research article

Comparative analysis of clinical and pathological lymph node staging data in head and neck squamous cell carcinoma patients treated at the General Hospital Vienna

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Background. Results from publications evaluating discrepancies between clinical staging data in relation to pathological findings demonstrate that a significant number of head and neck squamous cell carcinoma (HNSCC) patients are not correctly staged. The aim of this retrospective study was to analyze potential discrepancies of radiological assessment versus pathological data of regional lymph node involvement and to compare the results with data published in the literature.

Patients and methods. In a retrospective analysis we focused on patients with HNSCC routinely treated by surgery plus postoperative radiotherapy between 2002 and 2012. For inclusion, complete pre-operative clinical staging information with lymph node status and patho-histological information on involved lymph node regions as well as survival outcome data were mandatory. We included 87 patients (UICC stage III-IV 90.8%) for which the aforementioned data obtained by CT or MRI were available. Overall survival rates were estimated by the Kaplan–Meier method. The Pearson correlation coefficient and Spearman`s rank correlation coefficient (non-linear relationship) was calculated.

Results. Discrepancies at the level of overall tumour stage assessment were noticed in 27.5% of all cases. Thereof, 5.7% were assigned to patho-histological up-staging or down-staging of the primary tumour. At the lymph node level, 11.5% of the patients were downstaged, and 10.3% were upstaged.

Conclusions. The study showed that in approximately one-fifth (21.8%) of the patients, lymph node assessment by CT or MRI differs from the pathologic staging, an outcome that corresponds well with those published by several other groups in this field.

Key words: lymph node staging; head and neck squamous cell cancer; clinical staging; pathological staging

Introduction

Methods for staging of head and neck squamous cell carcinoma patients rely primarily on the assessment by CT, PET-CT or MRI in combination with a clinical examination by endoscopy and the use of ultrasound.[1-4] Head and neck carcinoma are usually treated, depending on the stage of disease, as well as based on various risk factors, by surgery, radiotherapy (RT), chemotherapy, cetuximab and

combinations thereof.[5-8] While the location, as well as the extent of the primary tumour, is usually known with a sufficient degree of precision, most of the uncertainties about the evaluation of the exact tumour spread are related to the regional lymph node status. Disparities between pathological and clinical nodal staging data for head and neck carcinoma have been described in the literature by several authors.[9-12] In order to maximally utilize the tumour dose escalation as well as the normal tissue sparing potential of modern radiation technologies, it is important to be able to correctly delineate the target volume based on preclinical imaging data as well as on the statistical likelihood of microscopic tumour spread.[13-15] It is therefore of importance to be aware of the potential extent of disparity that may exist between pathological and clinical staging methods. Also, it should be kept in mind that additional factors may impact correct diagnosis, in particular, the utilization of different imaging modalities as well as the different professional expertise of the examiners.[16,17]

In this study, we assessed clinical (pre-treatment) as well as post-surgery (patho-histological) staging data in a retrospective series of patients who were treated with surgery and postoperative radiotherapy (PORT) at the Vienna General Hospital. We aimed to conduct a comparative analysis of clinical and pathological data of regional lymph node involvement and to compare our results with published data from the literature.

Patients and methods

Patient selection

A retrospective review of clinical data was conducted from a series of patients (squamous cell carcinoma, n = 87) treated by surgery plus PORT between 2002 and 2012, for which complete pre-operative clinical staging information including explicit description of lymph node involvement, complete patho-histological information on involved lymph node regions as well as survival outcome data were available.

Tumour staging

Tumour staging was conducted according to the 7th Edition TNM Classification for Head and Neck Cancer. Pre-therapeutic staging examinations were routinely performed with contrast agent enhanced CT scans of the head and neck. Alternatively, MRI scans, alone or in combination with CT scans (*e.g.*, in cases of allergy, or according to the physicians' preferences) were performed. CT examinations alone were conducted in 55, MRI in 21, and both CT and MRI scans were done in 11 patients. In case of discordant diagnoses between the imaging modalities, the ultimate staging was based on the results of the CT scans. In cases of suspicious findings in the chest X-ray or after abdominal sonography, additional thoracic or abdominal CT scans were indicated. Only patients who were treated with curative intent without evidence of previous or accompanying malignancies, and who were operated and irradiated at the Vienna General Hospital, were included in this retrospective analysis.

