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Viable tumor in salvage neck dissections in head and neck cancer: Relation with initial treatment, change of lymph node size and human papillomavirus

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ABSTRACT

Objectives: To identify predictive factors for the presence of viable tumor and outcome in head and neck cancer patients who undergo therapeutic salvage neck dissections.
Materials and Methods: Retrospective analysis of 76 salvage neck dissections after radiotherapy alone (n = 22), radiotherapy in combination with carboplatin/5-fluorouracil (n = 42) or with cetuximab (n = 12).
Results: Viable tumor was detected in 41% of all neck dissections. Univariate analysis revealed initial treatment with radiotherapy without systemic therapy (OR 6.93, 95%CI: 2.28–21.07, p < .001), increased lymph node size after initial treatment compared to pretreatment CT scan (OR 20.48, 95%CI: 2.46–170.73, p = .005), more extensive neck dissections (OR 8.40, 95%CI: 2.94–23.98, p < .001), and human papillomavirus negative cancer (OR 4.22, 95%CI: 1.10–16.22, p = .036) as predictors of viable tumor. Patients with decreased or stable, but persistently enlarged lymph node size after chemoradiation had a significantly lower chance of viable tumor (OR 0.15, 95%CI: 0.05–0.41, p < .001). Disease-specific 5-year survival was 34% in case of viable tumor, and 78% when no viable tumor was found (p < .001).
Conclusions: Viable tumor in salvage neck dissections is associated with reduced survival. Radiotherapy alone, human papillomavirus negative cancer and increase in lymph node size, are associated with viable tumor in salvage neck dissections. In case of decreased or stable lymph node size after chemoradiation, watchful waiting could be considered.

Introduction

Radiotherapy with or without concomitant systemic treatment is one of the main treatment strategies for patients with locally advanced head and neck squamous cell carcinoma (HNSCC).

These patients have high recurrence rates despite the evolution of treatment strategies [1]. In case of persistent enlarged or recurrent lymph nodes after complete response of the primary tumor, a salvage neck dissection is the treatment of choice [1]. However, this treatment has been associated with considerable morbidity like wound complications in more than 30% of the patients. Complication rates are lower after selective salvage neck dissections compared to (modified) radical salvage neck dissections [2].

After (chemo)radiation, the diagnostic value of CT and MRI, and the specificity of ultrasound-guided fine needle aspiration cytology for evaluating lymph node metastases is low [2], which complicates

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decision making about neck dissection.

PET-CT guided surveillance after chemoradiotherapy is advised. The indication for a salvage neck dissection is lymph node size > 1 cm with FDG uptake. In case of lymph nodes > 1 cm without FDG-uptake and FDG-positive lymph nodes < 1 cm a neck dissection can be considered [3]. Therefore, in recent studies, salvage neck dissections are generally performed in patients with enlarged PET-negative lymph nodes or persistent normal-sized PET positive nodes [3,4].

Other studies have shown that 20–68% of the therapeutic salvage neck dissections contain viable tumor [5]. Identification of variables predicting the presence of viable tumor in neck nodes after various forms of treatment (i.e. radiotherapy with or without systemic therapy) would be helpful for selecting the right patients for neck dissection and for avoiding unnecessary surgery.

In this study we aimed to identify clinical, histopathological, radiological and treatment related predictors for the presence of viable tumor in salvage neck dissections. Furthermore we assessed the influence of presence of viable tumor in salvage neck dissections on clinical outcome.

Patients and methods

The study cohort was composed of 76 patients. All patients who were treated with a salvage neck dissection after definitive radiotherapy with or without concomitant systemic treatment for HNSCC between January 2005 and March 2015 at the University Medical Center in Groningen were included in this retrospective analysis.

The indication for salvage neck dissection was residual cervical lymph nodes suspicious for regional metastases in the absence of a residual primary tumor. Patients with distant metastases or surgical treatment of the primary tumor site simultaneously with the neck dissection were excluded from the study. The study was approved by the Institutional Review Board.

