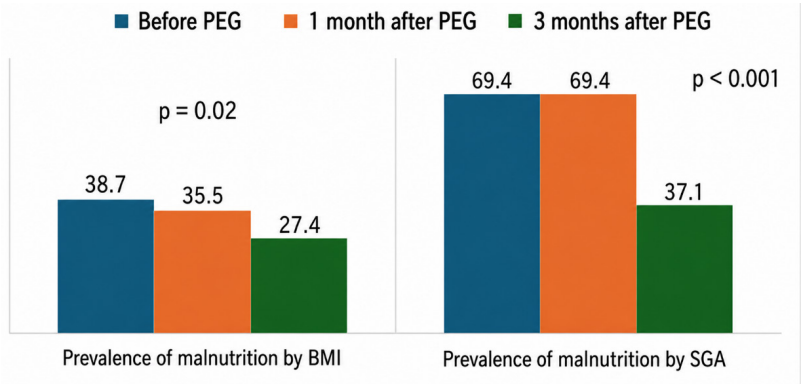

Chart 1. Changes in nutritional status based on BMI and SGA before and after PEG placement

Comment: At 1 month after PEG placement, there were no significant changes in the prevalence of malnutrition assessed by BMI and SGA. However, at 3 months post-PEG, the prevalence of malnutrition decreased significantly according to both BMI and SGA classifications, with a statistically significant difference ($p < 0.05$).

Table 4. Improvement in nutritional status according to SGA

SGA classification	Before PEG(0)	After 1 month(1)	After 3 months(2)	p(1-0)	p(2-0)
SGA A (n, %)	19 (30,6%)	19 (30,6%)	39 (62,9%)	0,002	< 0,001
SGA B (n, %)	24 (38,8%)	40 (64,5%)	21 (33,9%)		
SGA C (n, %)	19 (30,6%)	3 (4,8%)	2 (3,2%)		

Comment: At 1 month after PEG placement, there was no significant change in the overall prevalence of malnutrition according to SGA; however, there was a shift in distribution, with an increase in mild malnutrition (SGA B) and a decrease in moderate and severe malnutrition (SGA B and C). At 3 months after PEG placement, there was a marked improvement in nutritional status, with the proportion of well-nourished patients (SGA A) increasing from 30.6% to 62.9%.

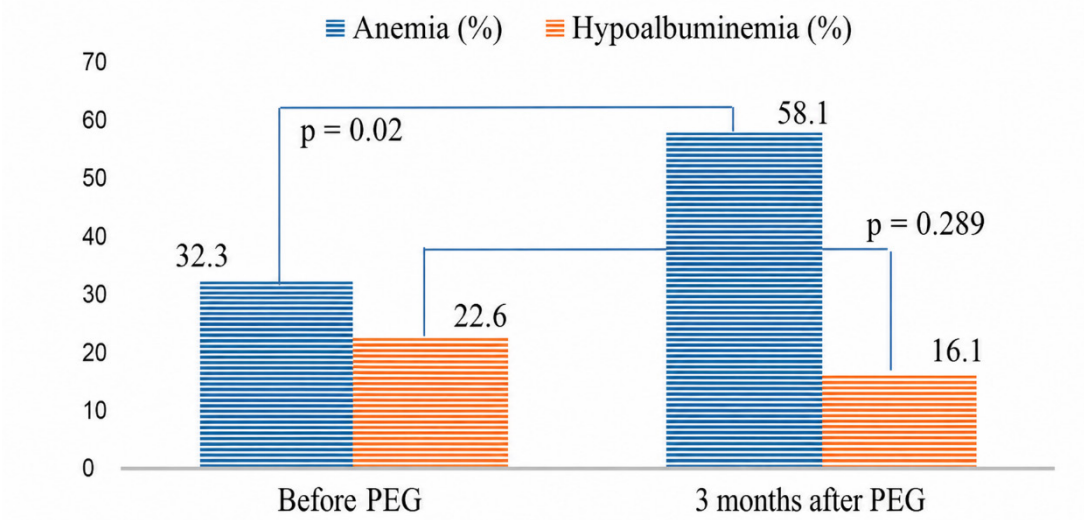

Chart 2. Changes in anemia and hypoalbuminemia before and 3 months after PEG

Comment: At 3 months after PEG placement, the prevalence of anemia showed a statistically significant increasing trend. In contrast, the proportion of patients with hypoalbuminemia decreased compared with the pre-PEG period; however, this difference was not statistically significant.

4. DISCUSSION

4.1. Characteristics of the study population

This study included 62 cancer patients who underwent PEG placement for enteral nutrition. The mean age was 57.7 ± 10.7 years, with 95.2% of patients aged over 40 years. The male-to-female

ratio was 4:1. Head and neck cancers and esophageal cancers accounted for 96.8% of PEG indications, and the majority of patients were diagnosed at advanced stages (stage III–IV), accounting for 90.3%. These findings are consistent with those reported by Diep BT et al., who found that head and neck and esophageal cancers accounted for 96.7% of PEG indications [5], and by Rabie AS et al., who reported a rate of 95% [6]. This highlights that PEG is primarily indicated in head and neck and esophageal cancer patients, as these malignancies often cause upper gastrointestinal obstruction or treatment-related swallowing impairment, leading to reduced oral intake, weight loss, and malnutrition. These results also suggest that head and neck and esophageal cancers are more common in middle-aged and older males, which may be associated with lifestyle, dietary habits, and behavioral risk factors.

Regarding treatment modalities, most patients in this study received chemoradiotherapy, a combined modality treatment involving chemotherapy and radiotherapy. This regimen is often prolonged and associated with treatment-related toxicities, particularly radiation-induced mucositis and swallowing dysfunction, which further contribute to impaired oral intake.

4.2. Improvement in nutritional status

The present study showed that the prevalence of malnutrition before PEG placement was 38.7% according to BMI and 69.4% according to SGA. These findings are consistent with previous studies, such as Nguyen TL, which reported a malnutrition rate of 78.6% [7], and Fernanda Silva R.M., who reported a rate of 71.1% [8]. These results confirm that malnutrition remains highly prevalent among cancer patients. At baseline, 35.5% of patients had anemia and 25.8% had hypoalbuminemia.

Regarding changes in nutritional status after PEG placement, at 1 month, there was a slight increase in mean body weight (0.2 kg) and BMI (0.1 kg/m²), although these changes were not statistically significant ($p > 0.05$). This is consistent with the clinical objective during active radiotherapy, which is to maintain body weight and prevent weight loss that may negatively affect treatment tolerance. At 3 months, after completion of cancer treatment in most patients, body weight increased by 1.3 kg and BMI increased by 0.5 kg/m² compared with baseline, with statistically significant differences ($p < 0.001$). These findings indicate that PEG feeding effectively maintained nutritional status during treatment and contributed to nutritional recovery in the post-treatment phase.