Patho-histological files and existing pre-treatment imaging reports were compared, and congruence of the data was evaluated by an experienced head and neck oncologist and cross-checked by a non-physician member of the team with experience in clinical trial documentation. A nodal region was scored as positive if at least one lymph node was diagnosed as positive in the patho-histological or clinical diagnosis. The absolute number of positive or negative lymph nodes per nodal region was not assessed.

Radiotherapy and surgery

Surgery was performed at the Department of Ear, Nose and Throat Diseases of the Medical University of Vienna. 88.5% of the patients were operated bilaterally. Patients with clinical N0 status had elective ipsilateral selective neck dissection (13% of the cases) including the submandibular (level I), upper jugular (leveI lI), and midjugular (level III) nodes. In patients with N+ disease, a modified radical neck dissection was performed by additionally including the lower jugular (level IV) and posterior triangle (level V) nodes (87% of the cases). PORT was indicated routinely for UICC stage III and IV cases. Lower disease stages were treated with postoperative radiotherapy if additional risk factors were present, such as large T2 tumours, or if, despite a patho-histological R0-status, according to the surgeon the resection status was uncertain. Postoperatively irradiated patients received a standard fractionation RT (2D/3D, 50–66 Gy total dose, mean dose 58 Gy) at 2 Gy per fraction. IMRT technique was not used on a routine basis. The prescribed dose depended on well-established risk factors such as patho-histological resection status and tumour stage. In the case of extracapsular spread or positive microscopic resection margins, cisplatin (100 mg/sqm) was added to postoperative

radiotherapy (week one and three) and the total radiation dose was escalated up to 66 Gy. Spinal cord dose was limited to a maximum of 50 Gy. All patients included in this retrospective analysis were presented at the Institutional Tumour Board of the Vienna General Hospital before treatment start and after surgery

Follow-up

Patients receiving PORT were clinically monitored weekly during treatment. After completion of therapy, follow-up examinations consisted of clinical examination, a CT or MRI scan of the head and neck region, chest X-ray and/or CT-scan, and upper abdominal sonography according to our institutional guidelines. Initial intervals were three months in the first post-therapeutic year followed by six-month intervals for the next four years. After that, follow-up interval was one year. Follow-up was conducted at the Department of Radiotherapy, at the Department of Ear, Nose and Throat Diseases and the Department of Internal Medicine in the case of additional chemotherapy treatment according to the institutional guidelines.

Statistical analysis

Overall survival rates were estimated by using the Kaplan-Meier method. The Pearson correlation coefficient and Spearman`s rank correlation coefficient (non-linear relationship) was calculated to evaluate a possible statistical relationship between various data sets as described below. The software package SPSS Version 23.0 (IBM®) was used for statistical analysis.

Ethics statement

This study was conducted following the Helsinki Declaration on medical protocol and ethics in its most recently amended version and approved by the hospital's Ethic Review Board (Medical University of Vienna - study reference number 612/2009).