Primary treatment regimens and evaluation of treatment response

Of the 76 included patients, 22 were initially treated with radiotherapy alone (without concomitant systemic treatment), 42 with radiotherapy and carboplatin/5-fluorouracil (5-FU) and 12 with radiotherapy in combination with cetuximab.

Patients were treated with definitive conventional three-dimensional conformal radiotherapy (3D-CRT) (n = 14) and since 2007 with intensity modulated radiotherapy (IMRT) (n = 62).

Patients treated with 3D-CRT received 23 × 2 Gy to the indicated elective neck levels and a sequential boost on the primary tumor and lymph node metastases to a total dose of 70 Gy. In patients treated with IMRT a simultaneous integrated boost technique was used. Most patients received bilateral elective irradiation of the neck to a total dose of 54.25 Gy, in fractions of 1.55 Gy, while the primary tumor and lymph node metastases were treated to a total dose of 70 Gy, in 2 Gy fractions.

Patients treated with concomitant chemoradiotherapy were irradiated with a schedule of 35 × 2 Gy, 5 times per week over 7 weeks. Patients not eligible for chemoradiotherapy were treated with an accelerated schedule of 6 fractions per week up to a total dose of 70 Gy, with or without cetuximab. Patients ≥70 years were treated with radiotherapy alone (35 × 2 Gy, 5 times per week over 7 weeks).

Chemotherapy consisted of 3 cycles carboplatin 300–350 mg/m^2 at day 1 in combination with 5-FU 600 mg/m^2 as continues infusion on day 1–4 in 3-week cycles. Cetuximab was given to patients with locally advanced disease < 70 years of age with a contraindication for chemotherapy. Cetuximab was started 1 week before start of radiotherapy with an initial dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2 during radiotherapy.

For evaluation of treatment response, a CT was performed approximately 8 weeks after completion of initial treatment. Lymph nodes exceeding 1 cm in short axis, or with pathological imaging characteristics such as a necrotic or cystic center, heterogeneous enhancement, indistinct margins and/or a round shape were considered suspect for residual or recurrent disease. The post-treatment scans were reviewed in the Multidisciplinary Tumor Board. In case of suspicious lymph nodes in the neck, the involved levels and size of the largest lymph node were recorded. The size of the largest lymph node on post-treatment response imaging was compared to the size on the CT before start of the initial treatment. Change in lymph node size was calculated as a percentage of the lymph node size on CT before initial treatment, and categorized in patient groups with an increased, stable or decreased lymph node size, reflecting the response to initial treatment.

In one patient treated with radiotherapy alone with persistently enlarged lymph nodes at the post-treatment response imaging, the pre-treatment CT was not available at the time of this study; therefore, change in lymph node size could not be assessed and the patient was excluded from the concerning analyses.

Before salvage neck dissection, locally persistent or recurrent primary tumor was ruled out by performing direct panendoscopy under general anesthesia. If suspicious tissue was seen at the initial primary tumor localization, biopsies were taken.

Salvage neck dissections

The extent of neck dissection was based on initial treatment and on the size and location of suspicious lymph nodes on post-treatment response imaging. Patients who were initially treated with radiotherapy alone underwent a (modified) radical neck dissection as standard treatment. Patients who received primary radiotherapy in combination with systemic treatment underwent, if possible, a selective neck dissection of the level(s) of the affected lymph nodes.

Neck dissection specimens were divided into separate levels, sliced and palpated for lymph nodes. Lymph nodes were formalin fixed and paraffin embedded. Standard single level Haematoxylin and Eosin (H&E) sections were cut. All slides were reviewed by a dedicated head and neck pathologist. The oropharyngeal carcinomas were tested for human papillomavirus (HPV) [6]. All other carcinomas were not tested for the presence of human papillomavirus, but were considered to be HPV negative because of the low prevalence of HPV-driven head and neck squamous cell carcinomas among these subsites [6–8], and because HPV positivity in hypopharyngeal carcinomas is not clearly associated with prognosis [9].

