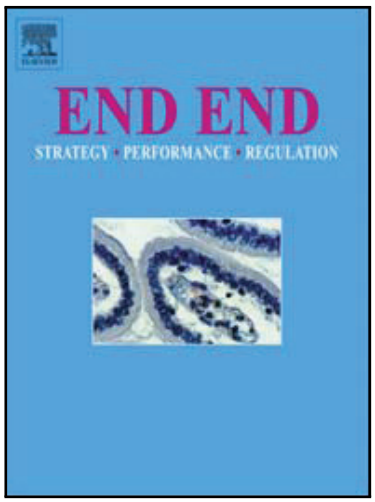

7th vs 8th edition of AJCC staging system: any improvement for patients with squamous cell carcinoma of the tongue?

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7th vs 8th edition of AJCC staging system: any improvement for patients with squamous cell carcinoma of the tongue?

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Running title.

New AJCC staging system in patients with tongue squamous cell carcinoma.

ABSTRACT

Objective. In this study we evaluate the 8th edition of American Joint Committee on Cancer (AJCC) staging criteria and lymph node ratio (LNR) to identify patients affected by squamous cell carcinoma of the tongue (SCCT) with worse prognosis.

Study Design. 73 patients with SCCT were analyzed retrospectively. Tumors staging was revised according to 7th and 8th editions of AJCC. Depth of invasion (DOI), extranodal extension (ENE), and LNR were evaluated.

Results. 25 patients were reclassified: 17 received an upstage in staging score, 8 changed pT or pN remaining in the same stage group. In pT upstaged group, 7 patients experienced recurrence and 8 died. In pN upstaged group, 9 patients developed recurrence and 10 died. The number of disease recurrence or death was higher in the groups who received an upstage in pN and in staging score ($P<0.05$). pN upstaged group showed worse disease-free survival (DFS) and overall survival (OS) ($P<0.05$). LNR was higher in patients with recurrence, and among these LNR was lower in patients with ENE ($P<0.05$).

Conclusions. The 8th edition of AJCC allows a better stratification of SCCT patients. The implementation of ENE and LNR to pN classification seems to identify patients with worse DFS and OS.

Keywords.

American Joint Committee on Cancer (AJCC); Tongue neoplasms; Depth of invasion; Extranodal extension; Lymph node ratio.

INTRODUCTION

Squamous cell carcinoma of the tongue (SCCT) is one of the most common types of head and neck cancers, comprises about 50% of the squamous cell carcinoma of the oral cavity (OSCC) [1]. Although the affected patients are typically males over the sixth decade of life with strong tobacco and alcohol history, there is a general increase in the incidence of SCCT in females and younger patients, especially in some regions of the World [2]. Furthermore, some investigations revealed that SCCT occur at younger age than cancers of any other subsites of the oral cavity [3]. This tumor is characterized by an aggressive clinical behavior, with high invasive capacity, early metastasis, and poor prognosis, showing a 5-year survival rate of around 60% [4]. Unlike late-stage SCCTs, early-stage tumors show favorable prognosis [5], although is reportedly poorer than that of early-stage cancers of other subsites of the oral cavity [6]. The unchanging survival in patients with SCCT underscores the need for better prognostic tools. One strategy is to analyze the lymph node ratio (LNR), defined as the proportion of metastatic lymph nodes related to the total number of examined

nodes, since the presence of lymph node metastases is the main determinant of poor prognosis in patients with OSCC [7].

Another way is to improve the staging system, in order to improve patient stratification. To achieve this purpose, the American Joint Committee on Cancer (AJCC) published in 2016 the 8th edition of the cancer staging manual. There are significant changes in staging system of OSCC, including the incorporation of two new parameters: depth of invasion (DOI) and extranodal extension (ENE). Patients with DOI of 5 mm or less in tumors less than 2 cm are staged as pT1, patients with DOI between 5 and 10 mm in tumors less than 2 cm or with DOI less than 10 mm in tumors less than 4 cm are staged as pT2, and patients with DOI greater than 10 mm or tumors greater than 4 cm are staged as pT3. Regarding the lymph node involvement, the presence of ENE (ENE+) in a single ipsilateral node less than 3 cm classified the patients as having pN2a, while ENE+ in a single ipsilateral node larger than 3 cm or in multiple nodes classified the patients as having pN3b [8].

Another important aspect is the determination of the cut-off values for ENE. The presence of ENE less than 2 mm defines the status of microscopic ENE (ENE_{mi}), while macroscopic ENE (ENE_{ma}) is defined by the presence of ENE greater than 2 mm beyond the lymph node capsule. Only ENE_{ma} is used to ascertain ENE+ nodal status [8]. Furthermore, as clearly stated by the 8th edition, the infiltration of the extrinsic muscles of the tongue is no longer a criterion for pT4a status, due to difficulties in the assessment of this parameter [8].

The aim of this study is to evaluate the 8th edition AJCC staging criteria in a cohort of patients with SCCT, and to find out prognostic differences between the 7th and 8th edition of AJCC staging system. Furthermore, the prognostic value of LNR was investigated in SCCT patients with lymph node metastases.

MATERIAL AND METHODS

Case selection and histopathologic evaluation

The present retrospective study considered 73 patients surgically treated for SCCT at Department of Maxillofacial Surgery, “Ospedali Riuniti” General Hospital, Ancona, Italy, between 2011 and 2016.

