國立臺灣大學醫學院臨床醫學研究所
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Master’s Thesis

淋巴轉移之局部晚期食道鱗狀細胞癌預後評分系統之建立：結合病理、影像與臨床因子的多變項模型（PRIME評分系統）

Development of a Prognostic Scoring System for Locally Advanced Esophageal Squamous Cell Carcinoma with Clinical Lymph Node Metastasis at Diagnosis: A Multivariable Model Integrating Pathological, Radiological, and Clinical Factors (The PRIME Score)

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MASTER'S THESIS(DOCTORAL DISSERTATION) ACCEPTANCE CERTIFICATE
NATIONAL TAIWAN UNIVERSITY

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Locally Advanced Esophageal Squamous Cell Carcinoma

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本論文係宗孟瑋 P12421312 在國立臺灣大學醫學系臨床醫學研究所完成之碩士學位論文，於民國 114 年 7 月 31 日承下列考試委員審查通過及口試及格，特此證明。

The undersigned, appointed by the Graduate Institute of Clinical Medicine on 31 July 2025 have examined a Master's Thesis entitled above presented by Meng-Wei Chung P12421312 candidate and hereby certify that it is worthy of acceptance.

口試委員 Oral examination committee:

李章銘　成佳憲　陳建勳

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中文摘要

背景：

食道鱗狀細胞癌在東亞地區相當常見，診斷時多已進展至局部晚期且合併淋巴結轉移。雖然術前輔助化學放射線治療合併手術已成為標準治療，並能改善部分患者預後，但術後復發風險仍高，臨床上極需更準確的預後評估工具，以輔助術後管理與追蹤決策。

方法：

本研究回顧分析接受術前輔助化學放射線治療與手術的臨床淋巴結陽性局部晚期食道鱗狀細胞癌患者之臨床、影像、治療及病理資料。透過單變項 Cox 回歸分析篩選預後因子，建立一套整合 14 項顯著預測變數的新型預後評分系統，並進行驗證分析以預測復發與死亡風險。

結果：

此預後評分模型具良好之區辨力與校正能力。預測總生存期方面，其準確率為76.9%，曲線下面積（AUC）為 0.734；預測無惡化存活期方面，準確率為71.4%，AUC 為 0.721。相較於傳統 AJCC 分期與僅使用病理因子的模型，本評分系統展現出更佳的預測表現。

結論：

本研究提出一套結合臨床、影像、治療與病理資訊的預後評估工具，不僅優於現行標準分期系統，亦具臨床實用性，可協助辨識高風險患者，進一步強化術後照護與追蹤策略。

關鍵字：局部晚期食道鱗狀細胞癌、淋巴結轉移、正子電腦斷層掃描、術前輔助化學放射治療、手術、預後評分系統

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Abstract

Background:
Esophageal squamous cell carcinoma is a common malignancy in East Asia, frequently diagnosed at a locally advanced stage with lymph node involvement. Although chemoradiotherapy followed by surgery has become the standard treatment and improves outcomes in selected patients, recurrence remains a significant concern. There is a need for accurate prognostic tools to guide postoperative management and follow-up strategies.
Methods:
This study analyzed clinical, imaging, treatment, and pathological data from patients with clinically node-positive, locally advanced esophageal squamous cell carcinoma who underwent neoadjuvant chemoradiotherapy and surgery. Univariable Cox regression was used to identify prognostic factors. A novel scoring system, integrating 14 significant predictors, was developed and validated to estimate survival and recurrence risk.
Results:
The prognostic scoring model showed good discrimination and calibration. For predicting overall survival, the scoring system achieved an accuracy of 76.9% and an area under the curve of 0.734. For progression-free survival, the accuracy was 71.4% with an area under the curve of 0.721. Compared with traditional staging methods and pathologic-only systems, the new complete scoring model demonstrated superior predictive performance.
Conclusions:
This study presents a new risk prediction tool that integrates clinical, imaging, treatment, and pathological data. It outperforms conventional staging and offers a practical approach for identifying high-risk patients who may benefit from more intensive postoperative care and monitoring.

Keywords: Locally advanced esophageal squamous cell carcinoma, lymph node metastasis, PET/CT, neoadjuvant chemoradiotherapy, surgery, prognostic scoring system

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Their combined efforts and encouragement made this research possible.

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Figures and Tables

Figure 1. Flowchart of patient selection and cohort allocation

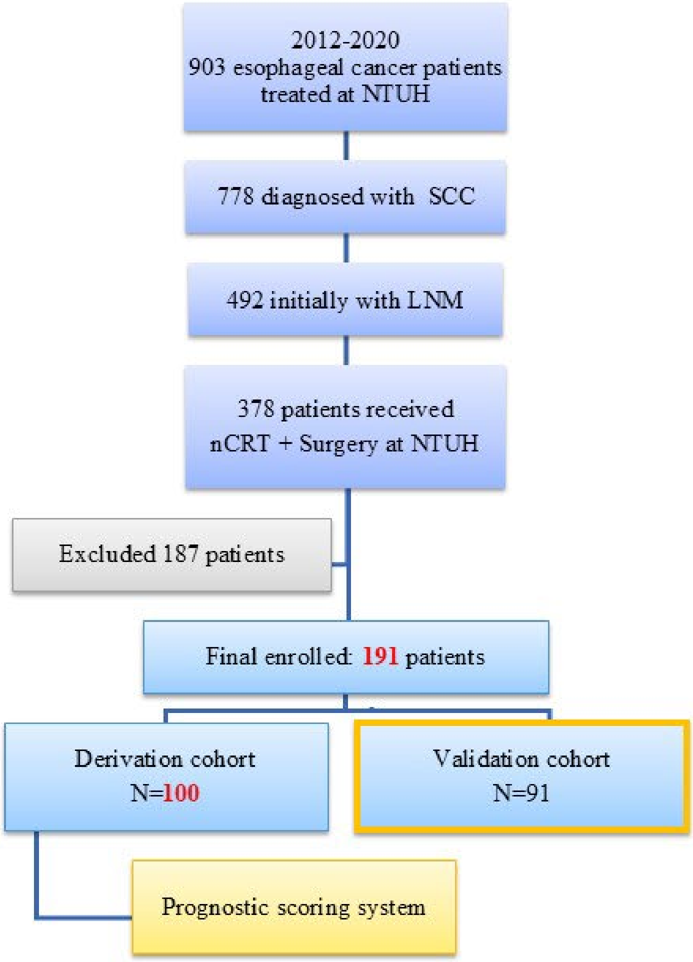

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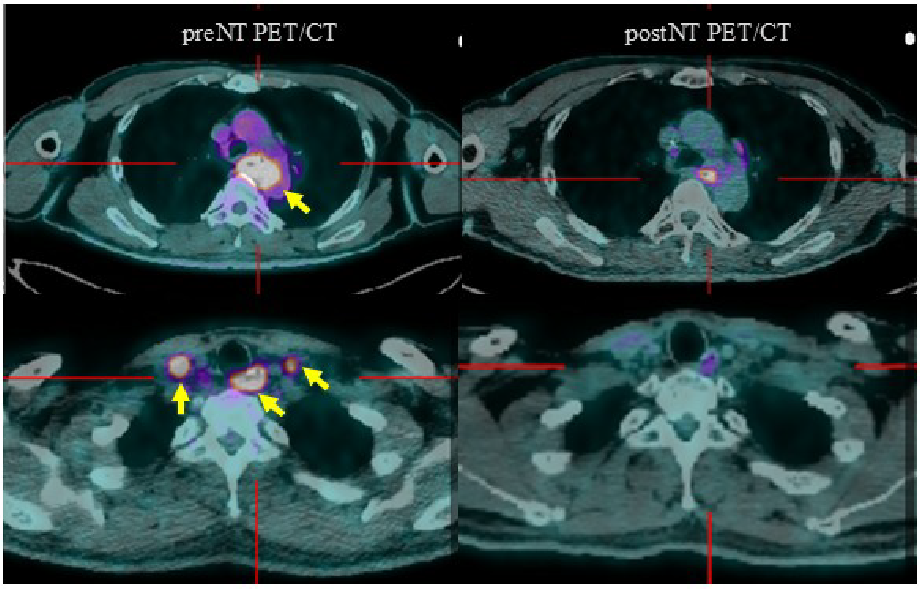
Figure 2 . Representative PET/CT images before and after neoadjuvant chemoradiotherapy (nCRT) showing metabolic complete response (CMR).

The Pre-NT PET/CT scan (left side) reveals intense FDG uptake in the primary esophageal tumor and multiple regional lymph nodes (yellow arrows), consistent with high metabolic activity.

Post-nCRT PET/CT follow-up imaging demonstrates complete resolution of FDG uptake in both the primary lesion and lymph nodes, indicating complete metabolic response (CMR).

This case illustrates the typical imaging appearance of metabolic complete response following nCRT. Despite complete resolution of metabolic activity on PET/CT, pathology later revealed residual disease, underscoring the limitation of relying solely on post-nCRT PET response for treatment planning



intense FDG uptake in main tumor and regional lymph nodes

metabolic complete response

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Figure 3. Risk Stratification and survival analysis with Kaplan–Meier Survival Survival Curves

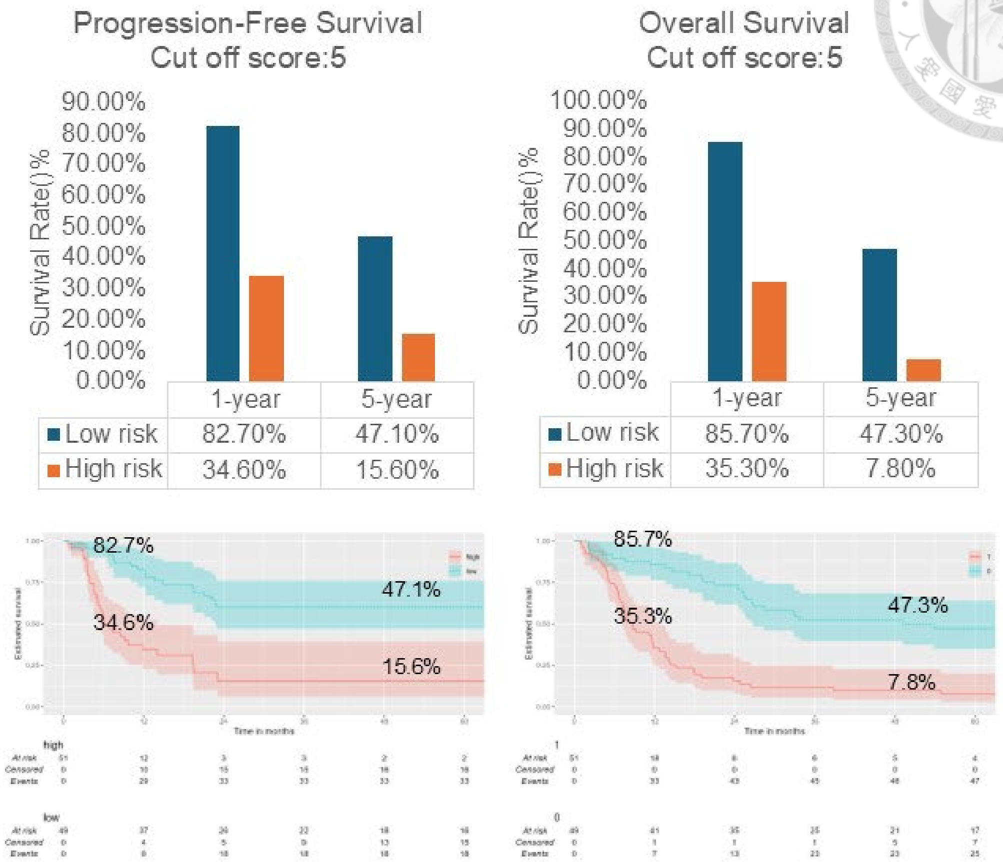

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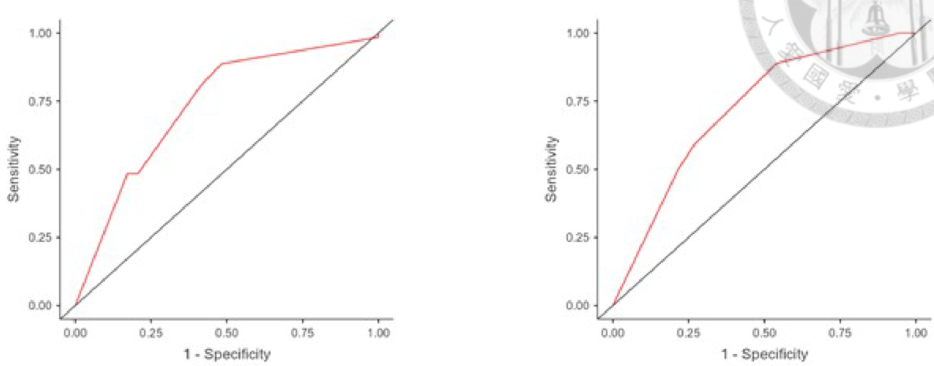
Figure 4. Validation of 1-Year Overall Survival Predictive Performance Using the PRIME Scoring System

