Identification of Factors Affecting Recurrence in Patients with Locally Advanced Head and Neck Cancer Treated by IMRT and VMAT

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Abstract:

Background: Recurrent disease in head and neck SCC is a major cause of morbidity and an obstacle to long-term survival in squamous cell carcinoma of the head and neck. Locoregional recurrence is a major factor contributing to deaths from head and neck cancer. Recurrent head and neck cancer is challenging to treat for multiple reasons, including the effects of prior treatment on tumor cells, as well as the fact that the recurrent disease is usually infiltrative and multifocal.

Patients and methods: The medical records of patients with locally advanced squamous cell carcinoma of the head and neck who underwent radical treatment with IMRT or VMAT were retrospectively reviewed for our study. The data were collected from the files regarding patient characteristics such as age, sex, and special habits with a focus on smoking, alcohol consumption, and comorbidity, as well as disease characteristics as tumor site and size, grade, nodal status, extracapsular extension, and margin status. All these factors were correlated with the pattern of failure either locoregional or distant metastasis.

Results: The highest percentage is laryngeal SCC (74.8%) followed by pharyngeal and oral cavity SCC (10%) and finally others as lip, external auditory canal, and paranasal sinuses (5%). Out of 110 patients with head and neck SCC treated with radiation treatment, either adjuvant by intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT), or radical therapy, 17 patients (15.4%) experienced a recurrence of the disease. A statistically significant correlation between recurrence and LVI, PNI and ECE. There was no significant correlation between recurrences in head and neck and chemotherapy received, surgery done, or neck dissection.

Conclusion: Recurrences in head and neck squamous cell carcinoma are an obstacle to long-term survival in squamous cell carcinoma of the head and neck. There was a great association between recurrence and biological parameters, such as positive surgical margin, LVI, and PNI as well as treatment regularity. There was no statistical significance between treatment failure and age, sex, smoking, family history, comorbidities, primary tumor site, size of clinically detected lymph nodes, and induction or concurrent chemotherapy received. It is important to avoid factors that can lead to radiotherapy failure to reduce the risk of local recurrence. This can be achieved by utilizing advanced radiotherapy techniques and carefully selecting the primary treatment method.

Keywords: Head and neck squamous cell cancer, IMRT, VMAT, locoregional recurrence, radiation therapy.

Received: 8 February 2024
Accepted: 20 February 2024

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Introduction:

Head and neck cancer (HNC) is the seventh most common cancer globally and is usually diagnosed in a curable locally advanced stage [1]. Due to the potential for long-term harm and impairments, surgical removal is no longer the preferred treatment for local and locoregionally advanced head and neck cancer (HNC). Instead, radiation therapy (RT), with or without concomitant chemotherapy, has become the preferred approach [2–4]. Intensity-modulated radiotherapy

(IMRT) and volumetric modulated arc therapy (VMAT) are two radiation techniques that allow steeper dose gradients, resulting in improved protection of the surrounding risk structures in comparison with the older 3D techniques. This leads to reduced toxicity [5] and a better quality of life [6, 7].

IMRT is an advanced technique of three-dimensional (3D) treatment planning and conformal therapy. It optimizes the delivery of radiation to volumes of irregular shapes and can produce concavities in radiation treatment volumes. IMRT offers several benefits in the head and neck region: (i) it allows more sparing of normal risk structures including salivary glands, esophagus, optic nerves, brain stem, and spinal cord [8]; (ii) it eliminates the need for electron fields to the posterior (levels II and V) neck nodes and allows treatment to be administered in a single treatment phase; and (iii) it allows the delivery of concurrently higher radiation doses to areas of gross disease and lower doses to areas of microscopic disease; this technique is known as simultaneous integrated boost (SIB) IMRT [9].

VMAT is another technique for delivering IMRT. Unlike normal IMRT, which employs fixed gantry beams, VMAT produces IMRT-like distributions in a single gantry rotation by altering the gantry speed and dosage rate during delivery. Shorter planning and treatment times, fewer monitor units needed for treatment administration, improved dose homogeneity, and normal tissue sparing are all shown by planning studies using RT [10,11].