All patients underwent to lateral neck dissection involving surgical clearance of at least levels I-IV. All patients considered were HPV-negative cases. HPV status was analyzed retrospectively using HPV 16-specific fluorescence in situ hybridization and $p16^{Ink4a}$-specific immunohistochemistry. Clinical and radiological data were obtained from each patient's medical record, and pathological data were retrieved from the archives of the Sections of Pathology, Marche Polytechnic University, Italy, by a single operator, to ensure uniformity of the collected data.

All patients were treated for curative intent by the same surgical team, and had postoperative follow-up every month for the first year, every 2 months during the second year, every 3 months during the third year, and every 6 months thereafter. If patient had symptoms or signs of suspected recurrence, an immediate postoperative visit was performed. At least 6 months of follow-up was required for inclusion in this study.

The pT and pN classification were revised by two expert pathologists (C.R. and F.D.M.) based on the 7th and 8th editions of the AJCC cancer staging manual. For assessment of pN, a minimum of 10 lymph nodes were examined. Due to the paucity of patients with lymph node metastases, we pooled pN2 and pN3 cases without distinguishing among pN2a, pN2b, pN2c, pN3a, and pN3b. The DOI was measured from the basement membrane through the deepest point of tumor invasion based on the 8th edition. Multiple sections were studied to identify the deepest point of invasion. The status of ENE+ was considered only in those cases that showed ENE_{ma}; therefore, ENE_{mi} was considered as ENE-. Furthermore, LNR was evaluated as an additional factor for estimating prognosis in SCCT patients with lymph node involvement. LNR is defined as the proportion of metastatic nodes to the total number of the examined nodes. The cut-off point of LNR was defined through the use of ROC analysis and Youden's index in N+ patients.

Follow-up time was calculated from the date of initial diagnosis to the date of recurrence for disease-free survival (DFS), to the date of death for overall survival (OS), or the date of the last visit without recurrence.

For all patients informed consent has been obtained, and the study was conducted in accordance with the "Ethical Principles for Medical Research Involving Human Subjects" statement of the Helsinki Declaration. This study was exempted from IRB review, due to its retrospective nature.

Statistical analysis

GraphPad Prism software version 7.00 for Windows (http://www.graphpad.com; GraphPad Software, San Diego, CA) was used. The comparison of frequencies between groups was performed using the χ^2 test or the Fisher exact test. The prognostic role of LNR was established through Mann-Whitney test. A P-value < 0.05 was considered statistically significant.

Disease-specific survival curves were calculated according to the Kaplan-Meier algorithm. Time zero was defined as the date of the patient's initial diagnosis. The DFS time was defined as the interval between the date of the patient's initial diagnosis and the last visit without recurrence (censored) or the date of recurrence (uncensored). The OS time was defined as the interval between the date of the patient's initial diagnosis and the last date when the patient was known to be alive (censored) or the date of death due to cancer (uncensored). Patients lost during the follow-up period were considered as censored. The Log-Rank test was used to compare survival curves. A P-value < 0.05 was considered statistically significant.

RESULTS

The complete clinicopathological data of the study patients are reported in Table 1. Overall, 73 patients with SCCT were considered in this retrospective study. Among all cases, 46 (63%) were males and 27 (37%) females, with a M:F ratio of 1.7:1. The age of patients ranged from 36 to 95 years, with a mean age of 65.2 ± 13.0 years. Lymph node metastases were found in 39 patients (53.4%); 10 of them (25.6%) showed the presence of ENE_{ma}, and 7 (17.9%) had ENE_{mi}. The lymph node characteristics of the patients are reported in Table 2. DOI ranged from 2 to 45 mm, with a mean value of 14.6 ± 10.8 mm. A total of 30 patients (41.1%) developed recurrences, and 34 (46.6%) died during the follow-up period.

In Table 1 are reported other clinicopathological data for completeness. No significant association was found between these data (grading, perineural invasion, alcohol and tobacco use) and the paramenters considered in this study (ENE, DOI, LNR, upstaging) (data not shown). Therefore, these data were not further considered in this study.

The comparison of pT, pN, and stage groups classification according to 7th and 8th editions is summarized in Table 3. 15 patients (20.5%) received an upstage when their DOI was included in the pT classification. Similarly, 10 patients (13.7%) were upstaged when adding their ENE+ status to the pN classification. Overall, 17 patients (23.3%) received an upstage in the staging score due to the inclusion of DOI or ENE, while 8 patients (11.0%) changed their pT or pN remaining in the same stage group.

In the pT upstaged group, 7 of 15 patients (46.7%) presented with disease recurrence and 8 patients (53.3%) died. These values are similar to those found in the non-upstaged group that showed 39.6% of disease recurrences and 44.8% of deaths ($P > 0.05$). 16 pT4a patients were excluded from the survival analyses for pT classification due to the fact that these patients could not be upstaged since the definition of pT4a was the same in 7th and 8th editions. Patients who were upstaged according to the new pT classification presented worse values of 5-year DFS (42.7% versus 50.0%) and 5-year OS (39.7% versus 40.3%) but without reaching statistical significance ($P > 0.05$). These results are described in Table 4, Fig 1, and Supplemental Figure S1.