TABLE 1A. Patient characteristics

Characteristic	abs. (rel.) 87 (100)
Age (mean/median) years	58.4/59.0
Male	67 (77.0)
Female	20 (23.0)
Primary tumour site	
Oropharynx	33 (37.9)
Oral cavity	30 (34.5)
Larynx	9 (10.3)
Hypopharynx	15 (17.2)
Localization	
right	42 (48.3)
left	40 (46.0)
midline	5 (5.7)

TABLE 1B. Pre- and postoperative staging results

Stage	Pathological staging	Clinical staging	p-value
T			
1	19 (21.8)	19 (21.8)	0.000[a]
2	42 (48.3)	34 (39.1)	
3	14 (16.1)	19 (21.8)	
4	12 (13.8)	15 (17.2)	
N			
0	21 (24.1)	17 (19.5)	0.000[a]
1	15 (17.2)	15 (17.2)	
2a	2 (2.3)	6 (6.9)	
2b	34 (39.1)	24 (27.6)	
2c	13 (14.9)	25 (28.7)	
3	2 (2.3)	0 (0)	
UICC			
I	4 (4.6)	2 (2.3)	0.000[a]
II	12 (13.8)	6 (6.9)	
III	11 (12.6)	17 (19.5)	
IV	60 (69)	62 (71.3)	

[a]Pearson correlation (significance 2-tailed). Correlations are significant below the 0.01 level

Results

A total of 87 patients was included in this retrospective analysis. Basic characteristics of patients included in the analysis according to pathological versus clinical staging data are shown in Table 1A and 1B. 37.9% of the patients analyzed had oropharyngeal, 34.5% oral cavity, 10.3% laryngeal, and 17.2% hypopharyngeal cancer. Primary tumour site localization was well balanced with 48.3% of the carcinomas originating at the right side, 46% on

TABLE 1C. Clinical and pathological lymph node staging results in relation to the type of neck dissection performed

Stage	Bilateral neck dissection	Unilateral neck dissection	Total
pN0	15	6	**21**
pN1	13	2	**15**
pN2a	2	0	**2**
pN2b	32	2	**34**
pN2c	13	0	**13**
pN3	2	0	**2**
Total	**77**	**10**	**87**
cN0	14	3	**17**
cN1	11	4	**15**
cN2a	6	0	**6**
cN2b	21	3	**24**
cN2c	25	0	**25**
Total	**77**	**10**	**87**

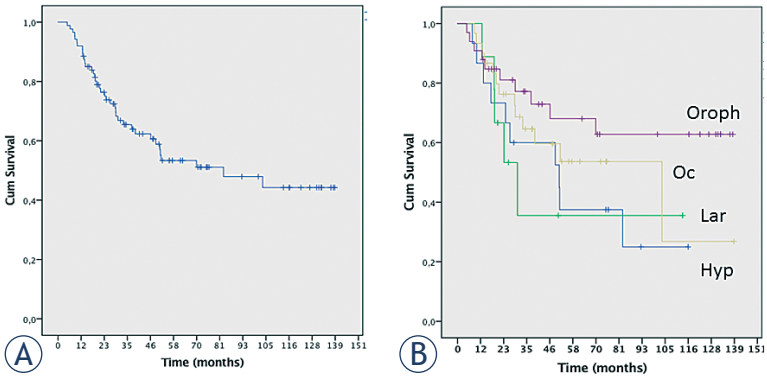

FIGURE 1. Kaplan Meier curves for the complete patient group **(A)** and according to primary tumour sites **(B).**

Hyp = hypopharyngeal carcinoma; Lar = laryngeal carcinoma; Oc = oral cavity carcinoma; Oroph = oropharyngeal carcinoma

TABLE 2A. Discrepancies of pathological and clinical findings according to imaging type

Number of discrepant results per patient	CT (n = 55)	MRI (n = 21)	CT/MRI (n = 11)	Total (n = 87)
0	43.6%	38.1%	36.4%	36 (41.4%)
1	25.5%	23.8%	45.5%	24 (27.6%)
2	18.2%	23.8%	9.1%	16 (18.4%)
3	5.5%	9.5%	0.0%	5 (5.7%)
4	7.3%	4.8%	0.0%	5 (5.7%)
5	0.0%	0.0%	9.1%	1 (1.1%)

the left side, and 5.7% midline tumours. Most of the patients (90.8%) had stage III/IV carcinomas. None of the patients was lost to follow-up. In Table 1C, cross-tabulated pathological and clinical N-staging data according to the type of dissection (unilateral versus bilateral) are presented.