Locoregional tumor recurrences after radiotherapy treatment might be caused by several factors, including the tumor's inherent resistance to radiation, insufficient target volumes, and/or suboptimal delivery of the radiation dose [12,13]. Technical advances in IMRT and VMAT have enabled the precise delivery of radiation doses to the tumor while minimizing damage to healthy tissues. The high-dose conformity of IMRT and VMAT highlights the importance of tumor delineation and optimizing the radiotherapy plan due to the greater risk of marginal recurrences [14]. Adaptation of consensus-based target delineation guidelines has reduced clinician-based variability in the management of head and neck malignancy. Examining the failure pattern is crucial for pinpointing the reasons for recurrences and, consequently, areas that require improvement in the future [15].

Patients and Methods:

The medical records of patients with locally advanced squamous cell carcinoma of the head and neck who underwent radical treatment with IMRT or VMAT at Alkasr Alainy Center of Clinical Oncology and Nuclear Medicine (NEMROCK) from 2017 until 2022 were retrospectively reviewed for our study. The data were collected from the files regarding patient characteristics such as age, sex, and special habits with a focus on smoking, alcohol consumption, and comorbidity, as well as disease characteristics as tumor site and size, grade, nodal status, extracapsular extension, and margin status.

Factors related to treatment modalities were also studied as the kind of surgery performed, concomitant chemotherapy, and treatment offered for metastatic disease.

All patients were treated by IMRT or VMAT techniques with 6MV photons beam by Varian linear accelerator. The prescribed dose was 70Gy in 35 fractions at 2Gy per fraction to the PTV-GTV margin including both primary tumor and positive lymph nodes, 60Gy to the PTV-CTV high-risk margin, and 54Gy to the PTV-CTV low-risk margin. Weekly doses of cisplatin 40 mg/m2 were given as concurrent chemotherapy to the patients.

The evaluation of a number of variables, such as age, co-morbidity, performance level, and tumor extent, guided the administration of neoadjuvant chemotherapy. Some of our patients received induction chemotherapy 2-3 cycles of Taxotere, cisplatin, and 5-fluorouracil (TCF protocol). Organs at risk were delineated, considering the dose constraints as in Table 1.

Definition of treatment failure:

Failure was defined as local recurrence if it occurred within the primary site or regional recurrence if it occurred elsewhere including neck lymph nodes. Loco-regional failure is categorized as either marginal recurrence, where the recurring tumor volume was out of field or less than 20% of the recurrent tumor volume was inside the 95% isodose, or infield recurrence, where 95% or more of the recurrent tumor volume was within the 95% isodose [16].

Treatment of recurrence was individualized either salvage surgery, reirradiation, or palliative chemotherapy according to the site of recurrence concerning previous irradiation and extension, patient performance status, comorbidities, and the time interval between relapse and previous irradiation.

Our primary outcome was evaluating the frequency and pattern of failure as well as the prognostic indicators associated with the likelihood of recurrent disease.

Statistical analysis:

Data analysis was performed using the SPSS program. Fisher's exact test and the Pearson c2 test were the tests employed in the analysis. The significance of correlations between replies and categorical variables was established using them. Progression-free survival was analyzed using the Kaplan-Meier curves. It was calculated from the date of diagnosis to the date of progression or the date of death (all causes), whichever occurred first; patients who had not progressed at final follow-up were censored. Differences between groups were assessed using the log-rank test. A two-sided P-value less than 0.05 was considered statistically significant.

Results:

Patient and tumor characteristics:

Medical reports of a total of 110 patients with HNSCC who were treated by radical IMRT or VMAT with concurrent chemotherapy, were reviewed. The median age of the group was 54 years old with 45% less than 60 years old and 55% more than 60 years old.

There was a male-to-female ratio of 3:1 in patients with HNSCC of different subsites. A large proportion of patients (68.1%) were found to be smokers (75 out of 110).

Percentage of laryngeal SCC (74.6%) followed by pharyngeal and oral cavity SCC (10%), pharynx (10%), and finally others as lip, the external auditory canal, and paranasal sinuses (5.4%); this is shown in figure 1.

Surgery such as total laryngectomy, total laryngopharyngectomy, complete excision, and total or partial glossectomy were done for 77 patients out of 110 (70%).

The tumor was divided into 3 grades, with a higher prevalence of grade 2 tumors (74.5%) compared to poorly differentiated or grade 3(21.8%).

Most were locally advanced either T3 (26%) or T4 (47%). About 47% of patients have neck nodes that were proved pathologically to be positive or clinically or radiologically.