In the pN upstaged group, 9 of 10 patients (90%) developed recurrence and all of them (100%) died. These values are significantly higher than those encountered in the non-upstaged group that showed 33.3% of disease recurrences ($P = 0.0010$) and 38.1% of deaths ($P = 0.0002$). Once again, for the pN analyses, 34 patients with pN0 were excluded due to the fact that these patients could not be upstaged. Patients who were upstaged according to the new pN classification presented worse values of DFS (0% versus 44.6%, $P = 0.0004$) and OS (0% versus 41.4%, $P = 0.0018$). These results are described in Table 4, Fig 2, and Supplemental Figure S2. Regarding the lymph node status, all patients underwent to lateral neck dissection and the mean number of lymph nodes

examined per patient was 39.4 ± 22.2 (range 10 - 82). A total of 2905 lymph nodes were histologically evaluated and the presence of metastases was demonstrated in 113 lymph nodes (3.9%). The evaluation of LNR showed that patients who developed recurrence had a mean value of LNR significantly higher compared to patients without recurrences (8.7% vs 6.7%, P = 0.0272) (Fig 3a). In the group of patients with recurrences, the presence of lymph node metastases with ENE+ showed a mean value of LNR significantly lower compared to patients without ENE+ (6.3% vs 10.6%, P = 0.0003) (Fig 3b). No statistically differences were found between the patients with recurrences that showed ENE+ and the patients without recurrences (6.3% vs 6.7%, P > 0.05) (Fig 3c). ROC analysis defined a cut-off point for LNR of 6.8%, defining two categories with significant differences in DFS (P = 0.0245) (Fig 4a), while no differences were found regarding OS (P > 0.05) (Fig 4b).

Regarding overall staging score (pTNM), 11 patients of the upstaged group developed recurrence and 12 died. These values are higher than those encountered in the non-upstaged group that showed 19 cases of disease recurrences (P = 0.0467) and 23 cases of deaths (P = 0.0290) during the follow-up period. Furthermore, a comparison was performed between stage groups of both editions of AJCC cancer staging manual in terms of DFS and OS. These results are described in Table 4, Fig 5, and Supplemental Figure S3.

DISCUSSION

The recently published AJCC 8th edition cancer staging manual contains several changes in the diagnostic criteria for OSCC, such as the inclusion of DOI and ENE. The present study evaluated the pathological classification in the 8th edition in an independent cohort of SCCT patients. Assessment of DOI was officially included in the 8th edition, although evaluation of this parameter was considered optional since the 6th edition [9]. DOI is used to evaluate only the invasiveness of OSCC, while tumor thickness refers to the entire tumor mass, including any exophytic component [8]. Histological measurement of DOI is performed by first finding the level of the basement membrane of the closest adjacent normal mucosa. Subsequently, a perpendicular “plumb line” is dropped from

this plane to the deepest point of tumor invasion. DOI measurements are reported in mm and pT category increases with every interval of 5 mm [10]. Although DOI is considered to be a better predictive parameter than tumor thickness, a clear advantage of this measurement is still a matter of debate [8, 10-12]. In fact, it can be difficult to obtain a precise measurement of both DOI and tumor thickness [13]. Furthermore, in the past years the terms "DOI" and "tumor thickness" were used interchangeably, and different authors used different techniques to report these parameters [13-15]. Since oral cavity is divided in multiple specific sites, we hypnotized that the impact of DOI as predictive parameter could be significantly different among these anatomical sites. Our data showed that 20.5% of patients with SCCT received an upstage of pT, higher than the percentages reported by other authors [11, 16]. However, the comparison made between upstaged and non-upstaged patients showed similar results in terms of disease recurrence (46.7% versus 53.3%) and death (39.6% versus 44.8%). Furthermore, no statistically significant differences were found between the two groups when comparing 5-year DFS (42.7% versus 50.0%) and 5-year OS (39.7% versus 40.3%). Our data are in accordance with the findings of Dirven et al., that showed no significant differences in DFS and OS when using DOI and tumor thickness [16]. Fakih et al. conducted a similar study regarding the possible prognostic significance of DOI in early-stage SCCT, showing no significant differences in DFS between the groups [17]. Several authors consider the advantages of the use of DOI instead of tumor thickness to be more theoretical than practical [12]. In fact, there is a high correlation between both measurements, suggesting a limited clinical utility of DOI and the possibility to use tumor thickness as a substitute when DOI data is missing in population-based survival analyses [11, 16]. A comparison of the DFS by pT classification based on 7th and 8th editions revealed that the 5-year DFS for pT1 improved from 56.2% to 71.4%; however, a countertrend regarding pT2 (from 44.0% to 40.7%) and pT3 (from 0% to 33.7%) emerged. Similar results have been obtained for the 5-year OS, showing improvement of pT1 (from 49.9% to 60.6%) and pT3 (from 15.9% to 29.5%), and worsening of pT2 (from 37.7% to 35.4%). Based on these results, pT1 patients in the 8th edition represent a homogeneous population, while the reclassification of pT2

and pT3 patients showed the presence of heterogeneous populations. Similar considerations have been recently made by Kano et al., that validated the 8th edition of clinical staging for SCCT through the study of imaging data [18]. Our results differ from those found by Matos et al., who showed significant improvement of pT2 patients, in terms of DFS and OS [11]. Possible explanations could be related to a smaller sample size used in our study, or could be a consequence of the selective evaluation of tongue tumors. Another reason could be the consequence of a "stage migration", that moved the patients with a worse outcome from pT1 to more advantage stages. Among the changes in diagnostic criteria, the 8th edition stated that extrinsic muscle invasion is no longer considered a criterion for the diagnosis of pT4 SCCT [8]. Although some authors justified the removal of this criterion [19], others recommend maintaining the classification of patients with extrinsic muscle invasion as having pT4 SCCT [1]. In our cohort of patients, no pT4 cases were downstaged.