Statistical analysis

Logistic regression analysis was used to evaluate predictive factors for presence of viable tumor, and to estimate correlations between variables. A p value < .05 was considered statistically significant. For statistical analysis, extent of lymph node levels resected was dichotomized into 3 or less lymph node levels (reflecting selective neck dissections) and 4 or more levels (reflecting more extensive neck dissections).

Negative and positive predictive values were calculated to analyze the combination of initial treatment and change in lymph node size in relation to presence of viable tumor.

Kaplan-Meier survival plots were constructed to estimate disease-specific survival, which was defined as the duration from the salvage neck dissection to death as a consequence of head and neck cancer or last follow-up of the patient, with evaluation of the differences by the Mantel-Cox log-rank test.

Statistical analysis was performed using SPSS (version 22 for Windows, Armonk, NY: IBM Corp.).

Table 1
Demographic and clinical data of patients, grouped per initial treatment group.

Variables		Initial treatment			
		RT alone (n = 22) n (%)	RT + carboplatin/5-FU (n = 42) n (%)	RT + cetuximab (n = 12) n (%)	All patients (n = 76) n (%)
Median age, y		64.3	57.2	64.5	61.1
Sex	Male	20 (91)	27 (64)	9 (75)	56 (74)
	Female	2 (9)	15 (36)	3 (25)	20 (26)
Location primary tumor	Oral cavity	2 (9)	2 (5)	3 (25)	7 (9)
	Oropharynx	4 (18)	27 (64)	3 (25)	34 (45)
	Hypopharynx	3 (14)	9 (21)	6 (50)	18 (24)
	Larynx	13 (59)	4 (10)	0 (0)	17 (22)
T classification	T1	2 (9)	4 (10)	1 (8)	7 (9)
	T2	9 (41)	11 (26)	2 (17)	22 (29)
	T3	8 (36)	6 (14)	4 (33)	18 (24)
	T4	3 (14)	21 (50)	5 (42)	29 (38)
N classification	N0	3 (14)	0 (0)	0 (0)	3 (4)
	N1	3 (14)	1 (2)	1 (8)	5 (7)
	N2a	2 (9)	2 (5)	0 (0)	4 (5)
	N2b	11 (50)	11 (26)	3 (25)	25 (33)
	N2c	3 (14)	26 (62)	8 (67)	37 (49)
	N3	0 (0)	2 (5)	0 (0)	2 (3)
Type of ND	SSND, unilateral	4 (18)	26 (62)	5 (42)	35 (46)
	SSND, bilateral	1 (5)	4 (10)	2 (17)	7 (9)
	SND, unilateral	0 (0)	7 (17)	2 (17)	9 (12)
	SND, bilateral	1 (5)	2 (5)	1 (8)	4 (5)
	(M)RND, unilateral	14 (64)	3 (7)	1 (8)	18 (24)
	(M)RND, bilateral	2 (9)	0 (0)	1 (8)	3 (4)
Median follow-up, mo		14.6 (range 0.3–117.6)	33.6 (range 4.6–109.3)	31.5 (range 6.9–76.2)	30.8 (range 0.3–117.6)

Abbreviations: RT, radiotherapy; 5-FU, 5-fluorouracil; ND, neck dissection; SSND, super-selective neck dissection; SND, selective neck dissection; (M)RND, (modified) radical neck dissection.

Results

Patients

Demographic and clinical data are listed in Table 1. The cohort of 76 patients consisted of 56 men and 20 women with a median age of 61 years (range 44–83). Forty-five percent had a primary tumor in the oropharynx. Thirty-eight percent of the patients had a primary T1 or T2 tumor, and 62% a T3 or T4 tumor. Initial N classification was positive in 96% of the patients. Median follow-up for all patients was 30.8 months (range 0.3–117.6), and 53.0 months (range 14.2–117.6) for all living patients.

Of the patients who underwent a salvage neck dissection after radiotherapy alone, 73% had a (modified) radical neck dissection (Table 1). The median number of resected neck levels after initial treatment with radiotherapy was 5, after chemoradiotherapy 2, and after radiotherapy with cetuximab 3.