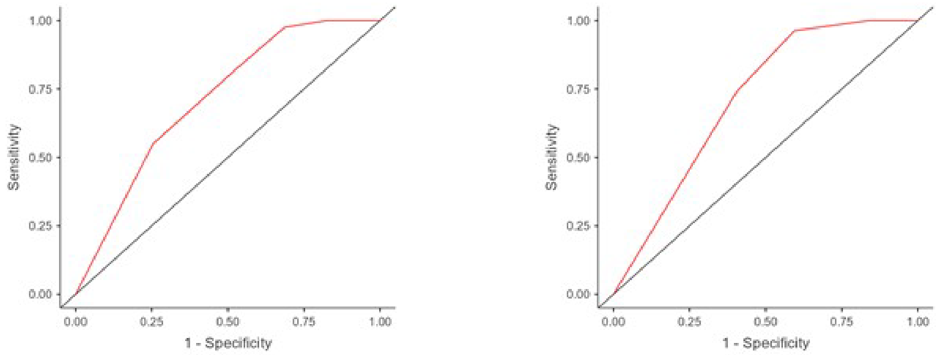
1year Overall Survival Prediction | 1year Progression Free Survival Predition

PRIME scoring system



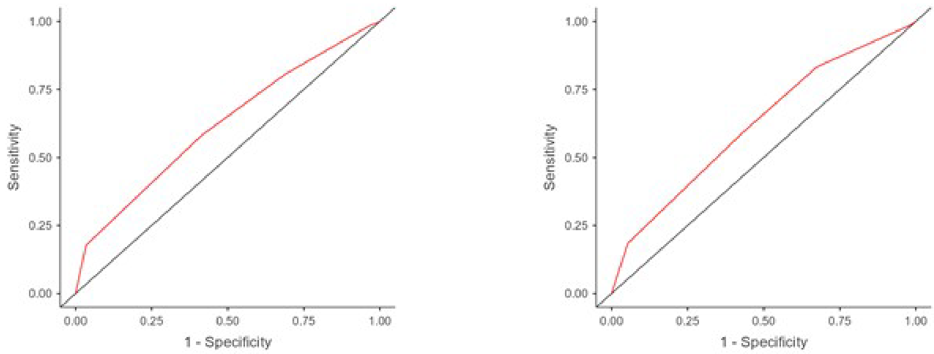
Accuracy	Specificity	Sensitivity	AUC	Accuracy	Specificity	Sensitivity	AUC
0.769	0.517	0.887	0.734	0.714	0.459	0.889	0.721

Pathologic -only System



Accuracy	Specificity	Sensitivity	AUC	Accuracy	Specificity	Sensitivity	AUC
0.659	0.745	0.550	0.712	0.681	0.595	0.741	0.712

Image -only system



Accuracy	Specificity	Sensitivity	AUC	Accuracy	Specificity	Sensitivity	AUC
0.681	0.335	0.984	0.619	0.626	0.324	0.833	0.622

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Table 1. Baseline Characteristics of the Derivation and Validation Cohorts.

			Derivation n=100	Validation n=91	p value
Patient-related factors					
	sex	male	89	84	0.59
		female	11	7	
	age	mean(95% CI)	57.8(56.1-59.5)	57.5(48.2-66.8)	0.06
	ECOG	0-1	79	68	0.6
		>=2	21	23	
	BW loss		60	54	0.18
	Comorbidity	CAD	2	0	0.52
		Neph	3	1	0.68
		COPD	3	2	1
		CVA	1	0	1
		Cirrhosis	4	3	1
		HT	26	11	<0.05
		DM	12	5	0.18
	Ever smoker		89	68	<0.05
	Current smoker		35	24	0.25
	Alcohol		69	63	1
	Betel nuts user		43	40	1
Imaging-related factors					
	Main tumor activity				
	PET tumor responder		87	79	1
	preNT tumor SUV max	mean	21.4(16.7-26.1)	16.1(9.1-23.1)	<0.05
	postNT tumor SUVmax	mean	6.78(5.9-7.6)	6.0(1.1-10.9)	0.05
	ΔSUV of tumor	mean	14.6(9.5-19.8)	9.7(2.1-17.3)	<0.05
	ΔSUV ratio of tumor	mean	0.58(0.5-0.6)	0.6(0.3-0.9)	0.89
	LNM activity				
	preNT LNM (station)	mean	2.8(2.5-3.2)	2.7(1.0-4.4)	0.49
	postNT LNM (station)	mean	1.7(1.4-2.0)	1.7(0.6-2.8)	1
	PET LNM responder		67	43	0.29
	preNT LN SUVmax	mean	9.17(7.9-10.4)	7.7(3.7-11.9)	<0.05
	postNT LN SUVmax	mean	5.05(4.4-5.7)	4.4(1.6-7.2)	0.14
	ΔSUV of LN	mean	4.5(3.1-5.9)	3.0(-1.4-7.4)	<0.05
	ΔSUV ratio of LN	mean	0.34(0.2-0.4)	0.3(-0.2-0.8)	0.87
	Location				
	Main tumor location	M/3	62	52	0.59
		other site	38	39	
	LNM by JEOG classification	reginal	64	51	0.33
		nonregional	36	40	
	preNT Abd-LNM	yes	30	26	0.95
		no	70	65	
Treatment-related factors					
	nRT dose	<4.5Gy	90	85	0.56
		>=4.5Gy	10	6	
	nCT regiment	DCF	44	35	0.52
		ECF	37	42	0.26
		Others	19	14	
	Operation method	Three-Field Esophagectomy	81	78	0.49
		Ivor Lewis Esophagectomy	19	13	
	RT to OP time(weeks)	mean	5.1(4.1-6.1)	5.3(4.5-6.1)	0.16
	any adjuvant treatment		39	27	0.23
Pathology parameters			n(%)		
	pCR		29	34	
	Main tumor parameters				
	TRG	no residual tumor	34	43	0.09
		<10% residual tumor	19	11	0.26
		10-50% residual tumor	23	24	0.7
		>50% residual tumor	24	13	0.13
	Resection margin	R0	76	79	0.08
		R1	17	11	0.45
		R2	7	1	0.09
	LVI	no	72	83	0.25
		yes	28	18	
	LNM parameters				
	pLN(node)	mean	46.2(42.6-49.7)	45.5(27.2-63.7)	<0.05
	pLN (station)	mean	10.1(9.6-10.6)	11.3(8.7-13.9))	<0.05
	log(LN index + 1)	mean	6.0(5.9-6.2)	6.2(5.9-6.5)	0.16
	pLNM(node)	mean	1.49(0.9-2.1)	1.7(0.6-2.8)	0.15
	pLNM (station)	mean	0.85(0.6-1.1)	0.7(0.3-1.1)	0.3
	unexpected LNM	no	63	83	0.97
		yes	10	8	
Tumor characteristics					
	cT	1b	2	2	0.76
		2	9	6	
		3	83	73	
		4a	6	10	
	cN	1	32	29	0.29
		2	44	48	
		3	24	14	
	cM	0	95	86	1.00
		1	5	5	
	ycT	0	1	2	0.44
		1	7	4	
		2	12	8	
		3	78	76	
		4a	2	1	
	ycN	0	23	20	0.92
		1	51	48	
		2	23	21	
		3	3	2	
	ycM	0	99	90	
		1	1	1	
	ypT	0	35	41	0.07
		1	9	9	
		2	22	14	
		3	33	79	
		4	1	0	
	ypN	0	54	62	0.06
		1	29	25	
		2	13	3	
		3	4	1	
	ypM	0	95	89	0.52
		1	5	2	

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Table 2. Continuous variable cutoff analysis Derivation cohort: N = 100 (80%)

Variable	Mean (SD)	PFS HR (p)	OS HR (p)	Cutoff (OS/PFS)
preNT LNM (station)	2.8 (1.7)	1.12 (p=0.181)	1.19 (p=0.013)	2 / -
postNT LNM (station)	1.7 (1.7)	1.09 (p=0.257)	1.09 (p=0.151)	- / -
pre-NT tumor SUVmax	21.4 (23.5)	1.01 (p=0.062)	1.01 (p=0.201)	- / -
pre-NT LN SUVmax	9.2 (6.1)	1.04 (p=0.042)	1.04 (p=0.027)	6 / 3.4
post-NT tumor SUVmax	6.8 (4.0)	1.11 (p=0.001)	1.08 (p=0.002)	7.3 / 7.4
post-NT LN SUVmax	5.0 (3.0)	1.11 (p=0.047)	1.00 (p=0.995)	- / 2.2
ΔSUVmax of tumor	14.6 (24.5)	1.01 (p=0.151)	1.00 (p=0.435)	- / -
ΔSUVmax ratio of tumor	0.6 (0.3)	0.48 (p=0.190)	0.36 (p=0.029)	0.54 / -
ΔSUVmax of LN	4.5 (6.0)	1.03 (p=0.353)	1.04 (p=0.060)	- / -
ΔSUVmax ratio of LN	0.3 (0.4)	1.22 (p=0.612)	1.59 (p=0.178)	- / -

Table3. Ranking of Prognostic Factors Based on the Absolute Value of log(Hazard Ratio) in Univariable Cox Regression

<table>
<tr><th colspan="4">OS</th><th colspan="4">PFS</th></tr>
<tr><th>Rank</th><th>Prognositc factors</th><th>HR</th><th>|log(HR)|</th><th>Rank</th><th>Prognositc factors</th><th>HR</th><th>|log(HR)|</th></tr>
<tr><td>1</td><td>Tumor without complete response</td><td>3.9</td><td>1.36</td><td>1</td><td>Tumor without complete response</td><td>4.81</td><td>1.57</td></tr>
<tr><td>2</td><td>LN metastasis without complete response</td><td>0.31</td><td>1.17</td><td>2</td><td>Unexpected LNM found in final pathology but not shown on pre-nCRT PET</td><td>3.26</td><td>1.18</td></tr>
<tr><td>3</td><td>Present of distant metastasis</td><td>2.75</td><td>1.01</td><td>3</td><td>Resection margin unclear</td><td>3.02</td><td>1.11</td></tr>
<tr><td>4</td><td>Resection margin unclear</td><td>2.56</td><td>0.94</td><td>4</td><td>Present of distant metastasis</td><td>2.74</td><td>1.01</td></tr>
<tr><td>5</td><td>Lymphovascular Invasion</td><td>2.54</td><td>0.93</td><td>5</td><td>Lymphovascular Invasion</td><td>2.46</td><td>0.90</td></tr>
<tr><td>6</td><td>Unexpected LNM found in final pathology but not shown on pre-nCRT PET</td><td>2.33</td><td>0.85</td><td>6</td><td>Pre-nCRT SUVmax of main tumor >=7.5</td><td>0.45</td><td>0.80</td></tr>
<tr><td>7</td><td>Alcohol user</td><td>2.27</td><td>0.82</td><td>7</td><td>Current smoker</td><td>2.22</td><td>0.80</td></tr>
<tr><td>8</td><td>Age>=70 year-old</td><td>2.23</td><td>0.80</td><td>8</td><td>LN metastasis without complete response</td><td>0.49</td><td>0.71</td></tr>
<tr><td>9</td><td>Pre-nCRT SUVmax of main tumor >=7.5</td><td>0.49</td><td>0.71</td><td>9</td><td>Pre-nCRT PET shows positive abdominal LNM</td><td>1.86</td><td>0.62</td></tr>
<tr><td>10</td><td>Body weight loss at diagnosis</td><td>1.93</td><td>0.66</td><td>10</td><td>Body weight loss at diagnosis</td><td>1.8</td><td>0.59</td></tr>
<tr><td>11</td><td>Pre-nCRT SUVmax of lymph node >=6</td><td>0.52</td><td>0.65</td><td>11</td><td>Pre-nCRT SUVmax of lymph node >=6</td><td>0.59</td><td>0.53</td></tr>
<tr><td>12</td><td>LN metastasis without complete remission on post-nCRT PET</td><td>1.92</td><td>0.65</td><td></td><td></td><td></td><td></td></tr>
<tr><td>13</td><td>Pre-nCRT PET shows positive abdominal LNM</td><td>1.73</td><td>0.55</td><td></td><td></td><td></td><td></td></tr>
</table>

This table presents the univariable Cox proportional hazards regression results for each prognostic factor associated with progression-free survival (PFS). The factors are ranked according to the absolute value of the natural logarithm of the hazard ratio (|log(HR)|), which reflects the relative strength of association—regardless of whether the factor is a risk or protective variable. A higher |log(HR)| indicates a stronger impact on prognosis. Both risk-enhancing (HR > 1) and protective (HR < 1) variables are included for comprehensive comparison.