Estimate (Kaplan-Meier) of median overall survival for the whole treatment group was 85.9 months (SE 31.9; 95% CI 23.4–148.3). The patient collective investigated corresponds with regard to overall survival (64.5% after 3-years) to previously published results derived from larger data sets (N = 148; OS 69% after 3-years) at our institution.[18] Kaplan-Meier curves for the entire patient collective, as well stratified according to the primary tumour, are shown in Figure 1. To directly compare the results of pathological and clinical staging data, patho-histological files were compared with preoperative staging examinations (CT or MRI).

Table 2 shows results regarding congruency of patho-histological and clinical staging data. The numbers and percentage of discrepantly staged lymph node levels per patient according to the type of imaging performed (CT, MRI, CT&MRI) are shown in Table 2A. No statistically significant association between type of preoperative imaging modality (MRI, CT, CT&MRI) and clinical staging data was observed (data not shown). Cross-tabulation data (concordance) of patho-histological lymph node stage versus clinical lymph node stage findings are presented in Table 2B. This table shows the initial clinical lymph node staging data (left column) and the corresponding corrected pathological staging results. Of note, in two cases a cN2c stage was upstaged to pN3. Table 3A shows the percentage of patients according to the origin of the primary tumour and pathologically positive lymph node levels (level I to V). Nodal level I was involved in 16.1%, level II in 59.8%, level III in 40.2%, level IV in 20.7%, and level V in 9.2% of the patients. As expected, levels II and III were predominantly involved.

We performed a statistical analysis of the correlation of regional pathological lymph node involvement and asked, whether the involvement of a given lymph node level is statistically correlated with an involvement of any other node level in the ipsilateral neck. The corresponding data are shown in Table 3B. Detailed staging data for all cases in which a discrepant finding between the clinical and pathological involvement of lymph node regions as well as of the primary tumours was found necessitating a re-assessment of the overall tumour stage are shown in Table 4.

Discussion

We retrospectively investigated the correlation of pre-therapeutic clinical staging data with the findings of the patho-histological examination of the lymph nodes of the neck in patients with squamous cell carcinoma of the head and neck who underwent surgery plus postoperative radiotherapy. The principal intention of the study was to determine the possible extent of disparity between the findings of clinical versus pathological staging procedures. Also we sought to compare the results from our institution, at which such a comparative analysis has not been conducted to date, with those from other groups.

We are aware of certain limitations regarding our study, as this analysis was performed in a retrospective manner and data were accumulated over almost ten years. It is possible that changes in the quality of diagnostic imaging as well as variations in the professional experience, amongst others, may have contributed to unknown biases in our analysis.

One of the most comprehensive comparative analysis of clinical and pathological staging data in head and neck carcinoma patients (results from Intergroup Study ECOG 4393/RTOG 9614) was published by Koch *et al.*[12] The authors found disparities between the staging procedures in almost 50% of 501 investigated patients. In summary, a perfect match between clinical and pathological T-, N-classification and the overall stage was found in 52.2%, 53.5%, and 54.9%, respectively. Nevertheless, Koch *et al.*[12] found that both clinical and pathological staging methods showed an association of stage with overall survival. They concluded that both staging methods are useful in predicting survival, although staging after neck dissection regarding nodal metastases allowed further refinement in prognostic results. They found that only 69.7% of the patients judged to be clinically metastasis-free were pathologically N0, corresponding to 30.3% false-negative clinical staging. The percentage of CT versus MRI was not reported in this publication.

Other investigators found a 34% rate of occult lymph node disease in cN0 oral tongue carcinoma patients.[10] Buckley *et al.*[19] investigated the prevalence and distribution of cervical lymph node metastases in 100 laryngeal and hypopharyngeal patients who were treated by neck dissection for either N0 or N+ disease. They found 36% nodal metastases of the ipsilateral neck and 27% of the contralateral neck in clinically staged N0 cases. In N+ cases, prevalence was 90% ipsilateral and 37% contra-lateral, respectively. The imaging technique in this study used was CT only.