Human papillomavirus status

Fifty percent of the oropharyngeal tumors were positive for HPV, of which 16 for HPV 16 and 1 for HPV 33. Sixty-four percent of the HPV negative tumors, and 94% of the HPV positive tumors, were treated with radiotherapy with systemic therapy (Table 2).

Growth of lymph node size after initial treatment occurred in 17% of the HPV negative tumors, and in 6% of the HPV positive tumors. Limited neck dissections were performed in 88% of the patients with HPV positive tumor, and in 53% of HPV negative ones (Table 2).

Univariate analysis of presence of viable tumor

Table 3 shows the univariate analysis regarding the presence of viable tumor.

Table 2
Demographic and clinical data of patients in relation with human papillomavirus status.

Variables		HPV status	
		Positive (n = 17) n (%)	Negative[a] (n = 59) n (%)
Median age, y		58.1	62.0
Primary clinical N classification	N0	0 (0)	3 (5)
	N+	17 (100)	56 (95)
Initial treatment	RT with systemic therapy	16 (94)	38 (64)
	RT alone	1 (6)	21 (36)
Change in size of lymph node[b]	Same size or decrease	16 (94)	48 (83)
	Growth	1 (6)	10 (17)
Number of resected levels	1–3	15 (88)	31 (53)
	4 or more	2 (12)	28 (47)

Abbreviations: HPV, human papillomavirus; RT, radiotherapy; SalvND, salvage neck dissection; FU, follow-up.
[a] All non-oropharyngeal carcinomas were considered HPV negative.
[b] The pre-treatment CT of one patient was not available at the time of this study.

In 41% of the salvage neck dissections viable tumor was found. Viable tumor was present in 67% of the patients with an initial N0 classification, and in 40% of the patients with an initial N+ classification ($p = .374$). Of the 22 patients initially treated with radiotherapy alone, 73% had viable tumor. After radiotherapy with systemic treatment, significantly less neck dissections were positive for viable tumor (28%, $p < .001$). Increase in lymph node size was seen in 15% of the patients. In case of growth of lymph nodes on post-treatment response

Table 3
Univariate analysis of predictive factors for the presence of viable tumor.

		Univariate analysis			
Variables		No viable tumor n (%)	Viable tumor OR n (%)	OR (95% CI)	p value
Age, y (median)	Continuous variable	61.2	60.1	1.04 (0.98–1.10)	.224
Primary T classification	T1 or T2	17 (59)	12 (41)	1 (Reference)	
	T3 or T4	28 (60)	19 (40)	0.96 (0.38–2.46)	.934
Primary clinical N classification	N0	1 (33)	2 (67)	1 (Reference)	
	N+	44 (60)	29 (40)	0.33 (0.03–3.80)	.374
Initial treatment	RT with systemic therapy	39 (72)	15 (28)	1 (Reference)	
	RT alone	6 (27)	16 (73)	6.93 (2.28–21.07)	**.001**
Change in size of lymph node[a]	Same size or decrease	43 (67)	21 (33)	1 (Reference)	
	Growth	1 (9)	10 (91)	20.48 (2.46–170.73)	**.005**
Number of resected levels	1–3	36 (78)	10 (22)	1 (Reference)	
	4 or more	9 (30)	21 (70)	8.40 (2.94–23.98)	< **.001**
HPV status	Positive	14 (82)	3 (18)	1 (Reference)	
	Negative	31 (53)	28 (47)	4.22 (1.10–16.22)	**.036**

Abbreviations: OR, odds ratio; 95% CI, 95% confidence intervals; SalvND, salvage neck dissection; FU, follow up; HPV, human papillomavirus; RT, radiotherapy.
Significant values are shown in bold.
[a] The pre-treatment CT of one patient was not available at the time of this study and was left out of this analysis.

imaging, viable tumor was present in 91% of the patients, a significantly higher percentage than in patients with no change or decrease in size (33%, p = .005). There was a significant difference in the presence of viable tumor between more extensive neck dissection and limited neck dissection specimens (70% and 22%, respectively, p < .001). The percentage of viable tumor was significantly lower in the HPV positive oropharyngeal cancer patients compared to all others (18% and 47%, respectively, p = .036). Primary T classification and age were not significantly related to the presence of viable tumor.