The presence of lymph node metastasis is a well-established negative prognostic factor in OSCC patients [20], so the cervical lymph nodes must be carefully assessed. Clinical, radiological, and pathological parameters have been standardized for the evaluation of regional disease. Even if the prognostic role of ENE was established in some types of cancer [21], only the 8th edition added ENE as a prognostic variable for regional lymph node metastases, in addition to other well-established parameters (number and size of nodes) [8]. Pathological ENE is defined as dissemination of a lymph node metastasis from within a lymph node through its fibrous capsule and into the surrounding soft tissue. 2 mm is the cut-off used to distinguish ENE_{mi} from ENE_{ma}. Furthermore, if there are uncertainties regarding the presence of ENE, the case should be considered as ENE- [8]. The role of pathological assessment of ENE represents an important step for the patient's risk stratification, since clinical and radiological evaluations have severe limitations in identifying minor ENE, and their role may be only supportive [22]. Although the prognostic importance of ENE was found in literature, there is a considerable heterogeneity in the definition of this parameter in literature of the past years. In fact, there is a significant diversity in the terminology used (e.g. perinodal spread and

capsular rupture are used as synonyms) [23]. Furthermore, the criteria used to define if a lymph node is ENE+ or ENE-, especially in borderline cases, are not unanimously accepted [24, 25]. The consequence is the poor interobserver agreement among pathologists in the assessment of ENE in metastatic cervical nodes, with obvious consequences in the management of patients with OSCC [23]. Our data showed that 25.6% of patients with N+ SCCT received an upstage of pN (13.7% of all patients), similar to the results reported by other authors [11, 26]. The pN upstaged patients showed higher results in terms of disease recurrence (90% versus 33.3%) and death (100% versus 38.1%). Furthermore, significant differences were found between upstaged and non-upstaged patients when comparing 5-year DFS (0% versus 44.6%) and 5-year OS (0% versus 41.4%). These data are in agreement with previous reports demonstrating a worse DFS and OS for patients with ENE, and a major role for this parameter in the adverse outcome of OSCC [10, 11]. In our study cohort, 8 pN patients were reclassified as pN3b, confirming the significant worse prognosis in terms of DFS and OS of this group, as reported by other studies [10, 11]. Tirelli et al. evaluated the disease-specific survival in OSCC patients, highlighting that the upstaging due to the adoption of the new classification did not significantly change the prognosis of pN3 cases [26]. A comparison of the DFS by pN classification based on 7th and 8th editions revealed that the 5-year DFS for pN1 improved from 56.7% to 61.6%, and the same trend emerged in pN2 (from 13.6% to 23.3%). Similar results have been obtained for the 5-year OS, showing improvement of pN1 (from 34.8% to 38.7%) and pN2 (from 18.0% to 40.6%). The main reason for these results is the “stage migration” of the patients with a worse outcome from pN2 to pN3. Kano et al. described in a radiological study of SCCT patients a significant correlation of lymph node metastasis with DOI and with cT progression, although neither DOI nor cT classification could predict the probability of node metastasis in cN0 patients [18]. Regarding overall staging score, the comparison between stage groups of 7th and 8th edition showed better outcome of patients with stage II SCCT in terms of DFS and OS, while no significant differences were found between upstaged and non-upstaged patients.

The LNR is a promising prognostic tool to improve the classification of nodal disease in OSCC. The use of this parameter has been extensively studied in other tumor types [27] and several studies have been conducted to evaluate this parameter to predict outcomes in OSCC [7, 28, 29]. Although many investigations have highlighted the possible utility of LNR in OSCC, and suggested to include this parameter in TNM staging [7, 28-30], some authors questioned the prognostic role of LNR for OSCC [31]. The cut-off points for LNR range between 2.5% and 20% in different studies [7], and a LNR above 7% was significantly correlated with the increased risk of death from OSCC [30]. According to our results, the cut-off value defining SCCT patients with different prognosis was 6.8%. The reasons for such variability depends from several factors that can influence this parameter: 1) the number of nodes removed; 2) the number of positive nodes found; 3) the accuracy of the pathologic analysis; and 4) the heterogeneity of study methodologies in terms of tumor location, lymph node status, and methods to determine cut-off points [7]. The LNR found in patients who had ENE+ and recurrence was significantly lower than that of patients with recurrence and ENE- (6.3% vs 10.6%, $P < 0.05$), and was similar to LNR of patients without recurrence (6.3% vs 6.7%, $P > 0.05$). These results suggest that the presence of ENE could indicate the presence of more aggressive SCCT, influencing the DFS.

The passage from AJCC 7th to 8th edition of cancer staging manual has profound therapeutic implications regarding SCCT. As mentioned above, the new AJCC criteria indicates that extrinsic tongue muscle invasion does not lead to diagnosis of T4 cancer, due to the difficulty in identifying those muscles both clinically and pathologically [8]. Some authors have highlighted the risk in the use of these new criteria, that could lead to a downstaging to T3 in most cases with T4 SCCT [1]. On the contrary, other authors stated that the removal of invasion of extrinsic tongue muscles as a criterion for a pT4 SCCT is justified [19]. Regarding lymph node status, the use of ENE and LNR aims to identify more accurately those patients who require immediate postoperative adjuvant treatment [32]. Furthermore, these results emphasize the attention that must be given to neck dissection and lymph node excision to obtain a correct stratification of SCCT patients.

The opportunity to better stratify SCCT patients by improving the assessment of lymph node status could be used to investigate biological aspects of oral carcinogenesis. More specifically, these results could lead to re-examine the functional significance of several biomarkers that are closely associated with lymph-node metastasis in OSCC [33-35].