In terms of malnutrition according to BMI, the prevalence decreased by 3.2% at 1 month and by 11.3% at 3 months, with statistically significant differences over time. Similarly, SGA-based assessment showed no significant change at 1 month; however, at 3 months, the prevalence of malnutrition decreased from 69.4% to 37.1%. Although the overall prevalence of malnutrition did not change at 1 month, the proportion of severe malnutrition decreased markedly from 30% to 4.8%, while mild to moderate malnutrition increased from 38.8% to 64.5%, and this shift was statistically significant ($p < 0.05$). These findings suggest that PEG is an effective intervention in improving nutritional status among cancer patients. The observed improvements in weight, BMI, and SGA further support the role of PEG in preventing long-term malnutrition and supporting cancer treatment.

Regarding anemia and albumin levels, a statistically significant increase in anemia was observed at 3 months ($p < 0.05$). This may be explained by multiple mechanisms, including cancer-related chronic inflammation, treatment-induced bone marrow suppression, and tumor-related blood loss. Although PEG improves oral intake and protein-energy absorption, it

does not immediately correct micronutrient deficiencies or anemia caused by tumor burden and treatment effects. Serum albumin showed a slight improvement; This parameter serves as a prognostic indicator and reflects the degree of systemic inflammation ($p > 0.05$).

5. CONCLUSION

PEG feeding helped maintain nutritional status during the first month of treatment and contributed to significant nutritional improvement after 3 months.

These findings suggest that although macronutritional status, as assessed by BMI and SGA, improved after PEG placement, micronutrient deficiencies and anemia should be concurrently managed alongside caloric supplementation via PEG.

6. RECOMMENDATION

Early prophylactic PEG placement should be considered in cancer patients with swallowing difficulties who require long-term enteral nutrition support.

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CHANGES IN NUTRITIONAL STATUS OF PEDIATRIC PATIENTS WITH OSTEOSARCOMA TREATED WITH THE MAP REGIMEN IN 2022-2024 AND ASSOCIATED FACTORS

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ABSTRACT

Objectives: To evaluate changes in nutritional status among pediatric osteosarcoma patients treated with the MAP regimen at K Hospital between 2022 and 2024, and to explore potential associations.

Methods: A retrospective descriptive study was conducted on 50 medical records of pediatric patients with osteosarcoma who received MAP regimen and were discharged between 2022 and 2024.

Results: At treatment initiation, 34% of patients had malnutrition by BMI (14% underweight and 20% overweight/obese), and 4% were stunted. During treatment, body weight decreased and showed a slow recovery after the 4th cycle. The prevalence of anemia increased progressively, reaching 90% by 6th cycle. The malnourished group had a significantly longer mean hospital stay than the overweight/obese group (117.5 vs. 76 days, $p < 0.05$). The rate of good response to neoadjuvant chemotherapy was 70%. Patients with normal BMI and those who were overweight had higher response rates than the malnourished group, although the difference was not statistically significant ($p > 0.05$).

Conclusions: Pediatric osteosarcoma patients treated with the MAP regimen are at risk of malnutrition (including weight loss, anemia, and leukopenia) during treatment. Appropriate nutritional care strategies are needed to improve nutritional status, quality of life, and treatment outcomes.

Keywords: Osteosarcoma; nutrition; MAP regimen.

I. INTRODUCTION

Osteosarcoma is a rare primary malignant bone tumor arising from mesenchymal osteogenic cells [1]. The disease most commonly affects children and young adults. Osteosarcoma accounts for approximately 56% of all bone cancers in individuals under 20 years old. In Vietnam, it represents about 5% of all pediatric malignancies.

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The MAP chemotherapy regimen, consisting of high-dose methotrexate combined with cisplatin and doxorubicin, is currently used in osteosarcoma treatment at the National Cancer Hospital (K Hospital) and is considered the standard regimen in Europe and the United States.

Patients treated with the MAP regimen may experience multiple chemotherapy-related adverse effects that significantly affect nutritional intake. Doxorubicin may cause nausea, vomiting, abdominal pain, and diarrhea. Cisplatin induces nausea and vomiting in up to 95% of cases within 1-4 hours after administration, and is also associated with gastrointestinal disturbances and anorexia. High-dose methotrexate can cause oral mucositis, nausea, vomiting, diarrhea, and loss of appetite. Therefore, the nutritional status of osteosarcoma patients tends to deteriorate during treatment.

A retrospective study by Karen Ringwald-Smith et al. in 48 pediatric osteosarcoma patients showed that the prevalence of underweight at diagnosis was 8%, overweight 15%, and obesity 8%. After treatment, the proportion of underweight patients increased to 17%, while overweight decreased to 8% and obesity to 2% [2].

Nutritional status significantly influences treatment outcomes. Osteosarcoma patients receiving MAP chemotherapy typically undergo surgery at week 12. Malnutrition is associated with delayed wound healing due to prolonged inflammation, reduced fibroblast proliferation, decreased collagen synthesis, and impaired angiogenesis. Several studies have also shown that poor nutritional status is associated with higher rates of surgical site infection and delayed wound healing [3]. In addition, malnutrition and muscle wasting negatively affect postoperative functional recovery, reducing muscle strength, limiting mobility, and increasing the risk of joint stiffness.

In Vietnam, particularly at the National Cancer Hospital, studies on nutritional status in osteosarcoma patients, as well as factors influencing it and its relationship with treatment and surgical outcomes, remain limited. Therefore, this study was conducted to evaluate changes in nutritional status among pediatric osteosarcoma patients treated with the MAP regimen from 2022 to 2024 and to analyze associated factors.

2. SUBJECTS AND METHODS

2.1. Study population

The study included medical records of pediatric patients with osteosarcoma treated at the Pediatric Department, National Cancer Hospital (K Hospital), Vietnam. Patients received the MAP chemotherapy regimen (methotrexate, doxorubicin, and cisplatin) as neoadjuvant treatment, followed by surgery, and continued with at least ≥4 cycles of adjuvant chemotherapy after surgery. All patients were discharged between 01 January 2022 and 31 December 2024.

Inclusion criteria:

- Age from 5 to under 18 years.

- Histopathological diagnosis of osteosarcoma.

- Tumor located in long bones.

Exclusion criteria:

- Incomplete medical records with missing key study data.

- Patients who discontinued treatment for any reasons.

- Patients with other concomitant malignancies or prior chemotherapy treatment.

- Presence of significant comorbid diseases.

- Patients with congenital malnutrition and/or growth retardation.

2.2. Study design and methods

- Study design: Retrospective descriptive study.