In Table 4 we analyzed the combination of different initial treatment modalities and change in lymph node size in relation with viable tumor in salvage neck dissection specimens. Patients with persistent lymph nodes who were treated with radiotherapy alone had a significantly higher risk of viable tumor cells compared to other patients, independent of change in lymph node size. Patients with the lowest risk of viable tumor were patients with unchanged or decreased lymph node size on post-treatment response imaging after chemoradiotherapy (21% viable tumor, p < .001), with a negative predictive value for the presence of viable tumor of 79% and a positive predictive value of 64%.

We found a strong correlation between the variables viable tumor, change in lymph node size, HPV, initial treatment, and number of resected levels (Supplementary Table 1). Therefore, no multivariate analysis was performed.

Disease-specific survival

The estimated 5-year disease-specific survival for all patients who underwent salvage neck dissection was 58%. This was significantly worse for patients with viable tumor in salvage neck dissection specimens (34%) than for those without (78%, p < .001) (Fig. 1A). Patients with an HPV positive tumor had a significantly better 5-year disease-specific survival compared to patients with an HPV negative tumor (88% and 47%, respectively, p = .014) (Fig. 1B).

Discussion

In this study, viable tumor was found in 41% of all patients who underwent salvage neck dissection. Therefore, more than half of the patients were exposed to morbidity risk without having any survival benefit. Radiotherapy alone, negative HPV status and increased lymph node size were identified as predictors of viable tumor in salvage neck dissections.

Previous studies tried to find predictors of complete pathological response in salvage neck dissections. Clavel et al. [10] included patients treated with chemoradiotherapy and identified reduction in lymph node size as a predictor for a negative neck. In our study we confirmed the importance of change in lymph node size, but also showed a relation between initial treatment (i.e. radiotherapy alone or combined with chemotherapy or cetuximab) and the presence of viable tumor in salvage neck dissections.

Extent of neck dissection as a predictor for the presence of viable tumor could be explained by the correlation between initial treatment and extent of neck dissection; most patients after radiotherapy with concomitant systemic therapy underwent a selective neck dissection.

Table 4
Univariate analysis of different initial treatment modalities and change in lymph node size in relation with viable tumor in salvage neck dissection specimens.

Initial treatment	Change in lymph node size[b]	No. of cases	Viable tumor rate	% viable tumor	OR (95% CI)[a]	p value[a]
RT alone	Increase	8	7/8	88%	12.54 (1.46–108.10)	**.021**
RT alone	Same size or decrease	13	9/13	69%	4.09 (1.13–14.83)	**.032**
RT + carboplatin/5-FU	Increase	3	3/3	100%	NA	
RT + carboplatin/5-FU	Same size or decrease	39	8/39	21%	0.15 (0.05–0.41)	< **.001**
RT + cetuximab	Increase	0	0/0	NA	NA	
RT + cetuximab	Same size or decrease	12	4/12	33%	0.67 (0.18–2.45)	.541

Abbreviations: OR, odds ratio; 95% CI, 95% confidence intervals; RT, radiotherapy; 5-FU, 5-fluorouracil; NA, not applicable (could not be estimated).
Significant values are shown in bold.
[a] Reference: all other patients.
[b] The pre-treatment CT of one patient was not available at the time of this study and was left out of this analysis.