The strength points of this study include: 1) the analysis of a homogeneous group of tumors, the SCCT; 2) the homogeneity in the diagnostic and therapeutic approach (the same surgical team treated the patients and used the same postoperative protocol, and the same pathologists evaluated the cases). However, this study has some limitations: 1) the retrospective nature of this study, that increases the potential risk for bias; 2) not considering other variables such as the adjuvant treatment options (i.e. radiotherapy, chemotherapy).

In conclusion, we found that the AJCC 8th edition cancer staging manual allows a better stratification of SCCT patients. In particular, the implementation of ENE to the pN classification is capable to identify the patients with a worse DFS and OS. Furthermore, the use of LNR seems to improve the predictive capacity of the AJCC 8th edition cancer staging manual.

Conflict of interest

none.

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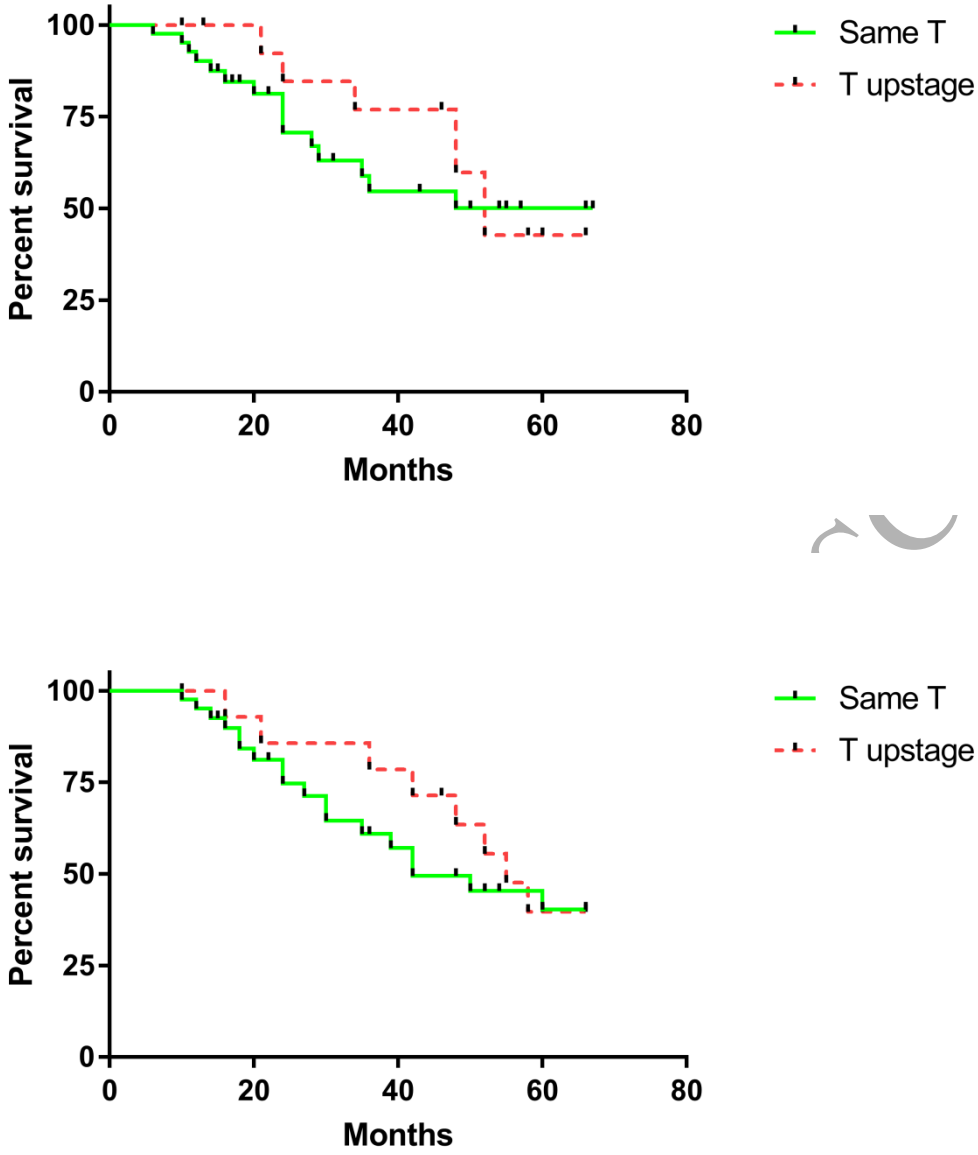


Fig 1. Kaplan-Meier analysis. DFS for upstaged and non-upstaged patients for pT (A) (42.7% vs 50.1%). OS for upstaged and non-upstaged patients for pT (B) (39.7% vs 40.3%).