To aid interpretation, prognostic factors are categorized by color:

Green: Pathology-related parameters

Orange: Imaging-related factors

Blue: Patient-related factors

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Table4 .Scoring System for Predicting Prognosis in Locally Advanced Esophageal SCC with Lymph Node Involvement

Category	14 Factors for Poor Prognosis
Patient-related factors	Age>=70 year-old
	Body weight loss at diagnosis
	Current smoker
	Alcohol user
Imaging-related factors	LN metastasis without complete remission on post-nCRT PET
	Post-nCRT SUVmax of main tumor >=7.5
	Pre-nCRT SUVmax of lymph node >=6
	Pre-nCRT PET shows positive abdominal LNM
Pathology parameters	Tumor without complete response
	LN metastasis without complete response
	Present of distant metastasis
	Unexpected LNM found in final pathology but not shown on pre-nCRT PET
	Resection margin unclear
	Lymphovascular Invasion

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Chapter 1. Introduction

1.1 Background

Esophageal cancer ranks as the seventh most common malignancy and the sixth leading cause of cancer-related death worldwide, with its high mortality largely attributed to late-stage diagnosis, regional lymph node metastasis, and invasion of adjacent structures at presentation [1]. In East Asia and Eastern Africa, esophageal squamous cell carcinoma (ESCC) is the predominant histological subtype, accounting for more than 90% of esophageal cancer cases in these regions [2]. A similar pattern is observed in Taiwan, where the 2022 National Cancer Registry report indicates that ESCC comprises over 90% of all esophageal cancer cases, with a markedly higher incidence in males. In fact, esophageal cancer ranks as the fifth leading cause of cancer-related death among Taiwanese men [3]. The poor prognosis of ESCC is primarily due to its late-stage diagnosis, often involving locoregional lymph node metastases or adjacent organ invasion, which makes curative treatment challenging and recurrence rates high.

For patients with locally advanced ESCC, the current standard treatment consists of neoadjuvant chemoradiotherapy (nCRT) followed by radical esophagectomy. This strategy has been validated by several large-scale randomized trials, including the CROSS trial and the NEOCRTEC5010 trial in China, both demonstrating significant improvements in overall survival (OS)[4, 5]. Nonetheless, even after complete treatment, the 5-year OS rate remains suboptimal at approximately 40–50%. Notably, among patients with residual lymph node metastasis (ypN^{+}) after surgery, the recurrence rate exceeds 60%[6].

1.2 Clinical Challenge and Research Rationale

Most thoracic surgeons consider neoadjuvant therapy instead of immediate surgery when preoperative PET/CT suggests possible lymph node metastasis. In clinical practice, patients with cN^{+} ESCC often receive nCRT, and some of them achieve significant metabolic response in both the primary tumor and lymph nodes, ultimately showing no residual nodal metastasis on pathology (ypN0). However, long-term survival outcomes in this subgroup remain highly variable [4, 7]. These patients, who initially bear a higher tumor burden, exhibit substantial prognostic heterogeneity, highlighting the need for a reliable tool to guide postoperative risk stratification and

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treatment planning.

While many previous studies have explored the prognostic impact of individual clinical, pathological, or imaging-related factors, such as pathological stage (ypTNM), tumor regression grade (TRG), SUVmax, or specific clinical variables, their real-world applicability remains inconsistent. This inconsistency arises from variations in healthcare resources, surgical strategies (particularly the extent of lymph node dissection), preoperative treatment modalities, and insurance policies across institutions and regions. As a result, clinicians often rely on personal judgment to determine postoperative treatment strategies, especially in high-risk patients.

Although such single-variable analyses have provided useful insights, the prognostic value of individual parameters is often limited due to patient heterogeneity and the multifactorial nature of disease progression. Therefore, there is a need for a comprehensive and integrative prognostic tool. The present study aimed to address this gap by incorporating clinicopathologic features, imaging characteristics, and pathological findings into multivariable models to construct clinically applicable nomograms for survival prediction in ESCC.

1.3 Study Objective

The primary objective of this study was to develop and validate a prognostic scoring system for patients with locally advanced ESCC who underwent nCRT followed by radical esophagectomy at a single tertiary medical center. The proposed model integrates PET-based prognostic indicators with key clinical, imaging, and pathological features. Focusing on high-risk patients with clinical lymph node positivity (cN^{+}) at diagnosis, this study utilized univariable statistical modeling to identify factors associated with recurrence and mortality. The goal was to establish a clinically practical nomogram to assist in postoperative decision-making—particularly regarding the administration of adjuvant therapy—and to improve the overall efficiency of treatment resource allocation.

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Chapter 2. Literature Review

2.1 Epidemiology of Esophageal Squamous Cell Carcinoma

According to GLOBOCAN global cancer statistics, esophageal cancer ranks seventh in incidence and sixth in cancer-related mortality worldwide [1]. The overall prognosis is poor, with a five-year survival rate generally below 20%, particularly in cases diagnosed at the locally advanced stage or with regional lymph node metastasis (LNM), where treatment becomes more challenging and the risk of recurrence increases significantly.

Histologically, esophageal cancer is mainly classified into two subtypes: adenocarcinoma and squamous cell carcinoma (SCC). Adenocarcinoma is more prevalent in Western countries and is associated with gastroesophageal reflux disease (GERD), Barrett's esophagus, and obesity. In contrast, esophageal squamous cell carcinoma (ESCC) predominates in East Asia, Eastern Africa, and Central Asia, accounting for over 90% of cases. Major risk factors for ESCC include smoking, alcohol consumption, and frequent intake of very hot beverages [2]. These geographical differences reflect not only varied risk factors but also fundamental differences in carcinogenesis and molecular biology between adenocarcinoma and SCC.

At the molecular level, genomic analyses have confirmed that ESCC and esophageal adenocarcinoma are biologically distinct entities. The Cancer Genome Atlas (2017) revealed that ESCC shares strong molecular similarities with squamous cell carcinomas of the lung and head and neck, while being genetically divergent from esophageal adenocarcinoma [8]. Burmeister et al. (2005) also emphasized that ESCC and adenocarcinoma differ in therapeutic response and prognosis, advocating separate treatment strategies[9]. Consequently, prognostic models and treatment protocols developed predominantly for adenocarcinoma in Western populations may not be directly applicable to ESCC-predominant Asian cohorts, highlighting the need for region-specific clinical tools and datasets.

In Taiwan, the histological distribution mirrors that of East Asia, with ESCC being the predominant subtype. According to the 2022 Cancer Registry Annual Report published by the Ministry of Health and Welfare [10], 2,831 patients were newly diagnosed with esophageal cancer that year, with 1,980 deaths. Among male cancer patients,

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esophageal cancer ranked sixth in incidence and fifth in mortality. ESCC accounted for 91.73% of male and 87.45% of female esophageal cancer cases. Regarding treatment patterns, only 11.76% underwent surgery alone, while 16.51% received surgery combined with chemotherapy and radiotherapy. Immunotherapy was used in merely 2.06%, indicating that most patients still rely on the traditional triplet approach (Neoadjuvant chemoradiotherapy with radical surgery) as the mainstay strategy.

In summary, ESCC is of considerable epidemiological importance in Taiwan and other East Asian regions, with challenging prognosis. With the advancement of imaging techniques and emerging therapies such as immune checkpoint inhibitors (ICIs) like nivolumab (anti-PD-1 monoclonal antibody), the development of an integrated prognostic evaluation tool based on regional epidemiological characteristics and clinical data may help improve treatment effectiveness and optimize resource allocation.

2.2 Current Treatment Strategies for Esophageal Squamous Cell Carcinoma

For patients with Locally Advanced Esophageal Squamous Cell Carcinoma (LAESCC), the current standard of care is neoadjuvant chemoradiotherapy (nCRT) followed by curative surgery.

This approach has been validated by two major randomized trials: the CROSS trial in Western countries and the NEOCRTEC5010 trial in East Asia, both demonstrating significant improvements in overall survival (OS).

Esophageal cancer has poor survival with five-year survival rates for surgery alone ranging from 15 to 39 % [11]. Unfavorable survival outcomes with surgery alone led to interest in the role of multimodality treatment. Neoadjuvant chemoradiation (NCRT) has been used to downstage the primary tumor, thereby increasing the resectability and eliminating micrometastasis.

Overall, notwithstanding a few controversies in the randomized controlled trials, NACRT is the current standard of care for locally advanced esophageal cancer and hence about 2/3 of the patients receive neoadjuvant treatment followed by surgery [12]. Histopathological examination of the resected specimen after definitive surgery remains the gold standard for evaluating the tumor response after chemoradiation [13]

In the Dutch CROSS trial, only 23% of patients had ESCC, with the majority being

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esophageal adenocarcinoma. Chemotherapy consisted of weekly administration of carboplatin (AUC 2 mg/mL per min) and paclitaxel (50 mg/m²), combined with radiotherapy (41.4 Gy in 23 fractions). This regimen improved five-year OS from 33% in the surgery-only group to 47%[4]。

The NEOCRTEC5010 trial conducted in China focused exclusively on ESCC patients and utilized a regimen of vinorelbine and cisplatin combined with 40 Gy radiotherapy. Among 451 patients with resectable thoracic ESCC (clinical stages T1-4N1M0/T4N0M0), the three-year OS improved from 58.9% to 69.1% in the nCRT plus surgery group[5]。

Current guidelines recommend radiotherapy doses of 41.4–50.4 Gy, typically delivered in 1.8 Gy fractions [14]. Common chemotherapy regimens include cisplatin with 5-FU and FOLFOX (5-FU, leucovorin, and oxaliplatin), in addition to the CROSS regimen [4].

Under mature protocol of nCRT over a decade, report shows as many as 40% of patients achieve complete pathologic response following radical resection in both SCC and adenocarcinoma esophageal cancer, which is a key predictor of long-term survival [15]. Pathological complete response (pCR) is achieved with higher rates in ESCC (49%) compared to adenocarcinoma (23%)[4].
In recent years, the integration of immune checkpoint inhibitors (ICIs) into neoadjuvant protocols—so-called neoadjuvant immunochemotherapy (NICT)—has shown promise in further improving pCR rates. Studies have demonstrated that NICT can yield pCR rates ranging from 19.2% to as high as 56%, depending on the regimen and patient selection [16]. Notably, while nCRT may achieve a higher local pCR rate, NICT tends to provide superior systemic control and a better safety profile, with fewer perioperative complications[17, 18]。
However, it is important to note that the patients included in our present study did not receive immunotherapy-based treatment. All participants were treated with conventional nCRT followed by surgery. Therefore, the recurrence patterns and survival outcomes observed in our cohort may differ from those reported in recent trials involving IO-

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based approaches. This distinction highlights the relevance of establishing contemporary prognostic tools tailored to current treatment strategies。

Timing of evaluation post nCRT is also crucial. The first evaluation is generally performed 4–6 weeks after completion of nCRT using imaging modalities such as PET/CT, CT, or MRI to assess tumor response. The second evaluation occurs preoperatively, combining endoscopic and radiologic findings to assess surgical candidacy and potential prognosis[14]。

After completion of nCRT, patients with resectable disease typically undergo surgical resection. Esophagectomy with lymphadenectomy remains the standard of care, especially in patients without evidence of distant metastases on restaging evaluations. Surgical approaches include transthoracic esophagectomy (TTE), transhiatal esophagectomy (THE), video-assisted thoracoscopic surgery (VATS), and robotic-assisted thoracoscopic surgery (RATS). Among these, three-field lymphadenectomy (3FL)—encompassing cervical, mediastinal, and abdominal lymph nodes—has been associated with improved long-term survival in selected cases, albeit at the cost of increased surgical complexity and postoperative complications compared to two-field lymphadenectomy (2FL) [19].