A clinically significant discrepancy between pathological and clinical neck staging (N = 256) was reported by Henriques *et al.*[20] Their results suggested that in 62% of the cases a clinical upstaging after pathological assessment of the lymph nodes was necessary.

Our data show that 67% of the patients were staged correctly at the lymph node level when N2a,

TABLE 2B. Concordance of pathological and clinical findings according to N stage

Clinical stage	Pathological stage					
N = 87	pN0	pN1	pN2a	pN2b	pN2c	pN3
cN0 (N = 17)	11	3	0	1	2	0
cN1 (N = 15)	4	6	0	3	2	0
cN2a (N = 6)	1	2	1	2	0	0
cN2b (N = 24)	3	2	0	18	1	0
cN2c (N = 25)	2	2	1	10	8	2
cN3 (N = 0)	0	0	0	0	0	0

TABLE 3A. Prevalence of regional lymph node involvement according to tumour site

	Primary tumour localization				
Lymph Node Level	Hypopharynx (n = 15)	Larynx (n = 9)	Oral cavity (n = 30)	Oropharynx (n = 33)	% of total collective
I	2 (13.3%)	1 (11.1%)	5 (16.7%)	6 (18.2%)	14 (16.1%)
II	8 (53.3%)	4 (44.4%)	22 (73.3%)	18 (54.4%)	52 (59.8%)
III	3 (20%)	4 (44.4%)	13 (43.3%)	15 (45.5%)	35 (40.2%)
IV	4 (26.7%)	2 (22.2%)	7 (23.3%)	5 (15.2%)	18 (20.7%)
V	2 (13.3%)	1 (11.1%)	4 (13.3%)	1 (3%)	8 (9.2%)

TABLE 3B. Statistical analysis of the correlation of involvement of adjacent lymph-node levels

N = 87		LI	LII	LIII	LIV	LV
LI	Corr.	1				
LII	Corr. Sig.	0.029 0.791	1			
LIII	Corr. Sig.	0.040 0.711	0.325[a] 0.001	1		
LIV	Corr. Sig.	-0.069 0.524	0.113 0.297	0.449[a] 0.000	1	
LV	Corr. Sig.	-0.139 0.198	0.088 0.419	0.145 0.182	0.427[a] 0.000	1

[a] Pearson correlation (significance 2-tailed). Correlations are significant below the 0.01 level.

TABLE 4. List of all cases associated with up- or down-staging according to the pre- and postoperative regional lymph-node status

No.	cT	cN	Overall clinical stage	pT	pN	Overall pathological stage
			Down-staging according to pN status n = 10 (11.5%)			
1	2	1	III	1	0	I
2	1	2a	IV	1	0	I
3	2	2b	IV	1	0	I
4	2	1	III	2	0	II
5	2	1	III	2	0	II
6	2	2b	IV	2	0	II
7	1	2b	IV	2	0	II
8	3	2c	IV	2	0	II
9	3	2b	IV	2	1	III
10	2	2c	IV	2	1	III
			Up-staging according to pN status N = 9 (10.3%)			
1	2	0	II	2	1	III
2	3	0	III	4	1	IV
3	2	1	III	2	2b	IV
4	2	1	III	2	2b	IV
5	3	0	III	3	2b	IV
6	2	1	III	2	2b	IV
7	2	1	III	3	2c	IV
8	1	0	I	1	2c	IV
9	1	2b	III	1	2c	IV

N2b, and N2c data were pooled into a single variable. Further sub-classification into N2a, N2b, and N2c leads to an increase in the fraction of discrepantly staged patients (48%). Of these, 25% had to be up-staged, and 23% were down-staged.