- Sample size: All eligible cases during the study period were included due to the rarity of the disease.

- Sampling method: Convenience sampling.

In total, 50 eligible medical records meeting the collected criteria were included in the analysis.

* Study setting and duration.

- Study period: March 2025 to December 2025.

- Study site: Pediatric Oncology Department, K Hospital.

* Study variables and indicators

- General characteristics: age, sex, ethnicity, place of residence, tumor location, surgical site, surgical method, treatment duration, disease stage, response to neoadjuvant chemotherapy (Huvos grading system), and postoperative complications.

- Nutritional status assessment: Body weight (at the start of 1st, 2nd, 4th, 5th, and 6th chemotherapy Cycle), Height, BMI, Weight-for-age index, Height-for-age index, Percentage of weight loss, Nutrition-related laboratory parameters: Creatinin, AST, ALT, Hemoglobin, Lymphocyte count, Total white blood cell count, Neutrophil count (before beginning of 1st, 2nd, 4th, 5th and 6th chemotherapy Cycle).

* Standard assessment

- Nutritional status was classification by WHO Growth Reference Data for 5-19 years (2007).

- Classification of anemia was based on the WHO criteria for anemia by haemoglobin (2011).

- Tumor response to neoadjuvant chemotherapy was assessed histologically using the Huvos grading system, with a good response defined as ≥90% tumor necrosis and a poor response as <90%.

2.3. Data analysis

- After data collection, the data will be cleaned and entered into a computer using Epidata 3.1 software. Statistical analyses will be performed using STATA version 12.0. Descriptive and inferential statistical analyses will be conducted, with a significance level of $\alpha = 0.05$ used for inferential statistics.

- The Chi-square (χ^2) test or Fisher's exact test will be used to compare differences between categorical variables.

2.4. Ethical considerations

- This retrospective study was conducted after approval by the Ethics Committee of the National Cancer Hospital (K Hospital), under approval number 1400/BVK-HĐĐĐ dated April 28, 2025.

- All information collected from study subjects was used exclusively for research purposes, was kept strictly confidential, and was not used for any other purposes.

3. RESULTS

50 medical records were included in the analysis, with ages ranging from 6 to 18 years. The most frequently observed ages were 14 and 15 years. The mean age was 13.2 years.

Table 1. General characteristics of study subjects (n=50)

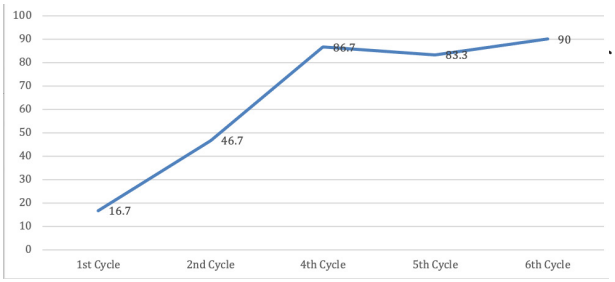
Characteristics		n	%
Gender	Male	31	62
	Female	19	38
Ethnicity	Kinh	47	94
	Others	3	6
Place of residence	Rural	29	58
	Urban/town/city	15	30
	Mountainous area	6	12
Tumor location	Humerus/forearm bones	6	12
	Femur/lower leg bones	44	88

Characteristics		n	%
Disease stage	Stage II	49	98
	Stage III	1	2
Surgical method	Limb-sparing surgery	43	86
	Amputation	7	14

Comment: Among the 50 patients included in the study, males accounted for the majority (62%), with a male-to-female ratio of 1.6:1. Most patients were of Kinh ethnicity (94%). A higher proportion of patients lived in rural areas (58%). The predominant tumor location was in the lower extremities, accounting for 88% of cases. Nearly all patients were diagnosed at stage II (98%). Limb-sparing surgery was performed in 86% of patients.

Table 2. Nutritional status of study subjects (n=50)

Indicators		n	%
Height-for-age	Stunted	2	4
	Normal	48	96
BMI-for-age	Underweight	7	14
	Normal	33	66
	Overweight/Obesity	10	20



Picture 1. Anemia status at the beginning of chemotherapy cycles (n=50)

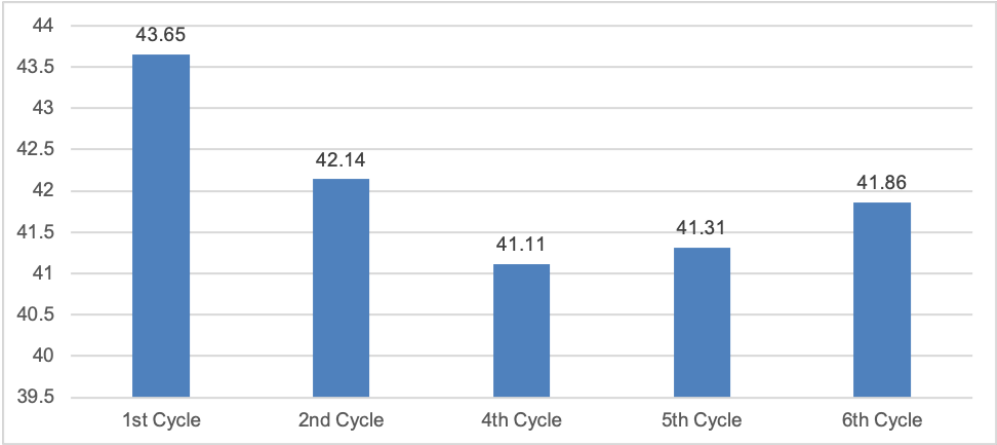
Comment: At treatment initiation, the prevalence of anemia among study patients was 16.7%. During the course of chemotherapy cycles, the rate of anemia increased progressively. The prevalence reached 86.7% at 4th Cycle and rose to 90% by 6th Cycle 6.

Table 3. Changes in white blood cell parameters during treatment

	1st Cycle	2nd Cycle	4th Cycle	5th Cycle	6th Cycle
Leukocytes (G/L)	9.3	7.0*	6.3*	5.4*	4.1*
Neutrophils (G/L)	5.6	4.6	3.9*	2.9*	2.1*
Lymphocytes (G/L)	2.8	2.0*	1.8*	1.8*	1.5*

*t-test, $p<0.05$

Comment: The total white blood cell count showed a progressive decline across chemotherapy cycles, with statistically significant differences between subsequent cycles compared to the previous ones and also compared to 1st Cycle , except for the comparison between 2nd Cycle and 4th Cycle, which was not statistically significant. Neutrophil counts also showed a gradual decrease over time. The differences were statistically significant between 4th, 5th, 6th Cycles compared with 1st Cycle, as well as between 5th Cycle and 4th Cycle, and between 6th Cycle and 5th Cycle. Lymphocyte counts demonstrated a decreasing trend as well; however, statistically significant differences were observed only between subsequent cycles and 1st Cycle.