Despite the survival benefits associated with nCRT followed by esophagectomy, long-term outcomes for patients with ESCC remain unsatisfactory. Multiple studies have reported that the 5-year overall survival (OS) rate typically remains below 50%, even in patients who undergo curative resection. In particular, the presence of residual pathological lymph node metastasis (ypN+) after nCRT has emerged as a critical prognostic factor, strongly associated with higher rates of disease recurrence and poorer survival outcomes. For instance, Shapiro et al. reported that among patients with ESCC who received the CROSS regimen, those with ypN+ had a recurrence rate of up to 58.8%, underscoring the aggressive biology of residual nodal disease [4]. Similarly, recent evidence from Liu et al. (2024) reinforced the adverse prognostic impact of ypN+, showing significantly lower disease-free and overall survival rates in this subgroup [6].

These findings have stimulated efforts to refine post-nCRT evaluation strategies. Trials such as preSANO and preSINO have highlighted the challenges of accurately

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identifying residual disease prior to surgery, especially when considering organ-preserving or active surveillance approaches. Although clinical complete response (cCR) after nCRT may suggest favorable tumor regression, studies show that residual nodal disease (i.e., ypT0N+) can still be present in up to 7–14% of ESCC patients, which may go undetected by conventional imaging or endoscopic assessment [20, 21]. Consequently, until more accurate restaging modalities are validated, esophagectomy remains indispensable for ensuring maximal oncologic clearance in LAESCC patients treated with nCRT。

2.3 The Prognostic Impact of Lymph Node Metastasis in ESCC

The presence of lymph node metastasis in the postoperative pathological assessment (ypN stage) is currently recognized as one of the most critical prognostic factors for patients with locally advanced esophageal squamous cell carcinoma (ESCC). Multiple studies have shown that even in cases where the primary tumor achieves complete pathological remission, residual lymphatic involvement significantly increases the risk of recurrence and cancer-related mortality [22]. For instance, in the randomized NEOCRTEC5010 trial, the recurrence rate reached 58.8% in ypN+ patients, markedly higher than the 21.7% observed in ypN− individuals. Moreover, patients with ypN+ disease experienced shorter median time to recurrence (5.8 vs. 7.8 months), reflecting not only its prognostic implications but also the aggressive biological behavior associated with nodal metastasis [4-6].

Beyond the mere presence or absence of nodal involvement, both the number and distribution of metastatic lymph nodes have increasingly been recognized as important prognostic indicators. The conventional AJCC staging system classifies nodal stage based on the number of positive nodes (pN0, pN1, pN2, pN3). However, recent evidence suggests that counting positive nodes alone may underestimate disease heterogeneity, particularly in patients undergoing extensive three-field lymphadenectomy (3FL), where the anatomical extent of metastasis has also been linked to surgical complexity and long-term outcomes[23]。

In addition to the number of involved nodes, several studies have demonstrated that a more extensive lymphadenectomy—especially involving the cervical, mediastinal, and

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abdominal regions (3FL)—confers survival benefits [19]. This advantage is attributed not only to more thorough removal of metastatic nodes but also to more accurate pathological staging, which can better guide adjuvant therapy and follow-up planning.

Interestingly, although ESCC arises in the esophagus, its gene expression profile closely resembles that of squamous cell carcinomas of the lung and head and neck, rather than esophageal adenocarcinomas, highlighting its distinct molecular identity. This similarity allows relevant prognostic insights—such as the impact of lymphadenectomy extent—to be drawn from SCCs of other sites. For example, Jaber et al. (2014) conducted a multi-institutional study and found that extensive neck dissection in patients with advanced, node-negative (pN0) oral SCC significantly reduced recurrence and improved survival. Likewise, Lemieux et al. (2016) analyzed 4,341 pN0 oral SCC patients and reported that those with >22 lymph nodes removed had better overall survival, with each additional node removed reducing mortality risk (HR = 0.995, p = 0.022). Farrokhian et al. (2022) further confirmed that in pN0 patients, removing fewer than 18 lymph nodes was associated with lower 5-year local control and disease-free survival [24-26]. Collectively, these findings support the prognostic significance of both the number and scope of lymph node removal, even in patients classified as node negative.

Extending this concept to ESCC, Chen et al. (2014) evaluated patients who underwent three-field lymphadenectomy and found that the five-year overall survival rate was only 10.2% in those with metastases spanning all three regions (cervical, mediastinal, abdominal), compared to 43.0% in those with a single-region spread—suggesting that the number of anatomical regions involved is an independent prognostic factor[23]. In a more recent retrospective study, Lu et al. (2024) focused on node-negative ESCC patients and found that each additional lymph node removed was associated with a 2% decrease in mortality risk (HR = 0.98, 95% CI: 0.98–0.99), with the most pronounced survival benefit seen when ≥25–28 nodes were dissected. Another study by the same team showed that dissection of ≥15 nodes across ≥9 nodal stations was significantly associated with better disease-free and overall survival outcomes[23, 27]. These results collectively highlight the importance of not just the quantity of metastatic nodes, but also the extent and thoroughness of nodal dissection as essential factors influencing prognosis in ESCC.

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In contrast to traditional metrics that rely solely on counting metastatic nodes, some researchers have proposed composite indices that incorporate both the number and anatomical breadth of nodal clearance. One such metric is the Lymph Node Index (LN index), defined as the product of the number of dissected nodes and the number of nodal stations sampled:

LN index = number of nodes × number of stations

Although the LN index has been explored in cancers such as oral and lung SCC, its prognostic value in esophageal cancer remains under investigation. Future studies are warranted to validate whether this metric can refine postoperative risk stratification and inform adjuvant treatment decisions in ESCC.

2.4 Prognostic Heterogeneity and Gaps in Current Research

At present, most operable esophageal cancer patients are classified according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system. However, in patients who have received neoadjuvant chemoradiotherapy (nCRT) followed by surgery, the prognostic accuracy of this system is limited. This is largely because tumor and nodal status can be significantly altered by treatment response, and as such, traditional pathological staging may not adequately capture residual disease burden or long-term recurrence risk.

This limitation is particularly evident in patients with locally advanced ESCC who present clinically positive lymph nodes (cN^+) at diagnosis. Although nCRT improves local control and increases the likelihood of achieving an R0 resection, these patients are still considered a high-risk population with generally poor long-term outcomes. Nonetheless, considerable prognostic heterogeneity exists within this group. For example, in the NEOCRTEC5010 trial, Yang et al. (2018) reported that 86.5% of patients were cN^+ prior to treatment, yet a substantial proportion experienced early recurrence despite receiving standardized therapy[5].

Further evidence by Zanoni et al. (2016) supports this observation, highlighting that

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"ypN0 does not necessarily equate to favorable prognosis." Patients who convert from cN^+ to ypN0 after nCRT may still carry a higher risk of recurrence than those who were cN0 at baseline [7]. Pre-treatment PET/CT findings, such as increased metabolic activity in regional lymph nodes, may reflect underlying tumor aggressiveness that is not captured by post-treatment pathology alone.

These findings suggest that relying solely on the postoperative pathological staging system may be inadequate for individualized risk assessment in this patient group. Therefore, although LAESCC patients with cN^+ disease are generally considered high-risk, meaningful differences in recurrence and survival exist within this population. Identifying which patients remain at elevated risk despite apparent pathological downstaging is essential to improving individualized postoperative management and guiding the use of adjuvant therapies.

2.5 Clinical, Imaging, and Pathological Prognostic Indicators of ESCC

2.5.1 Established Clinical & Pathological Prognostic Factors

Research has shown that smoking history is an independent predictor of poor survival in ESCC patients. One retrospective study demonstrated that cigarette smoking increased the risk of death, with hazard ratios (HRs) rising alongside pack-years smoked (HR ≈ 1.86; 95% CI, 1.42–2.44; $p < 0.001$) in ESCC patients receiving chemoradiotherapy with or without surgery [28].

Another large cohort study confirmed that smokers, particularly current and heavy smokers (>20 pack-years), had significantly reduced overall survival compared to non-smokers (median OS 23.2 vs. 64.9 months; $p = 0.001$) in patients receiving surgery plus chemotherapy [29]

Traditional pathological factors, notably residual tumor invasion (ypT), nodal status (ypN), and tumor regression grade (TRG), remain central to prognostication in ESCC after neoadjuvant therapy [30]. The TRG system proposed by Becker et al., developed initially for locally advanced gastric and gastro-esophageal junction cancers, is based on the proportion of residual tumor versus therapy-induced fibrosis within the surgical specimen. In this four-tier system, TRG 1 represents complete or near-complete regression (<10% viable tumor), TRG 2 indicates partial regression (10–50%), TRG 3

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reflects minimal regression (>50% residual), and TRG 4 signifies no regression [31]. Becker's original cohort comprised 36 patients treated with perioperative chemotherapy, demonstrating that those with TRG 1–2 had significantly better survival than patients with higher TRG grades [31] . A large-scale validation study of 480 patients confirmed TRG as an independent prognostic factor: patients with TRG 1 exhibited notably higher 5-year overall survival (OS) rates compared with TRG 2–4, even after adjustment for ypTNM stage [32]. A meta-analysis across gastrointestinal malignancies further showed that low TRG scores (≤2) correlate with both prolonged disease-free survival and overall survival (HR 0.53 for DFS and 0.59 for OS) [33].
However, TRG systems are not without limitations. Additionally, TRG may correlate with ypTNM staging, potentially diluting its independent prognostic power in multivariate analyses [34]. In some studies, TRG failed to predict outcomes once ypTNM and resection margins were considered. [34]

In summary, while TRG provides valuable prognostic information and quantifies treatment response, its standalone utility is limited by interobserver variability and overlaps with conventional staging. These limitations support the need for predictive models integrating TRG with additional clinical, imaging, and pathological markers to enhance accuracy in ESCC prognosis.

2.5.2 nCRT Dose, Chemotherapy Regimen, and Timing to Surgery
The radiation dose administered during neoadjuvant chemoradiotherapy (nCRT) is a critical yet debated factor in esophageal cancer management. A recent multicenter retrospective study by Mantziari et al. (2024) evaluated 319 esophageal cancer patients undergoing nCRT followed by surgery and compared the oncologic outcomes between those receiving low-dose (< 45 Gy) and standard/high-dose (≥ 45 Gy) radiation. The study revealed that patients treated with low-dose radiation had significantly lower rates of major pathological response (23.5% vs. 38.9%, p = 0.011), particularly in esophageal squamous cell carcinoma (ESCC) patients. However, the difference in overall survival (OS) was not statistically significant between groups, suggesting that radiologic downstaging and pCR may not always correlate with long-term survival outcomes [35]. Similarly, a systematic review concluded that escalating radiation dose beyond the standard 40–50.4 Gy does not improve OS or local control, suggesting that lower doses

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may reduce toxicity without compromising oncologic efficacy [36].
Timing between nCRT and surgery is another key clinical variable. A 4-6-week interval has been traditionally recommended [14], the evidence is mixed. A meta-analysis reported increased postoperative complications when the interval exceeded 8 weeks, with no clear survival advantage [37].
A Dutch registry study categorized patients by nCRT-to-surgery interval (5–11, 11–17, and >17 weeks), finding that longer intervals correlated with higher complication rates and anastomotic leak risk [38].

Collectively, these findings highlight that while radiotherapy dose escalation and variations in the interval between completion of nCRT and surgical resection may influence short-term outcomes such as pathological response and treatment-related toxicity, neither factor has consistently demonstrated a strong impact on long-term survival. Nonetheless, these parameters will be taken into consideration in the development of our prognostic scoring system to ensure a comprehensive clinical perspective.

2.5.3 Gaps: Imaging-Based Survival Predictors vs. Treatment Response Focus

A majority of PET/CT studies to date have concentrated on predicting pathological response (e.g., TRG, pCR), using SUVmax thresholds or ΔSUV percent changes to identify metabolic responders during nCRT. Unfortunately, many of these PET-based thresholds (e.g., SUVmax 2.5–5.5; ΔSUV >70%) fail to consistently predict long-term survival due to high false-positive/false-negative rates tied to inflammation, tissue edema, or persistent metabolic activity despite pathologic remission.