A statistical analysis of the correlation of lymph node level involvement was performed, as well as the frequency of pathological involvement according to the primary tumour site was calculated. As expected, level II was the most frequently involved node level (59.8% for all primary tumour sites combined). Level V (9.2% combined) was rarely involved. One patient presented with clinically and pathologically positive lymph nodes in level VI. We performed further statistical analyses of the lymph node data. Positivity in level I involvement was not found to be correlated to positivity or negativity in any other level investigated. As is shown in Table 3B, positivity only of the respective adjacent levels II and III, III and IV, and level IV and V was significantly correlated. The correlation of positive involvement between level II and III was calculated to be 0.352, between level III and IV 0.449, and between level IV and V 0.427. These results may be explained by the well-known fact that metastasis preferentially proceeds along lymph node levels and rarely bypasses or skips the succeeding level. As has been pointed out by other authors, spreading of metastatic cells along cervical lymph nodes is somewhat consistent, and the risk of involvement increases for each level if the neighboring level is affected.[15,21]

Some authors attempted to represent current data of nodal involvement in mathematical models.[22,23] However, such models are - at least for the time being - not of clinical significance. From a clinical point of view, the most relevant question to answer is, in how many cases an up- or down-staging of the overall tumour stage, after reclassification based on the patho-histological examination of lymph node levels, might be necessary. In summary, in 11.5% (10/87) of the cases a down-staging and in 10.3% (9/87) of the cases an up-staging was the consequence after pathological re-assessment of the lymph node involvement. These results correspond nicely to those recently published derived from larger retrospective data sets of 252[24] and 392[25] oral squamous cell cancer patients, respectively. Choi *et al.*[24] reported an 82.5% agreement between the overall pathological and clinical lymph node status, compared to 78% in our collective. The patients in this study had CT or MRI to evaluate the primary tumour and cervical nodal status. PET/CT was performed in all subjects. Underestimation of tumour stage based on clinical assessment was observed by Choi *et al.*[24] in 13% of the patients, compared to 10.3% in our collective. The concordance between the pathological and clinical staging for the N-classification was found to be 59% in the study by Kreppel *et al.*[25], who compared each cN and pN stage separately. By comparison, subclassification of our data into N2a, N2b, and N2c results in a comparable percentage of 52% concordantly staged patients. All the patients included in this study had CT as well as MRI scans. Of interest and in context with our study, we recently found, that after preoperative radio-chemotherapy of locally advanced head and neck carcinoma patients, a patho-histological response assessment by CT was associated with a substantial fraction of the patients with either false positive (13%) or false negative (22%) diagnoses.[11]

In our patient group, 55 (63%) patients had a CT scan only, 21 (24%) patients an MRI scan, and in 11

(13%) cases both an MRI and CT scan was available. Statistical analysis showed that the type of imaging modality used (CT, MRI, CT & MRI) was not correlated with the percentage of discrepant results. Of note, more than one discrepantly diagnosed lymph-node level was identified in 30.9% of all patients.

In summary, our results indicate that in a substantial percentage of patients a patho-histological assessment of lymph node involvement may differ from the clinical evaluation by CT, MRI or despite the combination of CT and MRI. The percentage of patients in which staging had to be either up or down-migrated was very similar. Over- or understaging of lymph-nodes occurred in our collective in a similar percentage of the patients. Other authors[25] reported a higher percentage (86%) of overstaging. As the authors discussed in their publication, differences in the clinical assessment of lymph-nodes in the area of functional imaging modalities, such as PET-CT and DW-MRI, may be related directly or indirectly to the biology of malignant lymph-nodes, such as inflammatory processes, vascularization, and the extent of necrosis and hypoxia, which may affect the uptake of contrast agents. Also, the process of obtaining and manipulating the specimen per se, as well as the exactitude of the patho-histological workup, such as the number of resected lymph-nodes[12,26] may affect the final staging results. Of note, the mean number (N = 22) of resected lymph-nodes in our study was similar to the number published by another group.[26]