Picture 2. Changes in body weight during chemotherapy cycles (n=27)

Comment: Among 27 patients with complete weight data across treatment cycles, body weight showed a decreasing trend up to 4th Cycle, from 43.65 kg at 1st Cycle to 41.11 kg at 4th Cycle . Subsequently, body weight showed a slight recovery, increasing to 41.86 kg at cycle 6.

Table 4. Hospital stay duration according to BMI classification (N=40)

BMI classification	Mean (days)	Standard deviation (SD)	Min - Max	Percentage (%)
Underweight	117.5*	49.1	57 - 205	15
Normal weight	91.5*	39.1	56 - 212	70
Overweight/Obesity	76*	9.5	62 - 89	15
Overall	93.1	38.9	56 - 212	100

* p> 0.05, Kruskal – Wallis test

Comment: The mean hospital length of stay among patients was 93.1 days. The undernourished group had the longest average hospitalization time (117.5 days), followed by the normal group (91.5 days), while the overweight/obesity group had the shortest duration (76 days). The difference between 3 groups was non-statistically significant.

Table 5. Hospital length of stay according to height-for-age classification (N=40)

Height-for-age classification	Mean (days)	Standard deviation (SD)	Min- Max	Percentage (%)
Stunted	67.5*	14.8	57 - 78	5
Normal	94.4*	39.4	56 - 212	95
Overall	93.1	38.9	56 - 212	100

*p>0.05, t-test

Comment: The mean hospital length of stay in the stunted group was 67.5 days, while it was 94.4 days in the normal group. However, the difference between the two groups was not statistically significant.

Table 6. Response rate (%) to neoadjuvant chemotherapy according to BMI classification (N=50)

Response to neoadjuvant chemotherapy	BMI			Total (%)
	Underweight (%)	Normal (%)	Overweight (%)	
Good	6	50	14	70
Poor	8	16	6	30
Overall	14	66	20	100

*Fisher exact test, p = 0.22

Comment: The normal BMI and overweight groups had a higher proportion of good response to neoadjuvant chemotherapy compared with poor response. In contrast, in the underwweight group, the proportion of poor response was higher than that of good response. However, these differences were not statistically significant.

4. DISCUSSION

4.1. General characteristics

At the end of the study, 50 eligible records were included in the analysis. Males accounted for the majority (62%), with a male-to-female ratio of 1.6:1. This proportion is similar to the overall epidemiology of osteosarcoma in patients under 24 years of age, where the reported male-to-female ratio is 1.43:1 [1].

Most patients were of Kinh ethnicity (94%). As a tertiary referral cancer center, K Hospital receives a large number of patients from across the country. The low proportion of ethnic minority patients in this study may be related to limited awareness of osteosarcoma among ethnic minority populations, geographical distance to major hospitals, and financial barriers to access healthcare. These factors may also negatively affect disease prognosis in osteosarcoma patients.

The tumor was predominantly located in the lower limbs (88%), which are the most common sites for osteosarcoma. All patients in this study were diagnosed at stage II or III, with nearly all cases (98%) being stage II. This is consistent with clinical practice, as patients are often diagnosed when presenting with pain and soft tissue swelling, indicating local invasion or medullary involvement.

After neoadjuvant MAP chemotherapy, patients typically underwent surgery at weeks 10-12. Surgical treatment included limb amputation or limb-sparing procedures. In this study, 86% of patients underwent limb-sparing surgery (tumor resection with endoprosthetic reconstruction). This rate is higher than that reported by Phan Đắc Phương et al. (80%) at the Pediatric Department during 2019-2022 [4]. This increase is a positive outcome, as limb-sparing surgery improves both functional outcomes and quality of life.

4.2. Nutritional status in pediatric osteosarcoma patients

Many studies have shown that malnutrition is a negative prognostic factor in pediatric cancer patients, with survival decreasing in proportion to the severity of malnutrition. Underweight children with cancer, especially those with metastatic disease, have lower survival rates. Malnutrition is also associated with reduced treatment tolerance, poorer response to chemotherapy, treatment delays, increased risk of infections, and decreased quality of life [5].

In our study, the prevalence of stunting assessed by height-for-age was 4%. Underweight status based on BMI-for-age was 14%, while overweight and obesity accounted for 20%. These results are consistent with the study by Karen Ringwald-Smith et al. in 48 children with osteosarcoma, which reported 8% underweight, 15% overweight,

and 8% obesity at diagnosis. After neoadjuvant chemotherapy, nutritional status tended to worsen, with underweight increasing to 11%, overweight decreasing to 9%, and obesity at 7%. By week 23, nutritional status further deteriorated (18% underweight, 0% overweight, and 2% obesity). However, by the end of treatment, a slight improvement was observed, with 17% underweight, 8% overweight, and 2% obesity [2].

In our study, mean body weight also decreased significantly across chemotherapy cycles, providing further evidence of nutritional decline during treatment. This deterioration may be explained by multiple factors, including tumor-related pain and metabolic effects leading to reduced food intake and increased energy expenditure, as well as chemotherapy-related side effects from the MAP regimen that impair appetite and digestion.

Nutritional deterioration during treatment is an adverse prognostic factor. Early weight loss at diagnosis is a risk factor for further malnutrition during treatment, and baseline malnutrition is associated with worse outcomes and increased mortality. Malnourished patients at the beginning of treatment have poorer survival. Malnutrition is also associated with a higher risk of infectious complications. Both low BMI at baseline and significant weight loss during treatment are strong predictors of bacterial and fungal infections and reduced survival [6]factors attributed to treatment, and specific individual risk factors in each patient. Patients with chemotherapy-induced neutropenia are at particularly high risk, and microbiological agents include viral, bacterial, and fungal agents. The etiology is often unknown in infectious complications, although adequate patient evaluation and sampling have diagnostic, prognostic and treatment-related consequences. Bacterial infections include a wide range of potential microbes, both Gram-negative and Gram-positive species, while fungal infections include both mold and yeast. A recurring problem is increasing resistance to antimicrobial agents, and in particular, this applies to extended-spectrum beta-lactamase resistance (ESBL. In particular, weight loss during the first 3 months of treatment is associated with a higher risk of sepsis [7].

4.3. Nutritional status and related factors

Nutritional deterioration during treatment may negatively affect drug tolerance, overall survival, infection risk, quality of life, and length of hospital stay. In osteosarcoma, there are still limited studies assessing the relationship between malnutrition and these outcomes.