In contrast, fewer studies have explored how PET-derived variables relate to survival outcomes, especially within high-risk subgroups. Notably, several PET LN metrics—such as number of PET-positive LNs, metabolic intensity, anatomical distribution, and the novel SD_{max} (LN–T) distance—show promising prognostic potential but require validation in integrated models.

2.6 Prognostic Utility and Limitations of PET/CT in Esophageal Squamous Cell Carcinoma

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The integration of 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) has become an essential tool in the management of esophageal squamous cell carcinoma (ESCC), particularly for staging, assessing treatment response, and identifying metastatic lymph nodes. Numerous studies have highlighted both the utility and the limitations of PET/CT in predicting patient outcomes following neoadjuvant chemoradiotherapy (nCRT) and surgery.

2.6.1 PET-Based Metabolic Response and Its Prognostic Implications

PET/CT provides high sensitivity and specificity in detecting main tumor and regional lymph node metastasis, significantly outperforming traditional CT alone [39, 40]. Karashima et al. noted that the positive predictive value (PPV) of PET/CT reached 84.2%, compared to 54.5% for CT, especially when combined with quantitative SUV (standardized uptake value) analysis [39].

SUVmax is commonly used to assess tumor metabolic activity, though optimal cutoff values vary across studies

DeYoung et al. (2002) used a fixed SUVmax cutoff of 2.5 to define metabolic responders, achieving sensitivity of 78% and specificity of 57% for pCR[41].Lai et al. (2024) proposed a preoperative SUVmax threshold of 5 to predict outcomes in patients undergoing surgery after nCRT, finding that high SUVmax was significantly correlated with poor tumor response, advanced ypT stage, and worse recurrence-free survival[42]. Dewan et al. (2017) reported that a post-nCRT SUVmax < 3.25 predicted pCR with sensitivity of 66.7% and specificity of 67.4% [43].

Significant reduction in SUVmax after treatment can predict pCR and was associated with improved progression-free and overall survival [42, 44]. Several studies have defined PET responders as patients with a ΔSUV of 70–80% after therapy, which was significantly associated with improved pCR and survival outcomes [43, 45].

However, some studies show limitation of PET prognostic value. Nagaki et al. (2022) found that even when lymph nodes showed complete metabolic response (CMR) on PET/CT, 14.6% of these nodes were still pathologically positive (ypN+), indicating a notable false-negative rate [46]. The preSINO trial similarly reported no significant correlation between PET-based CMR and actual tumor regression grade (TRG), with approximately 15% of patients classified as TRG 3 or 4 despite PET CMR ([20].

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2.6.2 PET Prognostic Implications on LNM activity and N stage

Jimenez -Jimenez et al. (2019) found that patients with PET-positive lymph nodes had significantly worse OS and DFS than those without. They also observed that higher SUVmax values and further nodal spread were linked to elevated risks of death, recurrence, and metastasis [47].

Beyond metabolic activity (SUVmax), other studies have examined the number of PET-positive lymph nodes as a prognostic marker and found that patients with three or more positive nodes post-treatment had drastically poorer outcomes [48].

2.6.3 Emerging PET Parameters: Spatial Metrics and Node-Based Analysis

In addition to traditional SUV-based evaluations, newer studies have explored new PET parameters to enhance the accuracy of lymph node metastasis prediction. Xu et al. (2019) assessed the predictive value of various PET/CT metabolic parameters—including SUVmax, SUVmean, metabolic tumor volume (MTV), and total lesion glycolysis (TLG)—for lymph node metastasis (LNM) in ESCC. In their retrospective analysis of 75 patients, SUVmax of lymph nodes and MTV were significantly higher in the LNM-positive group compared to those without nodal metastases. Among all tested variables, nodal SUVmax > 2.6 was identified as the optimal cutoff to predict pathological metastases, yielding an AUC of 0.814, sensitivity of 87.1%, and specificity of 72.1%. The study concluded that combining multiple PET-derived metabolic indices—particularly node-specific SUVmax and MTV—could improve diagnostic accuracy for LNM beyond conventional size or uptake-based criteria alone [49].

Another study introduced the SDmax (LN-T), defined as the distance from the most distant PET-positive lymph node to the primary tumor, normalized by body surface area. SDmax > 0.37 m^{-1} was associated with significantly poorer OS and PFS. When combined with metabolic tumor volume (MTV), SDmax provided additional risk stratification [50].

2.7 Evolution from Single Prognostic Markers to Integrated Risk Models

With neoadjuvant chemoradiotherapy (nCRT) followed by surgery becoming the standard treatment for patients with locally advanced esophageal squamous cell carcinoma (ESCC), accurate postoperative risk stratification and survival prediction have emerged as key clinical priorities. Traditionally, clinicians have relied on the

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American Joint Committee on Cancer (AJCC) TNM staging system and pathologic complete response (pCR) as the main prognostic indicators. However, multiple studies have suggested that these indicators have limited accuracy in patients who have undergone nCRT.

Deng et al. (2017) developed a prognostic nomogram based on clinical and surgical pathological features in a cohort of 407 ESCC patients who received nCRT followed by esophagectomy. Their model incorporated multiple variables including sex, age, tumor length, treatment response, resection margin status, proximal resection margin length, lymph node status, and presence of anastomotic fistula. Compared with AJCC staging or pCR status alone, this nomogram demonstrated significantly better predictive power and risk discrimination. The model stratified patients into four distinct risk groups, with corresponding 5-year overall survival (OS) rates of 57.3%, 40.7%, 18.3%, and 6.1%, respectively—highlighting its effectiveness in identifying subpopulations with distinctly different prognoses [51].

In another study, Zhang et al. (2023) constructed a separate prognostic nomogram using preoperative PET/CT imaging parameters to predict lymph node metastasis and 5-year survival. Their study focused on ESCC patients who had not received neoadjuvant treatment and incorporated variables such as metabolic tumor length and thickness, tumor SUVmax, lymph node SUVmax, short-axis diameter, the number of suspected lymph nodes, and tumor differentiation grade. The resulting model achieved a C-index of 0.76 in both the training and validation cohorts, indicating high predictive accuracy. Notably, patients classified into the high-risk group had significantly worse 5-year OS compared to the low-risk group (56.0% vs. 78.4%, $p = 0.0015$), underscoring the prognostic relevance of PET/CT parameters in pre-treatment risk stratification[18].

Taken together, existing literature demonstrates that whether based on postoperative pathological features or on preoperative imaging metrics multifactorial nomogram models can substantially improve the precision of survival prediction in ESCC[18] . Future development of prognostic scoring systems is likely to move toward integrating pre-treatment imaging data, clinical features, and postoperative pathology to construct more comprehensive and individualized risk assessment tools.

2.8 Clinical Application and Research Motivation

Despite the increasingly recognized role of PET/CT in preoperative assessment, a

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comprehensive prognostic risk stratification system that integrates pre-treatment metabolic response, surgical extent, and pathological findings remains lacking in clinical practice. According to pivotal trials such as CROSS and NEOCRTEC5010, neoadjuvant chemoradiotherapy (nCRT) improves R0 resection rates and local disease control. However, nearly 50% of patients still experience disease recurrence or death within five years after curative surgery, particularly those with residual pathological lymph node metastasis (ypN+)[4, 5]

Current international guidelines NCCN (2021) recommend adjuvant immunotherapy (e.g., nivolumab) as the only established postoperative treatment following nCRT, specifically for patients with residual nodal disease (ypN+), based on its demonstrated benefit in prolonging progression-free survival (PFS)[14]. However, given the high cost and potential adverse effects of immunotherapy, it is not feasible to apply this treatment universally. Therefore, a major clinical challenge lies in identifying which high-risk patients are most likely to benefit from adjuvant therapy.

This study aims to address this unmet clinical need by focusing on patients with clinically node-positive (cN^{+}) locally advanced ESCC who underwent nCRT followed by curative surgery. We propose the development of a composite prognostic scoring system centered on PET-based parameters and incorporating key clinical, surgical, and pathological indicators. The goal is to improve the prediction of both progression-free survival (PFS) and overall survival (OS), thus supporting more personalized postoperative management—including adjuvant immunotherapy decision-making—and laying the groundwork for future trials.

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Chapter 3. Methods

3.1 Patient selection

This retrospective study was conducted at National Taiwan University Hospital (NTUH). A total of 903 patients underwent esophagectomy for esophageal cancer between 2012 and 2020. Among them, 778 patients (86%) had pathologically confirmed squamous cell carcinoma (SCC), and 492 of these SCC cases (63%) initially presented with clinical lymph node metastasis (LNM). Of these, 378 patients received neoadjuvant chemoradiotherapy (nCRT) followed by curative esophagectomy at NTUH.

After applying the inclusion and exclusion criteria, 191 patients were eligible for analysis. The first 100 consecutive cases were assigned to the derivation cohort, and the remaining 91 patients were included in the validation cohort. Figure 1 illustrates the stepwise patient selection process and cohort allocation.

Pathologic staging was determined according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system【16】.

The inclusion criteria were as follows:

- Histologically confirmed esophageal squamous cell carcinoma (ESCC);
- Underwent treatment at NTUH between 2018 and 2020.
- Clinical stage of locally advanced disease with lymph node positivity (cN+).
- Received neoadjuvant chemoradiotherapy (nCRT) followed by radical esophagectomy.
- Underwent radical esophagectomy with complete three-field lymphadenectomy.

Patients were excluded if they met any of the following conditions:

- Cervical ESCC.
- Co-existing malignancy could confound survival analysis.
- Did not receive concurrent chemoradiotherapy (CCRT);
- Received definitive CCRT without surgery.
- Lacked PET imaging either before or after CCRT.
- Did not undergo complete three-field lymph node dissection.
- Were lost to follow-up or unable to complete treatment due to severe

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adverse events.

3.2 Statistical Analysis

In the derivation cohort, a comprehensive set of clinical, imaging, treatment-related, and pathological variables was collected. These variables were initially categorized as continuous (e.g., age, SUV values, lymph node [LN] counts) or categorical (e.g., smoking status, comorbidities). For continuous variables, optimal cut-off points were determined using Maximally selected rank statistics and subsequently transformed into binary variables for further analysis. Categorical variables were directly assessed through univariable Cox proportional hazards regression, with progression-free survival (PFS) and overall survival (OS) as the primary outcomes.

Variables with a p-value < 0.05 in univariable analysis were selected. A total of 14 prognostic factors were identified and incorporated into the scoring system. For simplicity and clinical applicability, each factor was assigned an equal weight of 1 point, resulting in a 14-point additive scoring model. No additional weighting was applied to individual variables.

To evaluate the relative contribution of each variable to prognosis, the absolute value of the logarithm of the hazard ratio (|log (HR)|) was calculated from the univariable Cox model. This metric provided a quantitative measure of each variable's prognostic impact.

Risk stratification was performed by applying Maximally Selected Rank Statistics to determine the optimal cut-off for total score. Patients were classified into two prognostic groups: low-risk (score ≤ 3) and high-risk (score > 3). Kaplan-Meier survival curves were plotted to evaluate PFS and OS between groups, and survival differences were assessed using the log-rank test.

For validation, the scoring system was applied to an independent cohort. Predictive performance was evaluated using receiver operating characteristic (ROC) curve analysis for 1-year recurrence and mortality, with area under the curve (AUC), sensitivity, specificity, and accuracy reported. Youden's Index was used to determine optimal

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prediction thresholds. The performance of the proposed model was compared against the pathologic-only and image-only system using both ROC metrics and survival analyses.

3.3 Treatment plan

Contrast-enhanced computed tomography (CT) from the neck to the abdomen, endoscopic ultrasonography (EUS), and positron emission tomography/computed tomography (PET/CT) were routinely performed both before treatment and surgery to determine clinical staging and treatment response.

Based on retrospective review of clinical records and initial staging assessments, all patients received concurrent chemoradiotherapy (nCRT) with cisplatin-based chemotherapy regimens. These included paclitaxel plus cisplatin (TP), cetuximab combined with TP (CTP), or cisplatin followed by 5-fluorouracil (PF). Preoperative radiotherapy was administered at a total dose ranging from 40 to 55 Gy (median, 40 Gy), delivered in 1.8–2.0 Gy daily fractions [52].

Post-nCRT evaluations were conducted within 3–4 weeks. Patients considered suitable for surgery based on preoperative assessment underwent curative subtotal esophagectomy, either via the three-hole approach or Ivor Lewis procedure. The surgical approach was selected according to tumor location and surgeon preference, and all procedures were performed within 3 months after the completion of chemoradiotherapy. Consistency was ensured across all operations in terms of operating room setup, surgical team composition, and instrumentation.