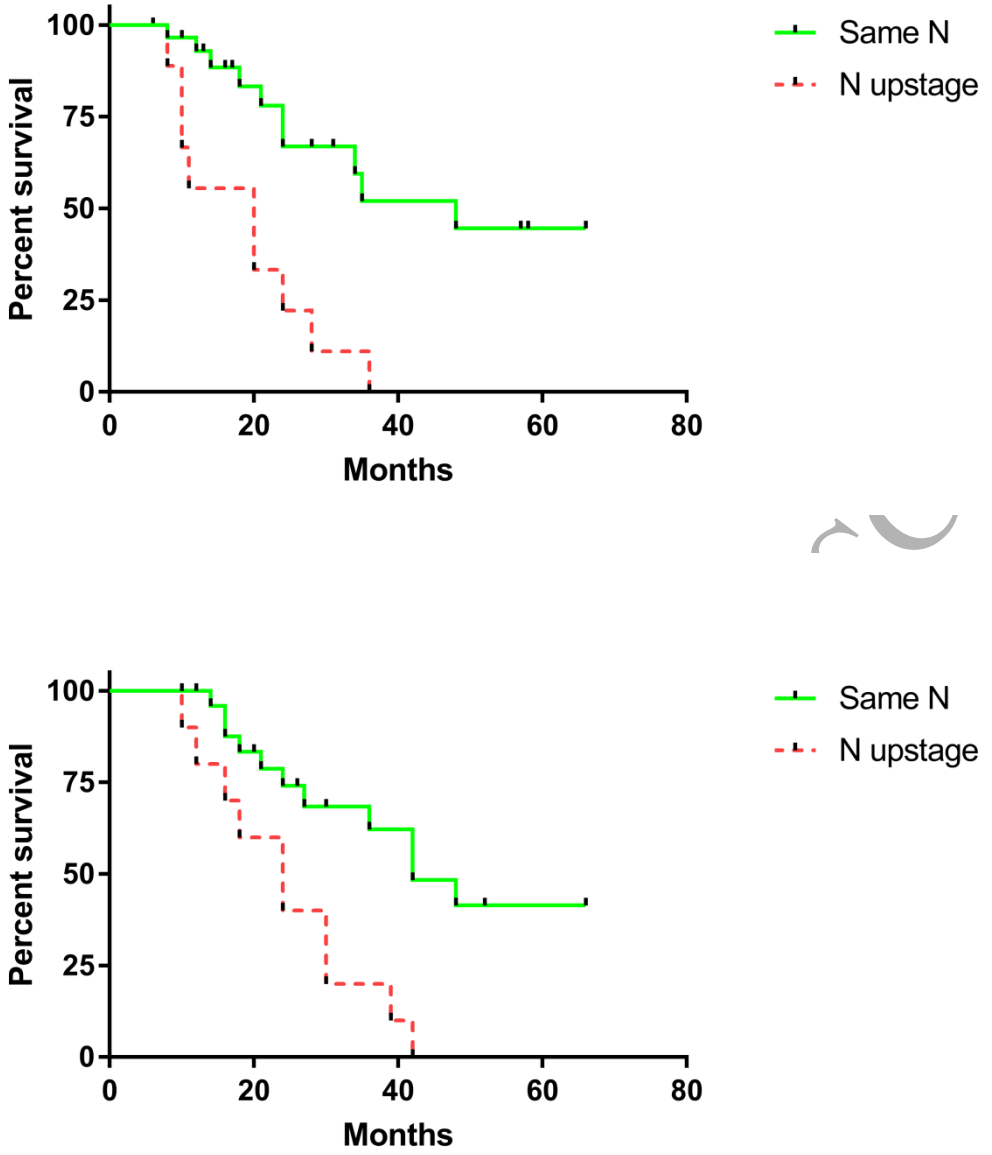
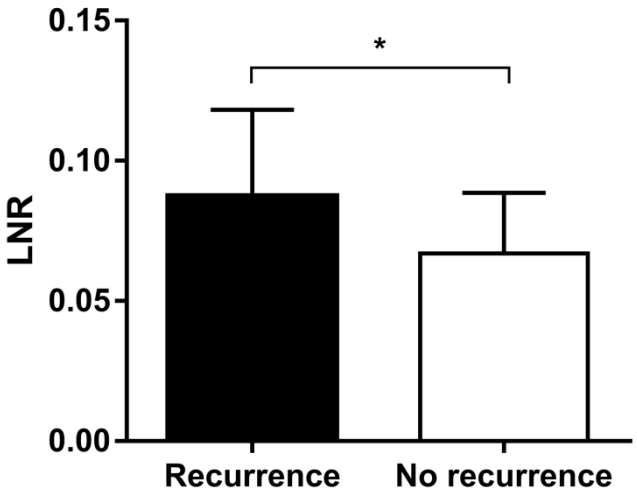
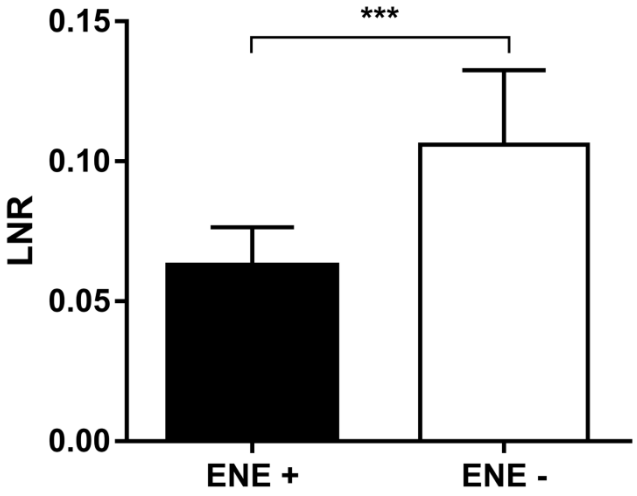


Fig 2. Kaplan-Meier analysis. DFS for upstaged and non-upstaged patients for pN (A) (0% vs 44.6%). OS for upstaged and non-upstaged patients for pN (B) (0% vs 41.4%).