Our study showed that the mean hospital length of stay in the malnourished group was longer than in the normal and overweight/obese groups. However, a statistically significant difference was observed only between the malnourished group and the overweight/obese group (117.5 days vs. 91.5 days). Malnourished patients were also at higher risk of chemotherapy toxicity, including hematologic toxicity and infection. The risk of leukopenia after treatment increased with the severity of malnutrition [8], leading to longer hospitalization and higher treatment costs.

In our study, height-for-age was used to classify nutritional status, and hospital length of stay was compared between the stunted and normal groups. Although the proportion of stunting was low (5%), the hospital stay in this group appeared shorter than in the normal group (67.5 days vs. 94.4 days). However, this difference was not statistically significant. This finding suggests a potential association that warrants further investigation, as few studies have evaluated the relationship between stunting and hospitalization duration in pediatric osteosarcoma.

The good response rate to neoadjuvant chemotherapy in pediatric osteosarcoma patients in our study was 70%. This result is consistent with the study by Yair Peled et al. and higher than that reported by Phan Đắc Phương (51.3% in 2019–2022) [4], [9]. This may reflect improvements in osteosarcoma treatment in recent years (2022–2024) and closer alignment with international outcomes.

This study has several limitations. First, its retrospective design relies on data extracted from medical records documented by different physicians, which may introduce variability in measurement techniques and a lack of standardized calibration of instruments. Such heterogeneity could affect the accuracy and consistency of the collected data. Second, the relatively small sample size (n = 50) limits the statistical power of the analyses, and therefore the findings should be interpreted with caution, as they may not be sufficient to draw definitive conclusions. In addition, more than 50 records were excluded from the analysis due to missing data and not meeting the inclusion criteria. This also represents a limitation of the study, as it may limit the ability to provide a comprehensive assessment of the study population.

5. CONCLUSION

This study showed that at treatment initiation, 34% of children were malnourished and 4% were stunted. During chemotherapy, patients experienced progressive weight loss and a marked increase in anemia up to 90% by 6th Cycle, followed by gradual weight recovery after the 4th Cycle. The overall good response rate to neoadjuvant chemotherapy was 70%. These findings demonstrate that children with osteosarcoma receiving the MAP regimen are at high risk of nutritional deterioration and need for early and appropriate nutritional support. Some potential association factor may be hospital length stay, response to neoadjuvant chemotherapy need to assess in future study.

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FIRST-LINE GEMCITABINE-CISPLATIN FOR ADVANCED, RECURRENT, OR METASTATIC BILIARY TRACT CANCER: TREATMENT OUTCOMES AT HANOI ONCOLOGY HOSPITAL

Nguyen Thi Mai Lan*, Trinh Thu Ha, Nguyen Quoc Hung, Truong Thu Hien

ABSTRACT

Objective: To evaluate the efficacy and adverse effects of the Gemcitabine–Cisplatin regimen in patients with advanced, recurrent or metastatic biliary tract cancer at Hanoi Oncology Hospital.

Subjects and methods: A retrospective and prospective research on patients with advanced, recurrent or metastatic biliary tract cancer (including intrahepatic, extrahepatic, and gallbladder cancer) with ECOG PS 0–1, treated with at least 3 cycles of the Gemcitabine-Cisplatin regimen. The efficacy was evaluated according to RECIST 1.1 and toxicity according to CTCAE version 5.0. Survival analysis using Kaplan–Meier and Log-rank verification.

Results: Sixty-five patients were enrolled with a mean age of 56.8 ± 10.1; men accounted for 66.2%. The most common tumor site is the intrahepatic biliary tract (66.2%). The majority of patients were in the recurrent or metastasis stage (64.6%). After 3 cycles, the disease control rate reached 83.1% with an objective response rate of 29.2%. After 6 cycles, the complete response rate was 2.6%, partial response accounted for 15.8%, stable disease for 57.9% and progressed disease for 23.7%. The disease control rate reached 76.3%. The median progression-free survival was 8.1 months (95% CI: 5.4–10.7), and the median overall survival was 13.1 months (95% CI: 8.2–18.0). Performance status (ECOG, PS) and response after 3 cycles were statistically significant prognostic factors for both progression-free survival and overall survival. Common grade 3–4 adverse effects were neutropenia (38.5%), elevated liver enzymes (15.4%), and anemia (10.8%).

Conclusion: Gemcitabine - Cisplatin is an effective and acceptable safety regimen. Response and performance status after 3 cycles (ECOG PS) are important prognostic factors, which are valuable to

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guide treatment decisions. This regimen could be the first-line chemotherapy option in patients with advanced biliary tract cancer.

Keywords: biliary tract cancer; Gemcitabine; Cisplatin; chemotherapy; survival; toxicity.

1. INTRODUCTION AND STUDY OBJECTIVESS

Biliary tract cancer is a rare malignancy with a poor prognosis, often diagnosed at a late stage when the tumor has advanced or metastasized, making the possibility of radical surgery very limited. The overall 5-year survival rate for patients with advanced biliary tract cancer ranges from only 5–10%, reflecting a large burden on public health [1]. Over the past decade, many chemotherapy regimens have been studied to improve treatment outcomes for patients with advanced biliary tract cancer. The results of the ABC-02 study showed that the median overall survival (OS) time reached 11.7 months, which is higher than that of Gemcitabine alone [1]. Thus, Gemcitabine - Cisplatin is the standard treatment for advanced biliary tract cancer. Subsequent studies included TOPAZ-1 (Oh et al., 2022) and MITSUBA (Ioka et al., 2022), which continued to confirm the fundamental role of gemcitabine - cisplatin, trials with new drugs such as immunotherapy or S-1 to improve efficacy [2,4]. The Gemcitabine - Cisplatin regimen has been used in the treatment of advanced, recurrent, and metastatic biliary tract cancer at Hanoi Oncology Hospital. However, so far there have been no studies evaluating the effectiveness of this regimen. Therefore, we conducted this study with the following objectives:

- To evaluate treatment outcomes and some related factors of Gemcitabine-Cisplatin regimen on patients with advanced, recurrent, metastatic biliary tract cancer.

- To identify adverse effects of this regimen on the studied patients.

2. OBJECTS AND METHODS

2.1. Study design

The descriptive observational study combining retrospective (from January 2019 to April 2024) and prospective data (from May 2024 to September 2025).

2.2. Location and time of the study

The study was conducted at Hanoi Oncology Hospital, the time of data collection is from March 2024 to September 2025.

2.3. Sample size and sampling method

Sample size calculation formula:

$$n = z^2_{1-\alpha/2}\frac{p(1-p)}{(p\varepsilon)^2}$$

n is the minimum number of patients

p = 0.5 is the one-year survival rate of patients with biliary tract cancer. The advanced stage treated with gemcitabine-cisplatin regimens in the ABC-02 study (2010) was 39% [1].