Regional lymphadenectomy included dissection of paraesophageal, mediastinal, and perigastric lymph nodes, as well as nodes in the supraclavicular region and along the recurrent laryngeal nerves, in accordance with the standard three-field lymphadenectomy protocol [19]. Additional cervical lymph node dissection was performed when the primary tumor was in the upper third of the thoracic esophagus or when cervical lymph node metastasis was suspected.

Esophageal reconstruction was carried out using either a gastric conduit or colon

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interposition, based on the surgeon's clinical judgment.

All surgical specimens, including resected lymph nodes, were submitted for pathological examination. Pathologists evaluated tumor characteristics, tumor grade, lymphovascular invasion, resection margins, and final staging based on the 8th edition of the American Joint Committee on Cancer (AJCC) guidelines.

Patients were followed up regularly in outpatient clinics or by telephone. Follow-up occurred one month after treatment completion, every three months during the first two years, every six months during years three to five, and annually thereafter until the last follow-up. Follow-up assessments included esophagogastroduodenoscopy (EGD), EUS, and contrast-enhanced CT, based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. If any suspicious findings of recurrence or metastasis were identified during routine evaluations, additional PET/CT and tissue biopsy were arranged to confirm diagnosis.

3.4 18FDG-PET/CT protocol

FDG-PET/CT was performed using a dedicated PET/CT scanner (Discovery LS; GE Healthcare or Biograph LSO; Siemens Medical Systems). Patients with blood glucose levels lower than 6.67 mmol/l (120 mg/dl) were injected intravenously with 7.4 MBq/kg of FDG after fasting for at least 8 h, and then PET/CT scan was performed 60 min after injection. Low-dose non-contrast CT images of 2 to 4 mm sections for attenuation correction and localization of lesions identified by PET were obtained from the skull to the mid-thigh of each patient using a standard protocol. The SUV of a lesion was obtained by manual placement of regions of interest around the lesion, and the most prominent SUV visible in the scanned body (SUVmax) within a region of interest was used to minimize partial-volume effects.

Tumors and LNs were regarded as positive for malignancy or metastasis when the SUV max value was >=2.5 on a PET scan and the size was >=1 cm on a CT scan,following previous studies [43-45].

3.4.1 PET-Based Metabolic Response Definitions

In the present study, we adopted a dual-criteria approach to define PET metabolic

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responders for both the primary tumor and lymph nodes.

PET responder, either for the primary tumor or lymph nodes, was defined as meeting either of the following criteria: (1) a ΔSUV > 70%, or (2) a post-CCRT SUVmax < 2.5 for the corresponding lesion (tumor or lymph node).

These thresholds were selected based on prior evidence. DeYoung et al. (2002) used a post-treatment SUVmax cutoff of 2.5 to identify metabolic responders, reporting a sensitivity of 78% and specificity of 57% in predicting pCR. Additionally, several studies have considered ΔSUV reductions of 70–80% as indicative of favorable treatment response and survival benefit [43, 45].

3.5 Follow-up and definition of recurrence

Patients were followed up every 4–6 months with medical history, physical examination, and chest and abdominal CT scan. Another one FDG-PET/CT was performed to all patients after treatment. Once a recurrence was suspected, patients underwent further workup that included upper endoscopy and biopsy to the suspected site of recurrence.

Recurrence or metastasis was considered when there was an abnormal finding. Diagnosis of recurrence was adjudicated by pathologic confirmation or by findings from other study modalities that led to changes in treatment. Local recurrence was defined as recurrence isolated to the treated esophagus while nodal recurrence was defined as involved nodes in the regional area. Distant recurrence was defined as any spread of disease beyond a locoregional recurrence.

3.7 Overall and recurrence-free survival

OS was defined as the period from the date of esophagectomy to the last contact date. An event was defined as the patient's death; if the patient was alive, it was defined as censored. Progression-free survival was defined as the period from the date of esophagectomy to the date of recurrence or death. If chest CT or PET revealed suspected recurrence and a biopsy revealed malignancy in the esophagus, we defined it as an event. If it showed stability or regression, it was considered censored.

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Chapter 4 Result

4.1 Baseline Characteristics and Cohort Comparability

Table 1 presents the comparative analysis of clinical, imaging, treatment, and pathological variables between the derivation cohort (n = 100) and the validation cohort (n = 91). Overall, the two cohorts showed comparable distributions across most baseline characteristics, with no statistically significant differences in demographic features, treatment modalities, or major pathological outcomes. This balanced distribution supports the internal validity of the model development and validation process.

Most patients were diagnosed with clinically staged T3N2M0, consistent with Stage III locally advanced ESCC. Notably, all cases classified as M1 at diagnosis had resectable cervical lymph node metastases and were considered eligible for neoadjuvant chemoradiotherapy (nCRT) followed by curative-intent surgery. Final pathology revealed one patient with ypT4 disease due to tracheal wall invasion; this case underwent successful en bloc resection with total laryngectomy and tracheal reconstruction, achieving R0 resection with negative margins. Additionally, several patients were intraoperatively diagnosed with distant metastases—such as pulmonary nodules or residual cervical lymphadenopathy—and were classified as ypM1 based on postoperative pathology. These cases reflect the challenge of staging accuracy in borderline-resectable ESCC and highlight the importance of combining PET/CT imaging with surgical-pathological correlation.

Among baseline variables, a few imaging-related factors showed statistically significant differences between cohorts, including pre-treatment tumor SUVmax, post-treatment tumor SUVmax, and ΔSUV (all $p < 0.05$), as well as the number of dissected lymph nodes and nodal stations (both $p < 0.05$). These discrepancies likely stem from variations in imaging protocols or tumor metabolic heterogeneity, rather than selection bias. In contrast, factors such as age, sex, ECOG status, body weight change, surgical approach, ypTNM stage, resection margin status, and lymphovascular invasion (LVI) did not differ significantly, underscoring the comparability of the two groups and reinforcing the robustness of our validation strategy.

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4.2 Prognostic Variable Selection and Impact in the Derivation Cohort

To identify independent predictors of progression-free survival (PFS) and overall survival (OS), we analyzed a total of 48 candidate variables from four major domains: patient-related, imaging-related, treatment-related, and pathology-related factors. Selection was performed using univariable Cox proportional hazards regression in the derivation cohort (n = 100), followed by ranking of prognostic impact using |log(HR)|. The complete results of univariable Cox regression used for variable selection in prognostic model development are presented in the Appendix.

4.2.1 Patient-Related Factors

Patient-level factors included age, comorbidities, nutrition status at diagnosis, alcohol consumption, and smoking status. Alcohol use and BW loss were significantly associated with poorer OS, while current smoking status was notably linked to inferior PFS. Although these lifestyle variables are not newly identified predictors, their consistent association with prognosis in this study reinforces their relevance even in the context of modern multimodal treatment for ESCC.

4.2.2 Imaging-Related Factors

PET/CT imaging variables were subdivided into main tumor activity and lymph node (LN) characteristics, and were extracted based on:

1. Response category (PET responder or not)
2. SUVmax values pre- and post-nCRT
3. Anatomical location of tumor or LN

Figure 2 shows a pair of PET/CT images of the same patient taken before and after neoadjuvant chemoradiotherapy (nCRT), demonstrating complete metabolic response (CMR). Pre-NT PET/CT (left row) shows increased FDG uptake in the primary esophageal tumor and multiple regional lymph nodes. Post-NT PET/CT (right row) reveals resolution of FDG avidity, suggesting a favorable metabolic response. This case illustrates the visual intuitiveness and practical utility of PET/CT in assessing metabolic complete response (CMR) following neoadjuvant chemoradiotherapy.

Post-nCRT SUVmax of the primary tumor (cutoff: 7.5) was significantly associated with both OS and PFS. LN-specific imaging variables, including pre-nCRT SUVmax

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≥6 and the presence of PET-defined abdominal LNM, showed independent associations with poor OS. Meanwhile, failure of metabolic LN response post-nCRT and PET-positive abdominal LNM significantly predicted inferior PFS.

4.2.3 Treatment-Related Factors

Evaluated parameters included radiotherapy dose (<45 Gy vs. ≥45 Gy), chemotherapy regimen, surgical type (three-field vs. Ivor Lewis), and use of adjuvant CCRT. Among these, only adjuvant therapy was significantly associated with OS benefit (HR = 1.80, p = 0.028). Neoadjuvant protocol variations showed minimal survival influence, reflecting protocol consistency within our institution.

4.2.4 Pathology-Related Factors

As expected, several pathological factors were strong predictors for survival. These included:

- Incomplete tumor response
- Residual nodal metastasis (ypN+)
- Presence of distant metastasis (ypM1)
- Lymphovascular invasion (LVI)
- Positive or unclear resection margins
- Unexpected LNM (defined as PET-negative but pathology-positive nodes)

Due to patient selection focusing on more advanced LAESCC cases, clinical TNM staging (cTNM, ycTNM) failed to stratify prognosis after nCRT and surgery. However, distinct prognostic subgroups were still identifiable within this high-risk cohort, whereas pathological TNM (ypT, ypN, ypM) remained highly significant. This supports the rationale for including only pathological staging in our scoring system.

LN burden was further quantified using LN index (nodes × station), which theoretically reflects the depth and extent of nodal dissection. However, no significant prognostic difference was observed in our cohort, likely due to the uniformly high quality of lymph node dissection performed at our institution, where extensive three-field esophagectomy is standard practice.

4.2.5 Continuous Variable Cutoff Analysis

We used maximally selected rank statistics to determine optimal thresholds(Table 2.).

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The following variables were significant in continuous analysis:

- OS: pre-nCRT LNM station number (cutoff ≥2), pre-nCRT LN SUVmax (≥6.1), post-nCRT tumor SUVmax (≥7.3), and post-nCRT LN SUVmax (≥2.2)
- PFS: post-nCRT tumor SUVmax (≥7.4) and ΔSUV ratio of tumor (cutoff 0.54)

Although pre-nCRT LNM station number and ΔSUV ratio of tumor were significant in continuous variable analysis, they did not retain statistical significance in the final Cox regression model and were therefore excluded from the final scoring system. Main tumor SUVmax showed significance only post-treatment, while LNM metrics retained prognostic value both pre- and post-nCRT.

4.2.6 Ranking of Prognostic Factors by Effect Size

Ranking of prognostic impact using |log(HR)| was in Table 3, which summarizes the top prognostic factors for overall survival (OS) and progression-free survival (PFS) based on univariable Cox regression analysis in the derivation cohort (n = 100). Prognostic variables were ranked by the absolute value of their log hazard ratios (|log(HR)|), reflecting their relative predictive strength. The variables are visually grouped into color-coded domains: pathology-related (green), clinical-related (blue), and imaging-related (orange).

This visual grouping facilitates a clearer understanding of the contributions from different clinical domains to overall prognosis. Notably, pathological variables such as incomplete tumor response, unexpected lymph node metastasis, resection margin status, and distant metastasis consistently ranked among the top predictors of both OS and PFS, highlighting their dominant prognostic weight in this cohort. Moderate predictors included PET-defined tumor SUVmax ≥7.5, PET-positive abdominal LNM, and patient factors such as alcohol use and BW loss.

4.3 Set up PRIME Scoring System

Based on these analyses, we established a 14-point additive scoring system—the PRIME (PET-based Risk stratification Integrating Multidomain Evaluation) Score—integrating clinical, imaging, and pathological predictors (Table 4.). Each variable contributed one point to balance usability and clinical relevance. We chose not to construct a nomogram due to the wide diversity of included variable types and the goal of maximizing bedside usability. The scoring system prioritizes simplicity and

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interpretability, allowing clinicians to quickly assess risk without the need for complex statistical tools or digital platforms.

Each 1-point increase in the prognostic score was associated with a 43% higher risk of recurrence (HR = 1.43, 95% CI 1.25–1.64, $p < 0.001$) and a 46% higher risk of death (HR = 1.46, 95% CI 1.30–1.64, $p < 0.001$). These findings support the robust predictive value of the PRIME scoring system in identifying patients at high risk for recurrence and mortality after nCRT and surgery.

4.3.1 Risk Stratification Based on PRIME Score

Using a cutoff score of 3, determined through maximally selected rank statistics based on survival distribution, patients were stratified into low-risk (score ≤3) and high-risk (score >3) groups.