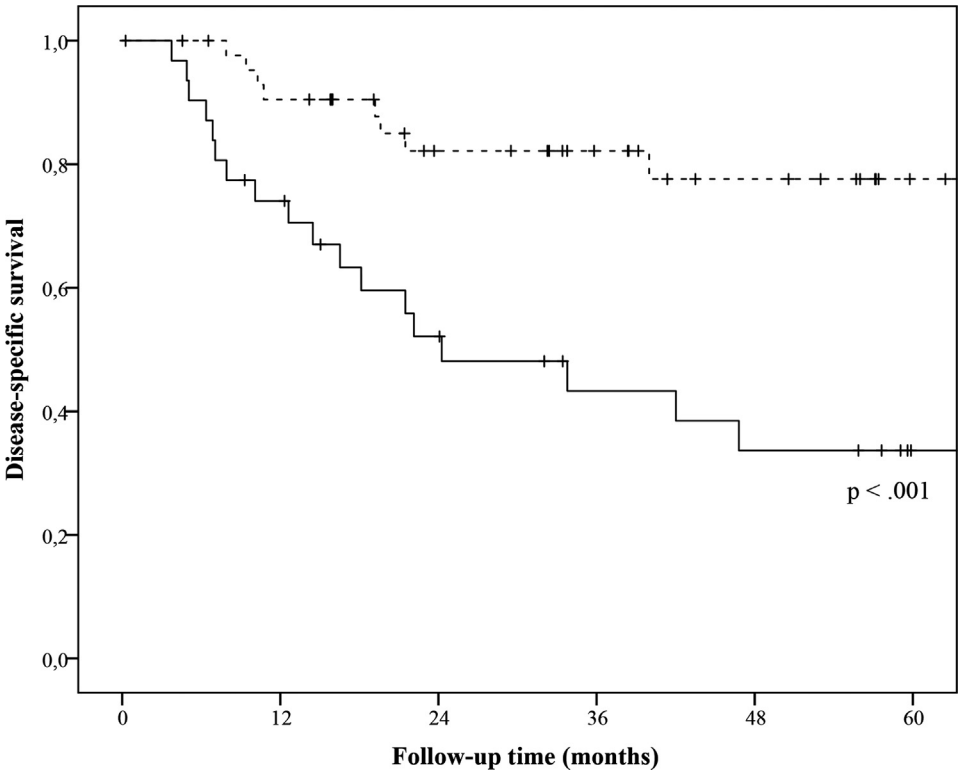

Fig. 1A. Disease-specific survival of patients with (—) or without (– – –) viable tumor.

Unfortunately, due to the high number of correlations, multivariate analysis to evaluate whether lymph node size, initial treatment, and extent of neck dissection are independent predictive factors could not be performed.

In the present study, patients with HPV positive oropharyngeal cancer had significantly lower chance of viable tumor in the neck dissection specimen. Huang et al. [11] showed that HPV positive tumors have a prolonged process of reduction in lymph node size after radiotherapy. These lymph nodes are consequently regarded as suspect for residual disease while there may have been ongoing reduction in size.

We routinely performed early response evaluation CT approximately 8 weeks after completion of radiotherapy between 2005 and 2015, when PET was not yet advised for standard evaluation. Assumedly, there is still ongoing resorption of non-viable tumor at that