α is the selected statistical significance level = 0.05.

z1−α/2 is the 95% confidence limiting factor, table trap = 1.96.

ε is the relative precision chosen between 0.1 - 0.4. In this study, because patients with biliary tract cancer are rare, ε = 0.117 was chosen.

Based on this formula, the calculated and actual sample size of our study was 65 patients.

Sampling method: non-random, intentional

sampling for patients with advanced biliary tract cancer with gemcitabine-cisplatin regimen that satisfied the inclusion criteria and did not violate the exclusion criteria.

2.4. Study Objects

Inclusion Criteria

- The patient was diagnosed with biliary tract cancer (including intrahepatic, extrahepatic and gallbladder biliary tract cancer) by histopathology.

- The disease was in an advanced, recurrent, or metastatic stage.

- ECOG PS 0–1.

- Treated with at least 3 cycles of the Gemcitabine–Cisplatin regimen.

- Having complete medical record and follow-up data.

Exclusion Criteria

- There are other concomitant primary cancers.

- ECOG PS > 1 or ineligibility to continue chemotherapy.

2.5. Treatment Regimen

Patients were treated with the standard Gemcitabine-Cisplatin regimen: Gemcitabine 1000 mg/m² intravenously on days 1 and 8, Cisplatin 25 mg/m² intravenously on days 1 and 8, a cycle lasted 21 days.

2.6. Efficacy and Toxicity Evaluation

- Treatment efficacy was assessed according to RECIST 1.1 by imaging tests every 2–3 cycles of chemotherapy.

- Toxicity was evaluated according to the CTCAE version 5.0.

- Progression-free survival (PFS) and overall survival (OS) were calculated from the time of initiation of chemotherapy to disease progression, death, or end of follow-up.

2.7. Data analysis

The data was processed using SPSS 20.0. Qualitative variables were represented by frequency and percentage. Survival time was analyzed using the Kaplan–Meier method and compared by Log-rank testing. The statistical significance level was determined when $p < 0.05$.

3. RESULTS

3.1. Characteristics of patients

Table 1: Characteristics of patients

Characteristic	Categories	Frequency (n=65)	Percentage
Age	Average Age (Min - Max)	56.8 ± 10.1 (22-76) years old	
Gender	Male	43	66.2
	Female	22	33.8
ECOG PS	ECOG PS 0	30	46.2
	ECOG PS 1	35	53.8
Tumor location	Intrahepatic	43	66.2
	Extrahepatic	22	33.8

Characteristic	Categories	Frequency (n=65)	Percentage
Stage	Spread in situ	12	18.5
	Progression after PT + adjuvant treatment	11	16.9
	Recurrence, metastasis	42	64.6
Biliary drainage before treatment	No	56	86.1
	Yes	9	13.9
CA19-9 before treatment	CA199 ≤ 35 U/ml	28	43.1
	CA199 > 35 U/ml	37	56.9
	Median CA199 (Min - Max)	64.5 (0.6-10500)	
Number of treatment cycles	3 cycles	16	24.6
	4 cycles	2	3.1
	5 cycles	8	12.3
	6 cycles	20	30.8
	> 6 cycles (6-14)	19	29.2
Chemo Dose	< 85%	9	13.8
	85-100%	56	86.2
Treatment Delay	No	40	61.5
	Yes	25	38.5

The Table 1 above showed that the study included 65 patients with an average age of 56.8 ± 10.1 (22–76 years), with males predominantly (66.2%). The majority of patients had ECOG PS 1 (53.8%). In terms of tumor location, intrahepatic biliary tract cancer accounted for 66.2%, extrahepatic biliary tract cancer accounted for 33.8%. The majority of patients were in the stage of recurrence and metastasis (64.6%), followed by local advanced (18.5%) and postoperative progression with adjuvant treatment (16.9%). Most patients did not need biliary drainage prior to treatment (86.1%). The median CA19-9 concentration was 64.5 UI/ml, with 56.9% of patients having CA19-9 > 35 UI/ml. In terms of treatment, the majority of patients received a full dose of chemotherapy (≥ 85%) and completed at least 6 cycles (60%), of which 61.5% did not delay treatment.

3.2. Treatment Effectiveness

3.2.1. Response Assessment

Table 2: Objective response rate (ORR)

Characteristics of response		After 3 cycles	After 6 cycles
		Number patient (%)	Number patient (%)
Controlled Disease	Complete response	2 (3.1)	1 (2.6)
	Partial response	17 (26.1)	6 (15.8)
	Stable disease	35 (53.8)	22 (57.9)
	Total	54 (83.0)	29 (76.3)
Uncontrolled Disease	Progressed disease	11 (17.0)	9 (23.7)
Total		65 (100)	38 (100)

Table 2 showed that after 3 cycles of treatment, the disease control rate reached 83.0%, in which 3.1% was complete response, 26.1% was partial response and 53.8% was stable disease; Meanwhile, 17% patients had disease progression. Among the 38 patients evaluated after 6 cycles, the disease control rate remained at 76.3%, with 2.6% patients achieved complete response, 15.8% had partial response, and 57.9% had stable disease while the rate of disease progression was 23.7%.

3.2.2. Progression free survival and overall survival

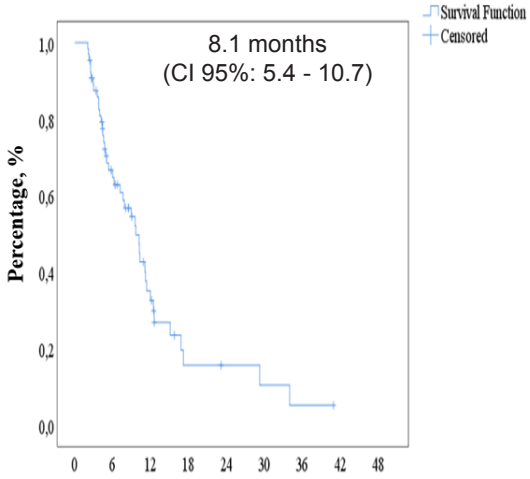

Figure 1: Kaplan–Meier curve for progression-free survival

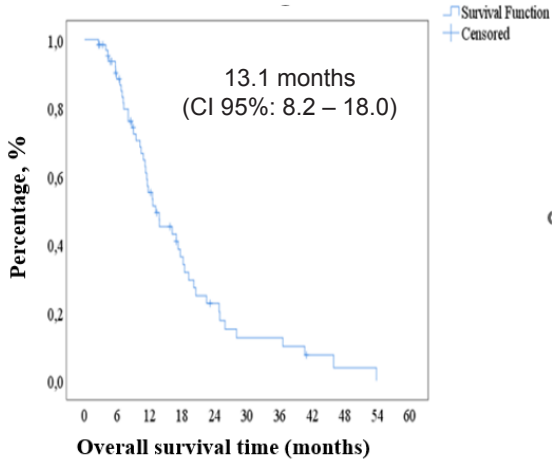

Figure 2: Kaplan–Meier curve for overall survival

The above Figure 1 illustrated the median PFS of 8.1 months (95% CI: 5.4 - 10.7). The 6-month progression-free survival rate was 61.0%, the 12-month rate decreased to 26.0%, and the 24-month rate was only 10.1%.