Kaplan-Meier survival analysis demonstrated significant survival differences between these two groups. For progression-free survival (PFS), the 1-year survival rate was 82.7% in the low-risk group vs. 34.6% in the high-risk group, and the 5-year survival rate was 47.1% vs. 15.6%, respectively. Similarly, for overall survival (OS), 1-year survival was 85.7% in the low-risk group vs. 35.3% in the high-risk group, and 5-year survival was 47.3% vs. 7.8%, respectively. (Figure 3.)

KM curves further illustrated the clear prognostic separation between risk groups. Despite prior findings that clinical TNM staging lacked discriminative value in this post-nCRT population, our risk model was able to uncover meaningful prognostic stratification within this high-risk cohort.

4.4 Validation of the PRIME Scoring System and Comparative Prognostic Performance

The prognostic performance of the PRIME scoring system was externally validated using an independent cohort (n = 91). Receiver operating characteristic (ROC) curve analyses were conducted to assess its accuracy in predicting 1-year progression-free survival (PFS) and overall survival (OS).

As illustrated in Figure 4 (top panels), the PRIME scoring system demonstrated favorable predictive capability, with an AUC of 0.734 for 1-year OS and 0.721 for 1-year PFS. The model also achieved the highest accuracy (76.9% for OS and 71.4% for PFS), supporting its value as a continuous scoring model for individualized prognostic

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estimation.
In contrast, the pathological-only model (middle panels) exhibited relatively strong predictive power (AUC = 0.712 for both OS and PFS), yet slightly lower accuracy than the full PRIME score. The imaging-only model (bottom panels) showed moderate performance, particularly in OS prediction (AUC = 0.619), and notably low specificity. These comparative findings are consistent with the prognostic factor ranking shown in Table 3, where pathological features held a stronger univariable impact than imaging alone.

Together, these results confirm the robustness of the PRIME scoring system, which outperformed individual-domain models in prognostic discrimination. Although pathological features remain clinically valuable, the integrated PRIME model offers superior overall performance, particularly when precise, patient-specific risk stratification is needed to guide postoperative surveillance and adjuvant therapy planning.

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Chapter 5. Discussion

5.1 Pathologic Complete Response (pCR) Rate in Comparison with Previous Studies

Pathological complete response (pCR) following neoadjuvant chemoradiotherapy (nCRT) is a well-recognized surrogate marker for improved long-term survival in esophageal cancer. In the landmark CROSS trial, which included both squamous cell carcinoma (SCC) and adenocarcinoma patients, the overall pCR rate was reported at 29%[4]. However, histological subtypes have been shown to influence treatment response, with ESCC typically demonstrating higher sensitivity to chemoradiation compared to adenocarcinoma.

Multiple surgical series focusing on ESCC have reported pCR rates ranging from approximately 17% to 40%, with most studies indicating an average around 30%[53-56]. These variations likely reflect differences in study design, chemotherapy regimens, radiation dose, tumor burden, and histopathological definitions across institutions.

In our PRIME study cohort, a pCR was achieved in 63 of 191 patients (33%), aligning closely with previously reported rates for ESCC. This consistency supports the validity of our population and treatment protocol and also suggests that our cohort is representative of real-world clinical outcomes in ESCC patients receiving standard nCRT.

Moreover, the comparable pCR rate reinforces the applicability of our prognostic scoring model to broader clinical practice, as it was developed based on treatment responses that mirror those observed in prior high-quality studies. Given that pCR is associated with significantly better survival outcomes, its inclusion as a variable in clinical decision-making tools and prognostic models remains essential.

5.2 Overall Survival, Progression-Free Survival, and Recurrence Rate in Comparison with Previous Studies

Our cohort represents a high-risk population that is often underrepresented in clinical trials. The CROSS trial reported a 5-year overall survival (OS) rate of 47% in the

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neoadjuvant chemoradiotherapy (nCRT) plus surgery arm [4], a figure that falls between the OS observed in our two prognostic subgroups (63.6% in the low-risk group vs. 32.9% in the high-risk group; Fig. 3). Notably, only 23% of patients in the CROSS trial had squamous cell carcinoma, with the majority having adenocarcinoma [4]. In addition, patients with advanced nodal disease (cN2–3) were underrepresented. These differences in histological subtype and baseline nodal burden limit direct comparability with our cohort but underscore how highly selective inclusion criteria can yield more favorable outcomes that may not reflect real-world ESCC populations.

Similarly, the NEOCRTEC5010 trial reported a median OS of 100.1 months in the nCRT plus surgery group; however, the trial excluded cN2–3 patients and included only T1–T4a, N0–1, M0 ESCC cases with good performance status [5]. In contrast, our cohort focused exclusively on patients with clinically evident lymph node metastases. The median OS was 45 months in the low-risk group and only 17 months in the high-risk group, highlighting the substantial survival gap between prognostic strata.

While our study cohort included only patients with clinically node-positive (cN^+) locally advanced ESCC, comparison with large-scale trials remains complex. For instance, the CROSS trial primarily enrolled adenocarcinoma patients [4], while the NEOCRTEC5010 trial—though limited to SCC—had milder nodal disease (mostly cN1 vs. our predominantly cN2) [5]. Furthermore, differences in neoadjuvant chemotherapy regimens and imaging availability (e.g., PET/CT) between institutions could have influenced clinical staging accuracy. In contrast, our institution's standardized three-field lymphadenectomy protocol, especially in the cervical and upper mediastinum, may have improved the accuracy of pathologic nodal staging. Taken together, these factors suggest that the survival outcomes observed in our cohort more accurately reflect the real-world clinical complexity and risk burden encountered in daily thoracic oncology practice.

These findings reinforce the prognostic heterogeneity among clinically node-positive ESCC patients and emphasize the value of our scoring system in identifying high-risk individuals who may benefit from intensified postoperative monitoring or adjuvant strategies.

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Subsequent analyses from the same NEOCRTEC5010 trial further emphasized the prognostic importance of nodal status [57]. That study reported that patients with pathologically confirmed lymph node metastasis (ypN^{+}) had significantly worse outcomes, with 3-year OS and DFS rates of 52.3% and 43.9%, respectively, compared to 88.5% and 85.8% in ypN0 patients. Hazard ratios for OS and DFS exceeded 4.5 and 5.2, underscoring the aggressive biology of residual nodal disease [57].
Our findings are consistent with these observations. Among our cohort, 75 patients were found to have ypN^{+} status after surgery, and their 3- year recurrence rate was 52% (39/75), closely mirroring recurrence data from the NEOCRTEC5010 trial [5].
Swisher et al. (2005) also observed that patients with complete response of the primary tumor but persistent nodal metastasis (ypN^{+}) remained at high risk for recurrence and mortality, reaffirming that ypN^{+} status is a major prognostic determinant regardless of primary tumor regression [58]. Among such high-risk patients, those with residual ypN^{+} disease had significantly poorer DFS and OS.

Many large trials include highly selective, lower-risk cohorts, the PRIME study reflects real-world clinical practice, and the prognostic challenges associated with high-risk ESCC. The observed OS and PFS in our study, though lower, are expected and justifiable based on this advanced disease profile.

5.3 Prognostic Performance and Limitations of PET-Derived Variables

In this study, we extensively evaluated the prognostic value of PET/CT imaging in patients with locally advanced ESCC who underwent nCRT followed by surgery. While PET has demonstrated considerable utility in treatment planning and staging, its prognostic role—particularly post-treatment—presents notable limitations.
We analyzed the diagnostic performance of post-nCRT PET/CT in predicting pathologic complete response (pCR). In the derivation cohort (N=100), 35 patients achieved tumor pCR, yet only 6 of them (17.1%) were PET tumor responders, yielding a high false-negative rate of 82.9% and a specificity of just 36.36%. The overall accuracy for predicting tumor pCR using PET was 32.08%. For lymph node pCR, PET accuracy was slightly better: 22 of 54 patients (40.7%) who achieved nodal pCR were

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correctly identified as PET LN responders, yielding a false-negative rate of 59.3%, specificity of 66.67%, and accuracy of 50.57%.

Compared to Karashima et al. (2015), who reported a nodal PPV of 84.2% and specificity of 98.7%, our study's lower PPV (66.7%) and specificity may reflect differences in patient selection and analytical design[39]. In Karashima's cohort, 67% of patients did not receive nCRT, reducing treatment-related inflammation, and they used a station-by-station analysis, whereas our study adopted a holistic, patient-based approach. This may better capture overall nodal burden but introduces variability from post-treatment metabolic changes.

Importantly, even among patients who achieved both PET and pathological complete nodal response (LN PET responder + LN-PCR), recurrence remained a concern: 4 of 22 patients (18.2%) experienced recurrence within one year postoperatively. This highlights the residual risk of disease progression even in seemingly favorable subgroups.

Taken together, these results suggest that no single PET-derived parameter—whether based on response, SUVmax, or nodal station count—can independently and reliably predict survival outcomes in this high-risk ESCC cohort. The limitations in sensitivity, specificity, and predictive accuracy underscore the need for multimodal prognostic models.

Thus, our study combines clinical, imaging, and pathological factors to enhance decision-making accuracy.

5.4 Number of PET-positive nodal stations with potential prognostic value

Although the number of PET-positive lymph node stations before neoadjuvant therapy (pre-NT PET LNM stations) was not statistically significant in univariable Cox regression during variable selection for the prognostic model, cutoff-based survival analysis did reveal a significant association with clinical outcomes ($p = 0.013$). Specifically, patients with ≥3 PET-positive nodal stations demonstrated markedly worse survival, with 5-year PFS of 18.4% and OS of 16.1%, suggesting a high-risk subgroup. Much lower than large trials such as CROSS and NEOCRTEC5010 have reported 5-year OS rates around 47–60% in the general ESCC population receiving nCRT followed by surgery [4, 5].

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This clinical observation is supported by findings from Miyata et al. (2016), who reported that patients with three or more PET-positive lymph nodes had nearly 0% five-year overall survival [48], and confirmed the number of PET-positive nodes as an independent predictor of prognosis. While this parameter did not enter our multivariable model due to statistical thresholds, its clinical relevance remains evident, and such PET-based nodal burden metrics may still hold additive prognostic value when considered alongside other risk factors.

These results reinforce the notion that PET-derived nodal characteristics, including both activity and spatial extent, may offer valuable prognostic information, especially in prospective cohorts.

5.5 Comparative Prognostic Performance of the PRIME Score, Pathologic-only system and AJCC Staging

In the validation cohort, the PRIME scoring system demonstrated superior prognostic accuracy compared to both the conventional AJCC ypTNM staging system and a pathology-only scoring system.

For predicting 1-year overall survival (OS), the PRIME system achieved an AUC of 0.734, with an accuracy of 76.9% and sensitivity of 88.7%, outperforming the AJCC system, which yielded an AUC of 0.718, accuracy of 64.8%, and sensitivity of 79.6%. Similar trends were observed for 1-year progression-free survival (PFS), where the PRIME system achieved an AUC of 0.721, accuracy of 71.4%, and sensitivity of 88.9%. In contrast, the AJCC system showed slightly lower performance across all metrics. These findings align with previous studies such as Sudo et al. (2021), which reported a concordance index (C-index) of 0.64 for OS using the 8th edition AJCC system [59].

In comparison to the pathology-only model developed in our study, PRIME still showed enhanced prognostic capability. Although the pathology-based model achieved similar AUCs (0.712 for both OS and PFS), its accuracy (65.9% for OS, 68.1% for PFS) and sensitivity (55.0% for OS, 74.1% for PFS) were consistently lower than those of the integrated PRIME score. These differences suggest that while pathological variables remain important, their predictive power alone is insufficient for optimal risk

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stratification.

Notably, the PRIME model consistently demonstrated better specificity across both endpoints, which enhances its clinical discriminatory power. This improvement likely stems from PRIME's multidimensional structure providing a more comprehensive reflection of tumor biology and therapeutic effect than AJCC staging, which was originally developed for patients treated with surgery alone.

Collectively, these results support the PRIME scoring system as a more robust and clinically applicable prognostic tool for patients undergoing nCRT followed by surgery. It holds promise for improving individualized postoperative risk assessment and guiding decisions regarding adjuvant therapy and surveillance strategies.

5.6 From Traditional Staging to Multidimensional Prognostic Models: Insights from the PRIME Cohort

With neoadjuvant chemoradiotherapy (nCRT) followed by surgery now standard for locally advanced esophageal squamous cell carcinoma (ESCC), accurate postoperative risk stratification has become a clinical priority. However, traditional indicators such as AJCC TNM staging and pathological complete response (pCR) show limited predictive value in this population.