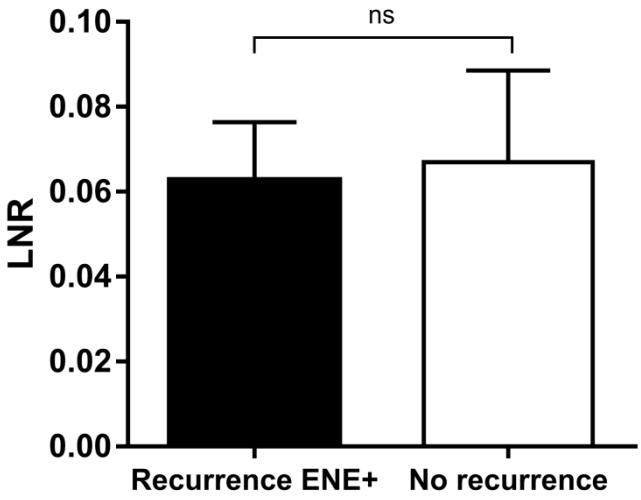
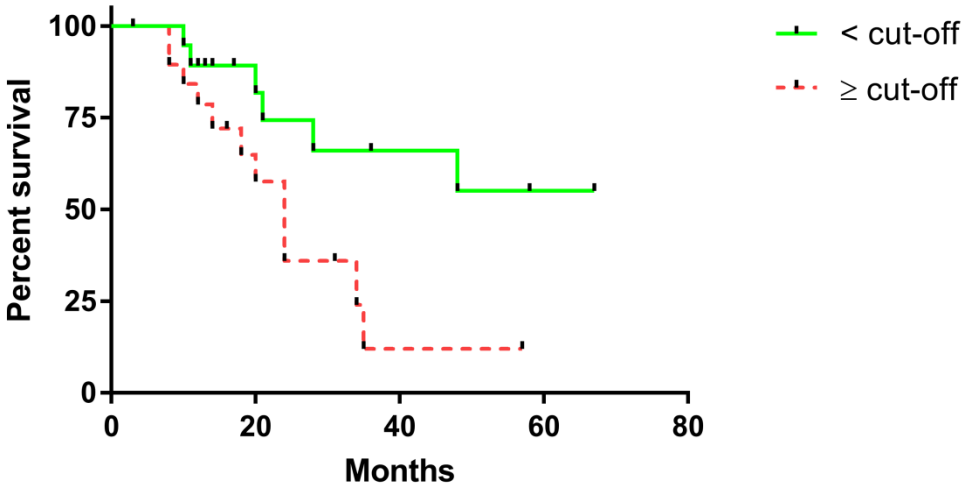


Fig 3. Evaluation of LNR in the patients included in this study. Comparison of LNR values between patients with recurrences and those without (A) (8.7% vs 6.7%, Mann-Whitney test), between ENE+ patients and ENE- patients (B) (6.3% vs 10.6%, Mann-Whitney test), and between ENE+ patients with recurrences and patients without recurrences (C) (6.3% vs 6.7%, Mann-Whitney test). ns = P > 0.05; * = P ≤ 0.05; *** = P ≤ 0.001.



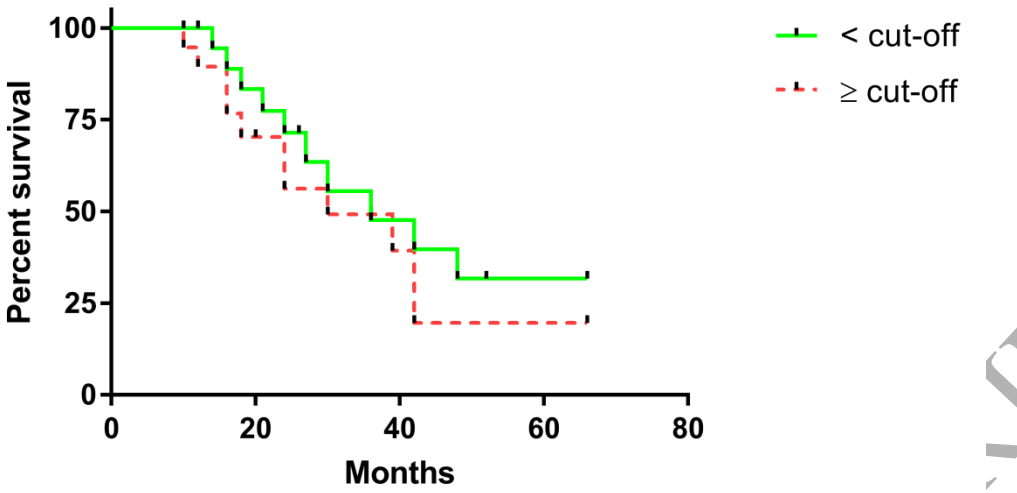
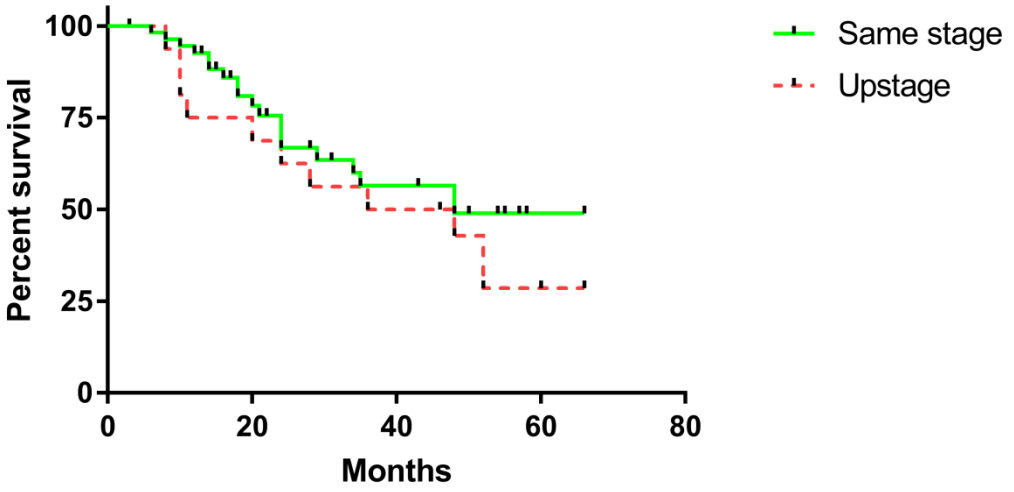


Fig 4. Kaplan-Meier analysis. Use of cut-off point for LNR to evaluate DFS (A) (55.0% vs 12.0%) and OS (B) (31.7% vs 19.7%).