The Figure 2 illustrated the overall survival (OS) median of 13.1 months (95% CI: 8.2 –

18.0). The 6-month overall survival rate was 88.5%, the 12-month rate was 55.2% and %, and the 24-month rate decreased to 22.7%.

3.3. Survival and Related Factors

Table 4. Analysis relationship of survival time and factors

Factor	Frequency	Median PFS (month) (95% CI)	p (PFS)	Median OS (months) (95% CI)	p (OS)
Performance status (PS)					
PS 0	30	10.8 (4.5 - 17.1)	0.032	17.2 (9.0 - 25.4)	0.041
PS 1	35	7.9 (4.4 - 11.4)		11.6 (9.2 - 14.0)	
Biliary obstruction					
No	56	9.0 (5.5 - 12.5)	0.208	13.1 (6.8 - 19.4)	0.693
Yes	9	7.9 (0.6 - 15.2)		13.8 (10.1 - 17.5)	
Tumour location					
Intrahepatic	43	9.0 (6.3 - 11.7)	0.084	12.5 (6.2 - 18.8)	0.3
Extrahepatic	22	5.0 (2.8 - 7.2)		13.7 (11.5 - 15.9)	
Pretreatment CA19-9					
≤ 35 UI/ml	28	7.9 (5.2 - 10.6)	0.507	12.5 (4.5 - 20.5)	0.748
> 35 UI/ml	37	9.0 (6.1 - 11.9)		13.8 (11.1 - 16.5)	
Response after 3 cycles					
Response (CR+PR)	19	12.6 (11.8 - 13.4)	< 0.001	18.2 (15.5 - 20.9)	0.016
Non-response (SD+PD)	46	5.4 (3.8 - 7.0)		11.2 (9.8 - 12.6)	
Response after 6 cycles					
Response (CR+PR)	7	15.1 (9.0 - 21.2)	0.097	16.9 (0.0 - 40.8)	0.05
Non-response (SD+PD)	31	10.2 (8.6 - 11.8)		13.1 (7.8 - 18.4)	

Among the factors analyzed, ECOG PS was a statistically significant independent prognostic factor for both OS and PFS. ECOG PS 0 had a markedly longer median PFS and OS than ECOG PS 1 (10.8 vs. 7.9 months, p = 0.032; and 17.2 vs. 11.6 months, p = 0.041).

Biliary obstruction, tumor location, and pretreatment CA19-9 levels had no statistically significant association with PFS and OS (p > 0.05).

Response after 3 cycles was the most valuable prognostic factor: the responsive group (CR + PR) had a markedly superior median PFS and OS compared to the non-responsive group (12.6 versus 5.4 months, p < 0.001; and 18.2 versus 11.2 months, p = 0.016). Response after 6 cycles showed a similar, statistically significant trend for OS (p = 0.05).

3.4. Adverse effects

Table 5. Adverse effects

Adverse Effect	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Total (%)
Hepatitis	28 (43.1)	6 (9.2)	8 (12.3)	2 (3.1)	44 (67.7)
Kidney Injury	15 (23.1)	0 (0)	0 (0)	0 (0)	15 (23.1)
Anemia	36 (55.4)	10 (15.4)	7 (10.8)		53 (81.5)
Leukopenia	20 (30.8)	16 (24.6)	6 (9.2)		42 (64.6)
Neutropenia	7 (10.8)	12 (18.5)	25 (38.5)		44 (67.7)
Thrombocytopenia	22 (33.8)	11 (16.9)	8 (12.3)		41 (63.1)

Adverse effect is most common on anemia (81.5%) and neutropenia (67.7%), of which grade 3 neutropenia account for the highest proportion (38.5%). Hepatitis AE occurred in 67.7% of patients with 15.4% in grades 3-4. Neutropenia and thrombocytopenia were mainly in grades 1-2, 64.6% and 63.1%, respectively. Kidney injury was the lowest (23.1%), all at grade 1.

4. DISCUSSION

4.1. Characteristics of patients

Our study recorded the average age of populations as 56.8 ± 10.1 years, with males predominantly (66.2%). This result is similar to studies in the world, in which biliary tract cancer is common in middle to elderly age and tends to be more common in male [1,2]. The proportion of ECOG PS 1 patients accounts for 53.8%, reflecting the clinical reality in Vietnam, where the majority of patients came to the hospital at the stage when the disease has affected their physical condition. Notably, 64.6% of patients in our study were in the stage of recurrent or metastasis-a higher rate compared to another national study [5]-which partly reflects the reality of late diagnosis and limited access to curative treatment. Intrahepatic biliary tract cancer accounted for 66.2%, which is similar to the epidemiological trend of recording an increase in this disease in Asia [1]. The majority of patients did not need biliary drainage prior to treatment (86.1%), suggesting that the level of bile obstruction in the study population was not too severe, which is favorable for systemic treatment.

4.2. Treatment outcomes

Objective response rate and disease control

The disease control rate after 3 cycles in our study reached 83.1%, of which the objective response rate (ORR = CR + PR) was 29.2%. These results are similar to studies around the world, studying ABC-02 with an ORR of 26.1% [1] and TOPAZ-1 with an ORR of 26.7% [3]. Compared to the domestic study by Ninh Thi Thao (2021), the ORR in our study was lower, this difference can be explained by the significantly higher proportion of patients in the recurrent and metastatic stages in our study (64.6%), resulting in a study population with a poorer prognosis [5]. After 6 cycles, the disease control rate remained at 76.3% on 38 patients, indicating that the Gemcitabine-Cisplatin regimen has the ability to control the disease sustainably during treatment.

4.3. Progression-free survival

The median PFS in our study reached 8.1 months (95% CI: 5.4–10.7), which is equivalent to the results of the ABC-02 trial (8.0 months)

[1] and the study by Ioka et al. (2022) [4]. The 6-month progression-free survival rate reached 61.0%, decreasing to 26.0% after 12 months, reflecting the natural progression of this disease. Analysis of prognostic factors showed that ECOG PS 0 and response after 3 cycles were two statistically significant factors influencing PFS ($p = 0.032$ and $p < 0.001$). Meanwhile, bile obstruction, tumor location, and CA19-9 level did not significantly associate with PFS in this study, which is similar to some studies around the world [2,4].