Due to the insufficient number of events in our collective, as defined by the number of cases that had to be up- or down-staged, a statistically valid comparison of the survival rates between these patient groups is not possible. However, three patients were down-staged from stage III/IV to stage I, and two patients were up-staged from stage I/II to stage III/IV. It is very likely that such massive changes in staging affect the prognosis as well as the type treatment of the individual patient affected. The study findings should also be seen in light of the increasing trend to spare healthy tissues or to selectively increase radiation doses using modern treatment techniques such as IMRT/VMAT and stereotactic radiation treatments.[27]

Conclusions

Results in the study indicated that an under or overestimation of clinical tumour stage may occur in approximately up to 20–30% of HNSCC patients.

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References

1. Abraham J. Imaging for head and neck cancer. *Surg Oncol Clin N Am* 2015; **24:** 455-71. doi: 10.1016/j.soc.2015.03.012
2. Johnson JT, Branstetter BFt. PET/CT in head and neck oncology: State-of-the-art 2013. *Laryngoscope* 2014; **124:** 913-5. doi: 10.1002/lary.23942
3. Liao LJ, Hsu WL, Wang CT, Lo WC, Lai MS. Analysis of sentinel node biopsy combined with other diagnostic tools in staging cN0 head and neck cancer: A diagnostic meta-analysis. *Head Neck* 2016; **38:** 628-34. doi: 10.1002/hed.23945
4. Zygogianni A, Kyrgias G, Kouvaris J, Pistevou-Gompaki K, Kouloulias V. A new role of PET/CT for target delineation for radiotherapy treatment planning for head and neck carcinomas. *Hell J Nucl Med* 2012; **15:** 139-43.
5. Cmelak AJ. Current issues in combined modality therapy in locally advanced head and neck cancer. *Crit Rev Oncol Hematol* 2012; **84:** 261-73. doi: 10.1016/j.critrevonc.2012.04.004
6. Kavanagh BD, Haffty BG, Tepper JE. Radiation oncology: a snapshot in time, 2014. *J Clin Oncol* 2014; **32:** 2825-6. doi: 10.1200/JCO.2014.57.3071
7. Pryor DI, Solomon B, Porceddu SV. The emerging era of personalized therapy in squamous cell carcinoma of the head and neck. *Asia Pac J Clin Oncol* 2011; **7:** 236-51. doi: 10.1111/j.1743-7563.2011.01420.x
8. Thariat J, Hannoun-Levi JM, Sun Myint A, Vuong T, Gerard JP. Past, present, and future of radiotherapy for the benefit of patients. *Nat Rev Clin Oncol* 2013; **10:** 52-60. doi: 10.1038/nrclinonc.2012.203
9. Biron VL, O'Connell DA, Seikaly H. The impact of clinical versus pathological staging in oral cavity carcinoma - a multi-institutional analysis of survival. *J Otolaryngol Head Neck Surg* 2013; **42:** 28. doi: 10.1186/1916-0216-42-28
10. Greenberg JS, El Naggar AK, Mo V, Roberts D, Myers JN. Disparity in pathologic and clinical lymph node staging in oral tongue carcinoma. Implication for therapeutic decision making. *Cancer* 2003; **98:** 508-15. doi: 10.1002/cncr.11526
11. Klug C, Keszthelyi D, Ploder O, Sulzbacher I, Voracek M, Wagner A, et al. Neoadjuvant radiochemotherapy of oral cavity and oropharyngeal cancer: evaluation of tumor response by CT differs from histopathologic response assessment in a significant fraction of patients. *Head Neck* 2004; **26:** 224-31. doi: 10.1002/hed.10373
12. Koch WM, Ridge JA, Forastiere A, Manola J. Comparison of clinical and pathological staging in head and neck squamous cell carcinoma: results from Intergroup Study ECOG 4393/RTOG 9614. *Arch Otolaryngol Head Neck Surg* 2009; **135:** 851-8. doi: 10.1001/archoto.2009.123
13. Gregoire V, Ang K, Budach W, Grau C, Hamoir M, Langendijk JA, et al. Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. *Radiother Oncol* 2014; **110:** 172-81. doi: 10.1016/j.radonc.2013.10.010
14. Gregoire V, Levendag P, Ang KK, Bernier J, Braaksma M, Budach V et al. CT-based delineation of lymph node levels and related CTVs in the node-negative neck: DAHANCA, EORTC, GORTEC, NCIC,RTOG consensus guidelines. *Radiother Oncol* 2003; **69:** 227-36. doi: 10.1016/j.radonc.2003.09.011
15. Vorwerk H, Hess CF. Guidelines for delineation of lymphatic clinical target volumes for high conformal radiotherapy: head and neck region. *Radiat Oncol* 2011; **6:** 97. doi: 10.1186/1748-717x-6-97
16. Bhargava P, Rahman S, Wendt J. Atlas of confounding factors in head and neck PET/CT imaging. *Clin Nucl Med* 2011; **36:** e20-9. doi: 10.1097/RLU.0b013e318212c872
17. Morgan B. Opportunities and pitfalls of cancer imaging in clinical trials. *Nat Rev Clin Oncol* 2011; **8:** 517-27. doi: 10.1038/nrclinonc.2011.62