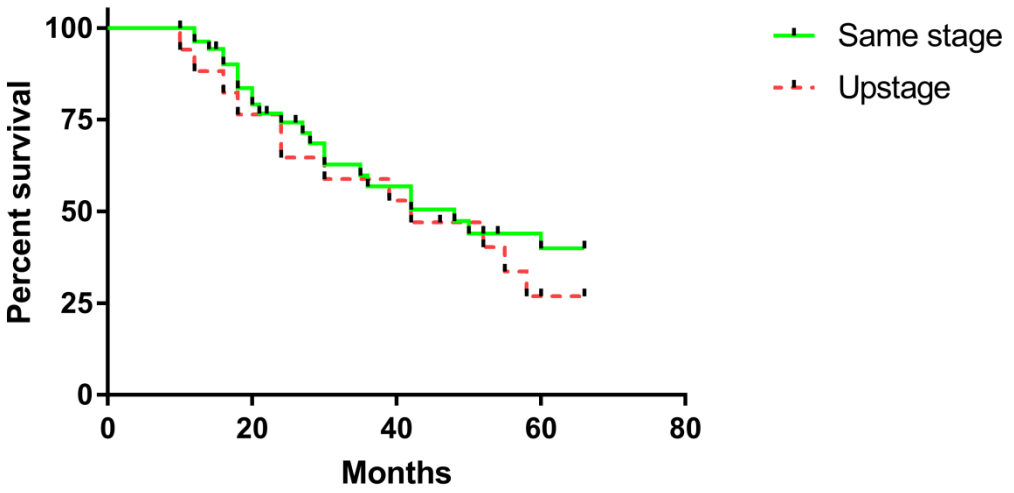


Fig 5. Kaplan-Meier analysis. DFS for upstaged and non-upstaged patients for pTNM (A) (28.6% vs 48.9%). OS for upstaged and non-upstaged patients for pTNM (B) (26.9% vs 40.0%).

Table 1. Clinical and pathological characteristics of the patients included in this study.

Clinicopathological data	
Parameters	**Results (%)**
Sex	
Male	46 (63)
Female	27 (37)
Age (years)	65.2 ± 13.0
Grading	
G1	24 (32.9)
G2	29 (39.7)
G3	20 (27.4)
Perineural invasion	38 (52.1)
ENE	
ENE+	10 (13.7)
ENE-	63 (86.3)
DOI (mm)	14.6 ± 10.8
Tobacco	
No	15 (20.5)
Yes	58 (79.5)
Alcohol	
No	24 (32.9)
Yes	49 (67.1)
Recurrences	30 (41.1)

Death	34 (46.6)
DFS (months)	30.5 ± 20.7
OS (months)	34.2 ± 19.7

Table 2. Lymph node characteristics of the patients included in this study.

Lymph node data	
Parameters	**Results**
Examined lymph nodes	
Total number	2905
Range	10 - 82
Mean ± SD	39.4 ± 22.2
Lymph node status	
N-	2792
N+	113
ENE_{ma}	15 (10 patients)
ENE_{mi}	11 (7 patients)
LNR	
Recurrences	6.7%
No recurrences	8.7%

Table 3. Comparison of the pT, pN, and pTNM classifications.

	Total cases		Recurrences		Deaths	
	7th	8th	7th	8th	7th	8th
pT						
pT1	21	13	7	3	8	4
pT2	27	28	11	12	12	12
pT3	9	16	4	7	5	9
pT4a	16	16	8	8	9	9
pN						
pN0	34	34	11	11	13	13
pN1	18	17	6	5	9	8
pN2	21	13	13	6	12	4
pN3	0	9	0	8	0	9
pTNM						
Stage I	5	5	2	1	2	1
Stage II	17	17	6	5	6	5
Stage III	13	17	3	5	7	9
Stage IVa	34	25	19	11	19	10
Stage IVb	0	9	0	8	0	9

Table 4. Comparison between upstaged and non-upstaged patients for pT, pN, and pTNM.

	pT			pN			Staging		
	Same	Upstaged	P value	Same	Upstaged	P value	Same	Upstaged	P value
Recurrences	23/58	7/15	> 0.05 [a]	21/63	9/10	**0.0010**	19/56	11/17	**0.0467** [a]
5-year DFS	50.0%	42.7%	> 0.05 [b]	44.6%	0%	**0.0004**	48.9%	28.6%	> 0.05 [b]
Deaths	26/58	8/15	> 0.05 [a]	24/63	10/10	**0.0002**	22/56	12/17	**0.0290** [a]
5-year OS	40.3%	39.7%	> 0.05 [b]	41.4%	0%	**0.0018**	40.0%	26.9%	> 0.05 [b]

Cases with recurrences or death are reported as number of cases/total cases. Bold values indicate statistical significance.

[a] χ^2 test or Fisher exact test.

[b] Log-Rank test.