4.4. Overall survival

The median OS was 13.1 months (95% CI: 8.2–18.0), which is higher than that of the majority of world studies on the Gemcitabine-Cisplatin regimen, ranging from 11.7 to 14.2 months [1, 3], although the percentage of patients with distant metastases in our study was quite high (64.6%). The 12-month overall survival rate reached 55.2%, decreasing to 22.7% after 24 months. Similar to PFS, ECOG PS 0 and response after 3 cycles continued to be statistically significant OS prognostic factors ($p = 0.041$ and $p = 0.016$), while response after 6 cycles tended to improve OS but did not reach a clear statistically significant threshold ($p = 0.05$). It may be because the sample size at this assessment time was limited. These results reinforce the role of early response as an important prognostic marker and underscore the clinical significance of assessing response after 3 cycles in the guidelines for subsequent treatment decisions.

4.5. Adverse Effects

The Gemcitabine-Cisplatin regimen in our study had a notable rate of hematotoxicity, with grade 3 neutropenia being the most common severe adverse effects (38.5%), which was higher than reported from ABC-02 and TOPAZ-1 [1,3]. Anemia occurred in 81.5% of patients but was predominantly at grades 1–2 (70.8%), without compromising regimen adherence. Hepatotoxicity which was elevated transaminase accounted for 15.4%, and should be closely monitored, especially in patients with underlying liver disease. In contrast, nephrotoxicity was very low, all at grade 1 (23.1%), no cases of renal failure of grade 2 or higher were recorded, indicating that active rehydration with cisplatin was well implemented. Higher grades of adverse effects compared to some international trials may be related to the more severe patient characteristics in the study population, however the proportion of patients who maintained the dose of ≥85% still reached 86.2% and the rate of no delay of treatment was 61.5%, indicating that adverse effects had been effectively managed in clinical practice.

5.6. Limitations of the study

We are aware of certain limitations in this study when analyzing the results. Retrospective data, limited sample size ($n = 65$), and single-center study site can affect the ability to extrapolate results. In addition, heterogeneity in disease stage in the study population-including local, recurrent, and distant metastases-should be remembered when compared to randomized controlled clinical trials. Prospective studies with larger sample sizes and clearer stratification are needed to confirm the prognostic factors identified in this study.

6. CONCLUSIONS AND LIMITATIONS OF THE STUDY

The Gemcitabine–Cisplatin regimen demonstrated clinically meaningful efficacy and an acceptable safety profile as first-line chemotherapy for patients with advanced, recurrent, or metastatic biliary tract cancer. Regarding treatment efficacy, the regimen achieved a disease control rate of 83.1% after three cycles and 76.3% after six cycles. The median progression-free survival was 8.1 months, and the median overall survival

was 13.1 months. These outcomes are comparable to those reported in major international studies and support the applicability of this regimen in real-world clinical practice at Hanoi Oncology Hospital.Regarding prognostic factors, ECOG performance status and treatment response after three cycles were significantly associated with both progression-free survival and overall survival. These findings suggest that early response assessment and baseline performance status may be useful for guiding subsequent treatment decisions. Regarding safety, hematologic toxicity was the most common adverse event, particularly neutropenia and anemia. However, most adverse events were manageable, and the majority of patients were able to maintain adequate treatment intensity. Renal toxicity was mild, with no grade 2 or higher nephrotoxicity recorded.

This study has several limitations, including its single-center design, limited sample size, retrospective–prospective nature, heterogeneous study population, and absence of multivariate analysis. Further prospective multicenter studies with larger sample sizes are needed to confirm the efficacy, safety, and independent prognostic factors of the Gemcitabine–Cisplatin regimen in Vietnamese patients with biliary tract cancer.

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MANY PATIENTS WITH LIMITED SENTINEL NODE-POSITIVE BREAST CANCER CAN SAFELY AVOID AXILLARY DISSECTION, STUDY SHOWS

Updated results from the phase III SENOMAC trial suggest that many patients with early-stage breast cancer and limited spread to sentinel lymph nodes can safely forgo axillary lymph node dissection (ALND), avoiding substantial long-term arm morbidity without compromising survival. The findings were presented at the 2026 ASCO Annual Meeting (Abstract LBA503).

Study Details

The international study enrolled 2,540 patients from Sweden, Denmark, Germany, Greece, and Italy with T1 to T3 breast cancer and one or two sentinel lymph node macrometastases. Participants were randomly assigned to undergo either completion ALND (n = 1,205) or omission of ALND (n = 1,335) after sentinel lymph node biopsy. More than one-third of patients underwent mastectomy, a population for whom evidence supporting omission of ALND has previously been limited.

Key Results

After a median follow-up of 60.1 months, survival outcomes were nearly identical between the two groups. Five-year overall survival was 93.4% among patients who underwent ALND and 94.4% among those who did not. Five-year breast cancer–specific survival was similarly high, at 97.2% and 97.9%, respectively. Overall, 203 participants died during follow-up, including 74 deaths attributed to breast cancer.

The study's findings reinforce the growing body of evidence suggesting that more extensive axillary surgery does not improve outcomes for patients with limited nodal disease who receive contemporary systemic therapy and regional nodal irradiation. According to lead investigator Jana de Boniface, MD, PhD, of Capio St. Göran's Hospital and Karolinska Institutet in Sweden, "The key finding is that more axillary surgery in itself does not improve survival in these patients. This is extremely important because it means that axillary surgery should be seen as a diagnostic instrument, not a therapeutic tool".

Omission of ALND resulted in significantly better patient-reported arm function and fewer arm-related symptoms over time. Arm morbidity was assessed using the Lymph-ICF questionnaire and the EORTC QLQ-BR23 breast cancer–specific quality-of-life instrument at 1, 3, and 5 years after randomization. Patients who avoided ALND consistently reported better outcomes across all assessments. On the Lymph-ICF scale, average score differences favoring omission of ALND were 10.64 points at 1 year, 10.73 points at 3 years, and 10.75 points at 5 years. Similarly, EORTC arm symptom scores favored omission of ALND by 10.90, 9.86, and 10.02 points at the same respective time points.

The findings address an important clinical issue because ALND has long been associated with chronic pain, numbness, restricted arm mobility, and lymphedema. Investigators noted that nearly one in five patients who undergo ALND report moderate arm dysfunction 5 years after surgery, and 13% report severe or very severe impairment.

Source: ascopost.com

https://ascopost.com/news/june-2026/many-patients-with-limited-sentinel-node-positive-breast-cancer-can-safely-avoid-axillary-dissection-study-shows/

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