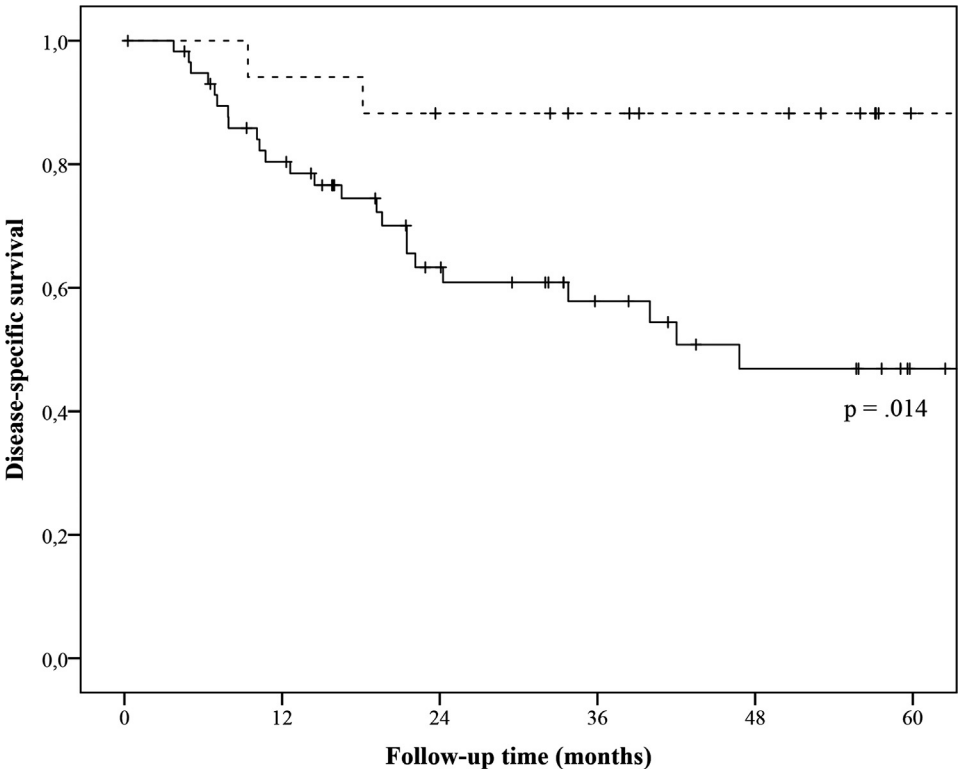

Fig. 1B. Disease-specific survival of patients with an HPV negative (—) or HPV positive (– – –) tumor.

moment, which might result in a higher false positive rate compared to scans performed around 12 weeks post-treatment [12,13].

Nowadays CT in combination with PET is advised for evaluation of treatment response [3,4]. However, FDG-PET has a low positive predictive value after (chemo)radiation since FDG uptake can be caused by postradiation inflammation [13]. In recent studies evaluating PET-CT, enlarged FDG-PET negative and normal-sized PET-positive lymph nodes are an indication for salvage surgery. Mehanna et al. [4] compared planned neck dissection to PET-CT guided active surveillance in patients with N2 or N3 nodal disease treated with chemoradiotherapy. PET-CT guided surveillance resulted in fewer neck dissections and fewer complications, with similar overall survival. A salvage neck dissection was performed in 36 patients, including patients who had mild or no FDG uptake in enlarged nodes or mild FDG uptake in normal-sized nodes. Since FDG uptake can be caused by postradiation inflammation [13], it would be interesting to know if viable tumor was present and which predictors of viable tumor could be identified.

A possible option to select those 21% of patients with viable tumor after chemoradiotherapy with an unchanged or decreased lymph node size is to repeat imaging by PET-CT. This is consistent with the 2017 National Comprehensive Cancer Network (NCCN) guideline [3], which advises a neck dissection or PET imaging at 12 weeks when CT at 8–12 weeks is suspect for residual disease. However, this guideline is independent of initial treatment and does not take change in lymph node size into account. In addition to this guideline, it can be considered to perform or repeat PET in those patients treated with chemoradiotherapy with unchanged or decreased lymph node size on post-treatment response imaging and to perform a salvage neck dissection in all other patients with persistent enlarged lymph nodes.

As reported in other studies [14–16], disease-specific survival after salvage neck dissection was negatively affected by the presence of viable tumor. However, the disease-specific survival might be influenced by the higher proportion of HPV positive tumor in the group without viable tumor. In line with other studies [6,8,17,18], we found that patients with HPV positive oropharyngeal cancer had a significantly better disease-specific survival than the others.

Conclusion

Initial treatment with radiotherapy alone, increase in lymph node size on post-treatment response imaging, and HPV negativity were predictive factors for presence of viable tumor and could be helpful in the decision-making whether to perform a salvage neck dissection or to follow wait-and-scan policy. Based on these results, a wait-and-scan policy could be considered in patients with stable or decreased size of lymph nodes after initial treatment with concomitant chemoradiotherapy, especially for HPV positive oropharyngeal cancers. An early salvage neck dissection is indicated for all other patients.

Conflict of interest statement

All authors disclose that there are no conflicts of interest.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.oraloncology.2017.12.017.

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