Patients who were subjected to prior urgent tracheostomy because of stridor were only 20 patients (18%). Chemotherapy in our group was administered either as induction before radiation therapy (8.1%) or concurrently together with radiation therapy (29%). Patients and tumor characteristics are shown in Table 2.

Relation between recurrence and different risk factors as shown in Table 3 and Table 4:

Out of 110 patients with head and neck SCC treated with radiation treatment, either adjuvant by IMRT or VMAT, or radical therapy, 17 patients (15.4%) experienced a recurrence of the disease. 14 patients experienced locoregional recurrences while 3 patients had distant metastases. Among patients with recurrences, the positive surgical margin was confirmed pathologically in 8 patients out of 17. (p-value 0.0001)

Regularity of treatment and finishing the radiotherapy sessions in the scheduled time significantly affect the outcome of treatment and the percentage of recurrence. (p-value 0.022)

It was of note that extracapsular extension was found in 12 out of 28 patients with pathologically proven nodal metastasis, 7 of them developed loco-regional failure. (P value 0.019)

Lymphovascular invasion was reported in 5 (29.4%) patients and was confirmed to be correlated with the incidence of recurrence with a p-value of 0.004. Only the positive surgical margin, extracapsular extension, and regularity of therapy were shown to be statistically significant in the multivariate analysis. On the other hand, the incidence of recurrence showed no statistically significant correlation with the following risk factors: age, comorbidities such as hypertension or diabetes, family history, smoking, site of the primary tumor, pathological nodal status, induction, and concurrent chemotherapy.

Table 1: Organs at risk dose constraints

Critical structures	Constraints
Brain stem	Max<50 Gy
Optic nerves	Max<54 Gy
Optic chiasma	Max<54 Gy
Spinal cord	Max<45 Gy
Mandible	Max<70 Gy
Brachial plexus	Max<65 Gy
Parotid glands	Mean ≤ 26 Gy in one gland Or at least 50% of one gland will receive 30Gy
Submandibular gland	Mean dose <39 Gy
Cochlea	Max<50 Gy
Lens	Max<5 Gy

Table 2: Patient and tumor characteristics

Variable	Levels	Number	Percentage	Number of Recurrences (total = 17)	P value
Age	< 60 years /> 60 years	49/ 61	45% /55%	7 / 10	0.7
Sex	Male/female	88 / 22	80% / 20%	15 /2	0.566
Family history	Yes/no	4/106	3.6% / 96.4%	17 /0	1
Diabetes	Diabetic / non diabetic	15 / 95	13.6% / 86.3%	1 /16	0.74
Hypertension	Hypertensive/ non	17 / 93	15.4% / 84.5%	2 /15	0.52
Smoking	Smoker / non	75/ 35	68.1% / 31.8%	13 / 4	0.43
Surgery	Yes/no	77 / 33	70% / 30%	15 / 2	0.072
	Larynx	82	74.6	12	
Site of primary	Oral cavity	11	10%	2	
	Pharynx	11	10%	1	0.574
	Others	6	5.4%	2	
Grade	1	4	3.6%	0	
	2	82	74.5%	11	0.134
	3	24	21.8%	6	
Surgical margin	Positive/negative	17/ 93	15.4% / 84.5%	8/ 9	0.001
Tumor stage	1/2/3/4	12/ 17/ 29/ 52	10.9%/ 15.4% / 26.3% /47.2%	1/ 4/ 6 / 6	0.419
Pathologic node status	Positive/negative	28 / 82	25.4% / 74.5%	5/ 12	0.367
Neck dissection	Yes/no	60 / 50	54.5% / 45.4%	12 / 5	0.165
Locoregional failure	Yes/no	14/ 96	12.7% / 87.2 %		
Distant metastasis	Yes/no	3/ 107	2.7% / 97.2%		
Regularity on treatment	Regular / not	75 / 35	68.1% / 31.8%	6/ 11	0.000
Urgent tracheostomy	Yes/no	20 / 90	18.1% / 81.8%	4 / 13	0.551
LVI	Present / not	10 / 100	9% / 90.9%	5 /12	0.004
PNI	Present / not	13/ 97	11.8% / 88.1%	6 / 11	0.001
ECE	Positive/negative	12 / 98	10.9 % / 89%	7/ 10	0.002
Induction chemotherapy	Received / not	9 / 101	8.1% / 91.8%	0/17	0.212
Concurrent chemotherapy	Received / not	32 / 78	29% / 70.9%	7/ 10	0.46