18. Selzer E, Grah A, Heiduschka G, Kornek G, Thurnher D. Primary radiotherapy or postoperative radiotherapy in patients with head and neck cancer: comparative analysis of inflammation-based prognostic scoring systems. *Strahlenther Onkol* 2015; **191:** 486-94. doi: 10.1007/s00066-014-0803-1

19. Buckley JG, MacLennan K. Cervical node metastases in laryngeal and hypopharyngeal cancer: a prospective analysis of prevalence and distribution. *Head Neck* 2000; **22:** 380-5.

20. Henriques V, Breda E, Monteiro E. Discrepancy between clinical and pathological neck staging in oral cavity carcinomas. *Acta Otorrinolaringologica Espanola* 2017; **69:** 67-73. doi: 10.1016/j.otorri.2017.02.008

21. Candela FC, Kothari K, Shah JP. Patterns of cervical node metastases from squamous carcinoma of the oropharynx and hypopharynx. *Head Neck* 1990; **12:** 197-203.

22. Benson N, Whipple M, Kalet IJ. A Markov model approach to predicting regional tumor spread in the lymphatic system of the head and neck. *AMIA Annu Symp Proc* 2006; 31-5.

23. Kalet IJ, Whipple M, Pessah S, Barker J, Austin-Seymour MM, Shapiro LG. A rule-based model for local and regional tumor spread. *Proc AMIA Symp* 2002; 360-4.

24. Choi N, Noh Y, Lee EK, Chung M, Baek CH, Baek KH, et al. Discrepancy between cTNM and pTNM staging of oral cavity cancers and its prognostic significance. *J Surg Oncol* 2017; **115:** 1011-18. doi: 10.1002/jso.24606

25. Kreppel M, Nazarli P, Grandoch A, Safi AF, Zirk M, Nickenig HJ et al. Clinical and histopathological staging in oral squamous cell carcinoma - Comparison of the prognostic significance. *Oral Oncol* 2016; **60:** 68-73. doi: 10.1016/j.oraloncology.2016.07.004

26. Safi AF, Kauke M, Grandoch A, Nickenig HJ, Drebber U, Zoller J et al. Clinicopathological parameters affecting nodal yields in patients with oral squamous cell carcinoma receiving selective neck dissection. *J Craniomaxillofac Surg* 2017; **45:** 2092-96. doi: 10.1016/j.jcms.2017.08.020

27. Gregoire V, Langendijk JA, Nuyts S. Advances in Radiotherapy for Head and Neck Cancer. *J Clin Oncol* 2015; **33:** 3277-84. doi: 10.1200/JCO.2015.61.2994