Deng et al. (2017) developed a nomogram incorporating clinical and pathological variables, stratifying patients into four risk groups. Although the model (C-index: 0.67) outperformed TNM staging, its moderate accuracy highlighted the need for further improvement [51]. Similarly, Zhang et al. (2023) reported a C-index of 0.763 using preoperative PET/CT parameters in a cohort without neoadjuvant therapy, composed largely of early-stage and favorable-risk patients [18].

Our PRIME cohort focused exclusively on high-risk patients with clinically node-positive (cN^+) LAESCC who underwent nCRT and curative surgery—a group underrepresented in prior studies and with greater biological heterogeneity. The superior performance of PRIME in this context reflects its design, which integrates clinical, pathological, and imaging-derived markers.

Importantly, while models such as Zhang’s achieved higher statistical indices, the PRIME system was designed with clinical usability in mind. Its simple additive

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structure avoids the complexity of nomogram-based scoring tools, which often require web-based or statistical interfaces. By prioritizing bedside applicability and retaining prognostic precision, PRIME addresses a critical gap in personalized postoperative management for high-risk ESCC patients.

5.7 Incorporating Emerging Biomarkers and Advanced Imaging Analytics

Recent advances in oncology have brought forward a new wave of prognostic tools aimed at enhancing recurrence and survival prediction in esophageal squamous cell carcinoma (ESCC). Two notable frontiers include circulating tumor DNA (ctDNA) analysis and radiomics-based PET/CT assessment.

On one hand, ctDNA has emerged as a promising non-invasive biomarker to detect minimal residual disease (MRD) following neoadjuvant chemoradiotherapy (nCRT). A recent prospective study in ESCC showed that post-nCRT ctDNA-positive patients had a recurrence rate of 77.8%, compared to 27.8% in ctDNA-negative patients, with significantly worse recurrence-free survival (HR 4.56, $P = 0.01$) [60]. These findings underscore ctDNA's ability to detect occult disease earlier and more accurately than imaging or pathology.

Given that ctDNA can reflect whole-body tumor burden, its addition could further improve risk stratification beyond the capabilities of localized imaging and pathology. However, clinical translation remains limited by technical sensitivity, lack of standardization, and accessibility constraints in routine practice.

On the other hand, radiomics—the extraction of high-dimensional features from medical imaging—has been applied to preoperative PET/CT scans to improve prediction of lymph node metastasis. In one study, a radiomics-integrated model combining clinical and PET features achieved an AUC of up to 0.82 in the development cohort. However, its performance declined in the external validation cohort (AUC = 0.69), indicating limited generalizability and the need for population-specific calibration before clinical deployment [61].

While these emerging technologies offer innovative perspectives, no consensus yet exists on a robust, generalizable, and clinically applicable prognostic framework. Looking ahead, our model may serve as a foundation for further enhancement through integration with AI-assisted PET/CT analytics, volumetric indices such as total lesion

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glycolysis (TLG), metabolic tumor length (MTL) and width (MTW), or even future liquid biopsy technologies like ctDNA. Additionally, with the evolving role of neoadjuvant immunotherapy in ESCC, further studies are warranted to assess whether immunological or molecular parameters can complement or refine current imaging-based risk models.

Ultimately, multicenter collaborations with larger sample sizes and harmonized data acquisition protocols will be essential to validate and evolve prognostic systems that balance sophistication with clinical practicality.

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Chapter 6. Limitations

This study has several limitations that should be acknowledged. First, the sample size was relatively small, particularly for a prognostic modeling study, which may limit the statistical power and generalizability of the findings. Additionally, our validation focused only on the prediction of 1-year progression-free survival (PFS) and overall survival (OS). Future studies should expand the follow-up duration to evaluate the model's performance for 3-year and 5-year outcomes to ensure its long-term applicability.

Second, although our PRIME scoring system demonstrated superior prognostic accuracy then other current model, PET-based parameters in our study showed limited sensitivity and specificity. The integration of artificial intelligence (AI) to assist in PET/CT interpretation, especially via radiomics feature extraction—may enhance the imaging component's contribution to prognosis.

Third, this was a single-center retrospective study conducted at a tertiary medical center with advanced surgical protocols, which may introduce selection bias and limit the external validity of our findings. Multicenter prospective validation is warranted to confirm the model's generalizability across different clinical settings.

Finally, while the PRIME score incorporates multidimensional clinicopathological and imaging features, it does not include molecular or circulating biomarkers such as ctDNA, which have shown promise in detecting minimal residual disease and refining risk stratification. Future studies may benefit from integrating such biomarkers to further enhance prognostic accuracy.

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Chapter 7. Conclusion

In this study, we developed and validated a novel prognostic scoring system for patients with locally advanced esophageal squamous cell carcinoma (ESCC) undergoing neoadjuvant chemoradiotherapy followed by surgery.

The PRIME model, which integrates clinical, imaging and pathological variables, demonstrated robust predictive accuracy and outperformed conventional staging systems.

Its simplicity and bedside applicability support its potential utility in guiding postoperative surveillance and adjuvant therapy decisions.

Future prospective and multicenter studies are warranted to confirm its external validity, and integration with emerging tools such as ctDNA analysis and radiomics may further enhance its prognostic performance in personalized ESCC care.

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Appendix.

Univariable Cox Regression for Variable Selection in Prognostic Model (Derivation Cohort)

			HR (univariable)	
Patient-related factors		n(%)	PFS	OS
sex	female	11 (11.0)	-	-
	male	89 (89.0)	3.15 (0.98-10.14, p=0.054)	2.20 (0.95-5.09, p=0.065)
age >=70	<70 y/o	91 (91.0)	-	-
	>=70 y/o	9 (9.0)	1.36 (0.48-3.82, p=0.562)	2.23 (1.08-4.59, p=0.030)
ECOG	0-1	79 (79.0)	-	-
	>=2	21 (21.0)	1.48 (0.76-2.89, p=0.249)	1.57 (0.91-2.68, p=0.102)
BW loss	no	40 (40.0)	-	-
	yes	60 (60.0)	1.80 (1.01-3.22, p=0.046)	1.93 (1.19-3.13, p=0.008)
Comorbidity	no	90 (90.0)	-	-
	yes	10 (10.0)	0.84 (0.26-2.71, p=0.773)	1.83 (0.88-3.82, p=0.108)
Ever smoker	yes	89 (89.0)	-	-
	no	11 (11.0)	0.41 (0.13-1.33, p=0.139)	0.53 (0.23-1.22, p=0.136)
Current smoker	no	65 (65.0)	-	-
	yes	35 (35.0)	2.22 (1.28-3.87, p=0.005)	1.52 (0.95-2.42, p=0.078)
Alcohol	no	19 (19.0)	-	-
	yes	81 (81.0)	1.81 (0.85-3.85, p=0.126)	2.27 (1.16-4.44, p=0.016)
Betel nuts user	no	57 (57.0)	-	-
	yes	43 (43.0)	1.40 (0.81-2.43, p=0.231)	1.40 (0.89-2.22, p=0.147)
Imaging-related factors				
Main tumor activity				
PET tumor responder	no response	13 (13.0)	-	-
	responder	87 (87.0)	1.08 (0.46-2.52, p=0.866)	1.13 (0.58-2.22, p=0.714)
post-NT tumor SUVmax >=7.5	1	42 (42.0)	-	-
	0	58 (58.0)	0.45 (0.26-0.79, p=0.005)	0.49 (0.31-0.77, p=0.002)
LNM activity				
PET N reponse	no response	33 (33.0)	-	-
	responder	67 (67.0)	1.67 (0.90-3.09, p=0.104)	1.92 (1.14-3.22, p=0.014)
preNT LN SUVmax >=6:1	1	63 (63.0)	-	-
	0	37 (37.0)	0.59 (0.32-1.07, p=0.080)	0.52 (0.32-0.86, p=0.011)
preNT LNM (station)>=3		0 12 (57.1)	-	-
		1 9 (42.9)	3.05 (0.83-11.24, p=0.094)	2.22 (0.66-7.48, p=0.198)
Location				
Main tumor location	other site	38 (38.0)	-	-
	M/3	62 (62.0)	1.51 (0.84-2.73, p=0.171)	1.23 (0.77-1.98, p=0.387)
LNM by JEOG classification	reginal	64 (64.0)	-	-
	nonregional	36 (36.0)	0.68 (0.38-1.23, p=0.204)	0.81 (0.51-1.31, p=0.398)
preNT Abd-LNM	no	70 (70.0)	-	-
	yes	30 (30.0)	1.86 (1.05-3.31, p=0.034)	1.73 (1.08-2.79, p=0.023)
Treatment-related factors				
NRT does(cutpoint 45Gy)	0	90 (90.0)	-	-
	1	10 (10.0)	1.20 (0.51-2.82, p=0.677)	1.20 (0.57-2.50, p=0.634)
op method	3 site	81 (81.0)	-	-
	ivor-lewis	19 (19.0)	1.30 (0.63-2.67, p=0.482)	1.65 (0.95-2.88, p=0.078)
post op CCRT	no	79 (79.0)	-	-
	yes	21 (21.0)	2.12 (1.15-3.90, p=0.016)	1.80 (1.06-3.03, p=0.028)
Pathology paramters				
Tumor CR	0	34 (34.0)	-	-
	1	66 (66.0)	4.81 (2.32-9.96, p<0.001)	3.90 (2.22-6.84, p<0.001)
Resection margin	0	76 (76.0)	-	-
	1	24 (24.0)	3.02 (1.62-5.64, p=0.001)	2.56 (1.54-4.26, p<0.001)
LVI	0	72 (72.0)	-	-
	1	28 (28.0)	2.46 (1.37-4.41, p=0.003)	2.54 (1.56-4.13, p<0.001)

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unexpected LNM	no	63 (86.3)	-	
	yes	10 (13.7)	3.26 (1.48-7.18, p=0.003)	2.33 (1.17-4.63, p=0.016)
AJCC TNM staging system				
cT	0~2		-	-
	3~4		1.26 (0.54-2.97, p=0.591)	1.37 (0.66-2.87, p=0.401)
cN	1	68	-	
	2~3	32	0.88 (0.48-1.61, p=0.677)	1.08 (0.66-1.76, p=0.761)
cM	0	95 (95.0)	-	-
	1	5 (5.0)	0.73 (0.27-2.00, p=0.544)	0.69 (0.30-1.56, p=0.372)
cyT	0~2	80 (80.0)	-	-
	3~4	20 (20.0)	0.89 (0.44-1.77, p=0.732)	0.85 (0.47-1.52, p=0.574)
ycN	>=1	77 (77.0)	-	-
	0	23 (23.0)	0.79 (0.38-1.61, p=0.512)	1.01 (0.58-1.77, p=0.965)
ycM	0	99 (99.0)	-	-
	1a	1 (1.0)	0.00 (0.00-Inf, p=0.996)	0.00 (0.00-Inf, p=0.995)
ypT	0	34 (34.0)	-	-
	>=1	66 (66.0)	4.81 (2.32-9.96, p<0.001)	3.90 (2.22-6.84, p<0.001)
ypN>=1	>=1	46 (46.0)	-	-
	0	54 (54.0)	0.49 (0.28-0.86, p=0.013)	0.31 (0.19-0.51, p<0.001)
ypM	0	95 (95.0)	-	-
	1	5 (5.0)	2.74 (1.16-6.44, p=0.021)	2.75 (1.41-5.36, p=0.003)

* Abbreviations are defined below

*Abbreviations	
LNM	Lymph node metastasis
pre-NT	pre-neoadjuvant CCRT treatment
post-NT	post-neoadjuvant CCRT treatment
ΔSUV	pre-neoadjuvant CCRT SUVmax - post-neoadjuvant CCRT SUVmax
ΔSUV ratio	ΔSUV /pre-neoadjuvant CCRT SUVmax
PET tumor responder	complete remision of main tumor on post-neoadjuvant CCRT PET image
PET LNM responder	complete remision of LNM on post-neoadjuvant CCRT PET image
preT Abd-LNM	pre-neoadjuvant CCRT PET image shows positive abdominal LNM
nRT dose	neoadjuvant radiotherapy dose(Gy)
nCT regiment	neoadjuvant chemotherapy regmiment
TRG	Tumor Regression Grading system by Becker et al., 2003
LVI	Lymphovascular Invasion
LN index	node × station
unexpected LNM	unexpected LNM found in final pathology but without any signs of LNM in pre-neoadjuvant CCRT PET image

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