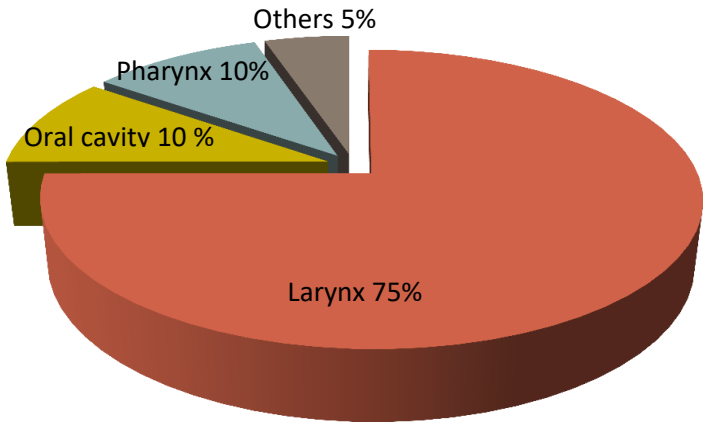

Figure 1: Percentage of different subsites in our patients with HNSCC

Table 3: Univariate analysis between recurrence and different variables.

Variable	Percentage of recurrence	P value
Age: <60 years old	14%	0.7
>60 years old	16%	
Sex: male/female	17% / 10%	0.566
Family history: positive/negative	0% / 16.4%	1
Smoking: yes /no	16.8% / 13.9%	0.43
Diabetes: Diabetic/non	9% / 91%	0.74
Hypertension: hypertensive/ no	9% / 17%	0.52
Surgery: yes/ no	19% / 3%	0.07
Site of the 1ry:		
larynx	15.3%	0.574
Pharynx	7%	
Oral cavity	21.4%	
Others	28%	
Grade: 2	13.4%	
3	26.6%	0.134
Surgical margin: positive/negative	45.4% / 10.2%	0.001
Tumor stage: 1	13.3%	
2	23.8%	0.419
3	19.4%	
4	10.6%	
Pathologic node status: positive/negative	21.2%/ 14.5%	0.367
Neck dissection: *yes*/no	19.7% / 11%	0.165

Table 4: Multivariate analysis of prognostic factors and recurrence

Variable	P value	Confidence interval 95%	
		lower	Upper
Surgical margin	**0.002**	.037	.475
LVI	.763	.058	48.230
PNI	.418	.010	6.676
Extracapsular invasion	**.019**	.024	.721
Regularity on treatment	**.022**	1.212	12.641

Discussion:

One of the main causes of morbidity and an obstacle to long-term survival in patients with squamous cell carcinoma of the head and neck is recurrent illness. Loco-regional recurrence is a major factor contributing to deaths from head and neck cancer. Locoregional recurrence will occur in thirty percent of patients with HNC, while therapy failure due to metastases is less common [17, 18]. Recurrent head and neck cancer is challenging to treat for several reasons, including the effects of prior treatment on tumor cells, and the fact that the recurrent disease is usually infiltrative and multifocal. After the failure of first-line therapy, the prognosis for HNC patients is poor, with a median overall survival of less than 1 year [19].

A large number of these recurrences present at advanced stages and cannot be fully removed. For head and neck malignancies that were previously treated with radiation and are incurable, re-irradiation offers a possibly curative option. There is a higher chance of serious and perhaps fatal radiation-related toxicities with reirradiation [20].

In this study, 110 locally advanced HNC patients receiving IMRT/VMAT treatment are followed up to determine the patterns of recurrence following RT.

Wu et al published data analysis from Taiwan National Health Insurance and cancer registry databases in 2017 which revealed that the incidence of loco-regional recurrence was 14.44% and 40.73 per 1,000 person-years [21], and also Leoncini et al conducted a multicenter study by using data from five studies members of the International Head and Neck Cancer Epidemiology consortium namely Milan, Rome, Western Europe, Sao Paulo, and Japan which revealed a locoregional recurrence in 29% (1161 of total 4005 patients) [22]. In our study and after reviewing the medical records of 110 patients of pathologically proven HNSCC who received their treatment at our department about 17 patients (15.4%) developed treatment failure either locoregional, distant metastasis, or both. This difference may be attributed to the fact that these studies were performed before the era of IMRT and VMAT which allow the delivery of high doses to the GTV and CTV, allowing better local control of the tumor.

The primary objective for an onco-surgeon treating SCC is to completely remove all tumor cells from the affected area, both at a macroscopic and microscopic level. This is achieved by removing a minimum of 5 mm of surrounding histopathologically normal tissue. In advanced carcinomas of the head and neck, the likelihood of local recurrence of the disease is closely associated with the presence of positive or close resection margins after surgical treatment [23]. Furthermore, Dillon et al. observed that oral cancer patients who had clear surgical margins had superior odds of disease-free survival compared to those with near or involved margins. Similarly, Yamada et al demonstrated that having a margin of 1, 2, or 4 mm at the tumor edge significantly increased the chance of local recurrence compared to oral cancer patients with margins of more than 5 mm. In our study, the positive surgical margin was associated with 45.4% of loco-regional recurrence (p-value: 0.001). However, a prospective study published in the Journal of Oral Maxillofacial Surgery in 2017 suggested that the practice of using close resection margins as a general indicator for local recurrence and poor prognosis may need to be reevaluated. Additionally, the presence of tumor cells within a distance less than 0.5 cm from the surgical margins does not necessarily provide a definitive indication for additional treatment, according to histopathologic evidence. In the decision-making process for subsequent treatment, it is important to consider other prognostic markers, such as the involvement of cervical lymph nodes and tumor depth. However, this study found no statistically significant relationship between surgical margin involvement and local recurrence, as shown by a p-value of 0.5 [24].

PNI is one of the selection criteria for post-operative radiotherapy [25,26]. A retrospective analysis was conducted on 1524 patients who had not received any prior treatment and had oral cavity squamous cell carcinoma (SCC) and underwent surgery. The study found that perineural invasion (PNI) is an independent prognostic indicator for overall survival (OS) and disease-free survival (DFS). Additionally, patients with early-stage cancer and no lymph node involvement who had perineural invasion were twice as likely to experience recurrence [27]. Our study found a strong correlation between histologically confirmed peripheral nerve invasion (PNI) and local recurrence. This was demonstrated as 54.5% of recurrent cases were positive for PNI with a p-value of 0.004.

Our study found a strong correlation between recurrence and the existence of pathologically extracapsular extension (ECE) as 70% of our patients who experienced recurrences had ECE. Lop et al. emphasized the strong association between the extent of extracapsular spread (ECS) and negative prognosis, as well as the existence of hidden nodal metastases, which negatively impact and reduce the five-year disease-specific survival rate [28]. Ghadjar et al 2010 also pointed out the importance of a CTV margin of 10 mm surrounding the gross tumor volume in radiotherapy planning.

A statistically significant correlation was also noticed between recurrence and regularity on treatment (35% of patients who developed recurrence were not regular on treatment p value 0.000). Thomas et al. conducted a retrospective cohort study using electronic medical and billing records to examine treatment interruptions between January 2011 and December 2014 at the University of Texas Southwestern Medical Center and the Parkland Health and Hospital System. The study found that non-compliant patients had a greater probability of experiencing local recurrence [29]. Thomas et al demonstrated that patients with head and neck squamous cell carcinoma (SCC) should complete their radiation therapy according to the predetermined timeline. Thomas et al. examined the possible socioeconomic factors that may lead to interruptions in radiotherapy, such as age and treatment intensity (e.g., the inclusion of chemotherapy with radiation) [29].

Our analysis did not reveal any statistically significant correlation between disease recurrence and factors such as sex, age, or comorbidities. This finding aligns with the results of a prospective observational study involving 157 patients with OSCC who underwent surgery between 2010 and 2015. The study found that age above 60 years old, sex, and smoking were not significantly associated with recurrence-free survival [30].

Evaluating and managing lymph nodes in the neck are crucial. Improper handling of lymph node metastases might lead to regional recurrence. Classic radical neck dissection (RND) has long been regarded as the most reliable surgical approach for treating lymph node metastases in HNSCC. [31]. In a comprehensive analysis of data on selective neck dissection (SND) for patients with clinically node-positive disease, the reviewed literature demonstrated that selective node dissection is a viable alternative for patients with cN1 and selected cN2 neck disease. This includes patients with non-fixed nodes, no palpable metastases at level IV or V, or multiple lymph nodes of large volume (≥ 3 cm) at multiple levels. Adjuvant chemo-radiotherapy is essential for achieving optimal

control rates in cases with pN2. Utilizing SND instead of CND may lead to less morbidity and improved functional outcomes [30]. In our analysis neck dissection was done in 54.5% (60 patients out of 110). Most of them were selective neck dissection but it did not significantly affect the loco-regional recurrence (p-value 0.165).

In 2017, the World Journal of Surgical Oncology conducted a retrospective review on the relationship between nodal size and the risk of recurrence. The study found that cervical nodes smaller than 10 mm were still significant in terms of the possibility of metastasis, particularly in cases of high-grade tumors, advanced-stage cancer, and lymphovascular invasion [32]. However, our analysis did not find a significant correlation between nodal size and locoregional recurrence.

A phase III randomized trial compared concurrent chemotherapy with radiation therapy and radiotherapy alone, one hundred patients randomized to receive either radiotherapy alone at a dose of 66 to 72 gray with 2 gray per fraction or receiving concurrently with flurouracil 1gm and cisplatin 20 mg/m² as continuous infusion on four days on day 1,22 of radiation therapy with median follow up of 5 years the results was as follow: distant free interval was 84 % in the arm of concurrent chemotherapy with radiotherapy (arm A) versus 75% in radiotherapy arm B (p value 0.001) alone and also local control of 77% in arm A versus 45% in arm B with final conclusion that addition of concurrent chemotherapy improved the recurrence free interval and primary site preservation, another trial EORTC trial at 22931 that discussed the addition of high dose cisplatin on day 1,22,43 in high risk head and squamous cell carcinoma revealed that addition of chemotherapy especially in patients with extracapsular extension and positive surgical margin improved treatment outcome. But in our analysis of patients, we couldn't significantly correlate the addition of chemotherapy to the incidence of loco-regional failure (7 patients out of 17 recurrent cases have received concurrent cisplatin with a p-value of 0.4) and this might be explained by the small number of patients (only 32 patients of the total cohort received concurrent chemotherapy) and also, we used concurrent cisplatin only at a dose of 40mg/m² on weekly basis.

Summary and Conclusion:

Recurrences in head and neck squamous cell carcinoma are an obstacle to long-term survival in squamous cell carcinoma of the head and neck. And it also contributes to deaths from head and neck cancer.

Offering treatment for recurrent head and neck cancer is challenging due to several factors, such as the impact of previous treatment on tumor cells and the invasive and widespread nature commonly observed in recurrent illness in this region.

Our study examined the results of patients who underwent radiation therapy, either radical or adjuvant, and we also identified the patterns of treatment failure associated with various risk factors.

The noteworthy association between recurrence and biological parameters, such as positive surgical margin (p-value 0.001), LVI (p-value 0.004), and PNI (p-value 0.001), should be emphasized. Additionally, the influence of treatment regularity on loco-regional control is considerable (p-value 0.000).

However, we couldn't find a statistically significant relation between treatment failure and age, sex, smoking, family history, comorbidities, primary tumor site, size of clinically detected lymph nodes, and induction or concurrent chemotherapy received.

To reduce the risk of local recurrence, it is important to avoid factors that can lead to radiotherapy failure. This can be achieved by utilizing advanced radiotherapy techniques and carefully selecting the primary treatment method, while also considering the patient's nutritional status. Additionally, it is crucial to closely monitor patients who are undergoing radiation therapy.

Abbreviations

3D-CRT: Three-dimensional conformal radiotherapy
CTV: Clinical target volume
CT: Computed tomography
CND: Comprehensive neck dissection
C²-test: Chi-square test
DFS: Disease-free survival
ECE: Extracapsular extension
ECS: Extracapsular spread
EORTC: The Eastern Cooperative Oncology Group
GTV: Gross tumor volume
Gy: Gray
HNC: Head and neck cancer
HNSCC: Head and neck squamous cell carcinoma
IMRT: Intensity-Modulated Radiotherapy
LVI: Lymphovascular invasion
OS: Overall survival
OSCC: Oral cavity squamous cell carcinoma
PTV: Planning target volume
PNI: Perineural invasion
RT: Radiotherapy
RND: Radical neck dissection
SPSS: Statistical Package for the Social Science
SND: Selective neck dissection
SCC: Squamous cell carcinoma
TPF: Taxotere-platinum-fluorouracil
VMAT: Volumetric Modulated Arc Therapy

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