



Original Research Article

Recurrence of head and neck squamous cell carcinoma in relation to high-risk treatment volume



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ABSTRACT

Background: Locoregional recurrence remains a major cause of failure in head and neck squamous cell carcinoma (HNSCC). Human papilloma virus (HPV)-associated HNSCCs generally have a good prognosis but may recur even after standard photon radiotherapy (RT). Another incentive in observing patterns of recurrence is increased use of highly conformal techniques such as proton therapy. We therefore studied geographic distribution of recurrent tumors in relation to the high-risk treatment volume in a cohort of patients with HNSCC receiving combined modality therapy.

Methods: Medical records of 508 patients diagnosed with HNSCC in 2010–2015 were reviewed. We identified a subgroup that had local and/or regional recurrence at hybrid positron emission tomography (PET)/computed tomography (CT) and/or magnetic resonance imaging (MRI). We adapted p16 as a surrogate marker for HPV-positivity and only patients with known p16 status were eligible for a detailed analysis where recurrent tumor was copied on the planning CT and the dose received by the recurrent tumor volume was determined using dose-volume histograms.

Results: Twenty-five patients who had received either cisplatin (n = 23) or cetuximab-enhanced (n = 2) RT were identified. 31 locoregional recurrent tumors were detected among 18 p16 negative and 7 p16 positive patients. Of recurrent tumors 14 (45%) were classified as in-field, 5 (16%) as marginal miss, and 12 (39%) as true miss. p16 positive patients had 4 in-field, 2 marginal, and 1 true miss. By contrast, p16 negative patients had 10 in-field, 3 marginal, and 11 true miss recurrences.

Conclusions: Both p16 positive and negative HNSCC recur in high-risk treatment volume despite the common view of high radiosensitivity of the former. Biomarkers predicting radioresistance should be characterized in p16 positive tumors before widely embarking on de-escalated CRT protocols. Another concern is how to decrease the number of true or marginal misses in p16 negative cases despite multimodality imaging-based target delineation.

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1. Introduction

Head and neck squamous cell carcinomas (HNSCC) constitute a heterogeneous group of tumors characterized by a tendency to

Abbreviations: CRT, chemoradiotherapy; CT, computed tomography; DFS, disease-free survival; ¹⁸F-fluorodeoxyglucose, FDG; HNSCC, head and neck squamous cell carcinoma; HPV, human papilloma virus; IMRT, intensity modulated radiotherapy; MRI, magnetic resonance imaging; OS, overall survival; PET, positron emission tomography; RT, radiation therapy.

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relapse. Approximately 50% of patients with locally advanced disease will develop a recurrence [1]. Locoregional recurrence remains a major cause of failure in HNSCC after definitive treatment. Concurrent chemoradiotherapy (CRT) is the cornerstone of management of locally advanced HNSCC. Studying geographic patterns of failure after radiotherapy can aid in determining the optimal dose and distribution of photon radiation in different patient subgroups. Such information is also critical for novel techniques using charged particles where rapid dose fall-off outside treatment volume imposes additional challenges [2].

Human papilloma virus (HPV)-associated HNSCC have substantially better prognosis after curative-intent therapy than their

HPV-negative counterparts. The risk of recurrence is lower for HPV-associated oropharyngeal cancer in particular [3,4]. Consequently, de-intensified therapy for HPV-associated oropharyngeal HNSCC is being widely investigated [5–7], with an aim of reducing treatment-associated morbidity and side effects. Outside of clinical trials patients with HPV-positive and negative tumors receive similar treatment. At present relatively little is known about the pattern of locoregional recurrence in relation to radiotherapy (RT) volumes of HPV-negative vs HPV-positive patients receiving CRT.

Bearing these observations in mind we decided to investigate geographic distribution of recurrent tumors in relation to the high-risk treatment volume in patients with HNSCC receiving CRT or cetuximab-enhanced RT. Moreover, we were interested in studying whether the location of recurrence would be different between p16 positive and negative HNSCC.

2. Methods

2.1. Study design and clinical assessment of recurrence

We retrospectively reviewed the medical records of all 507 patients who were diagnosed with HNSCC at Hospital District of Southwest Finland during 2010–2015. Overall survival and disease-free survival were analyzed, and patients with a recurrent disease were identified. p16 immunohistochemistry of the primary tumor, whenever available was used as a surrogate for HPV positivity.

Patient selection for more detailed analysis is described in Fig. 1. Inclusion criteria to be fulfilled were: i) locoregional recurrent tumor that appeared at least 3 months after end of first-line treatment, ii) RT as part of a curative treatment plan for primary

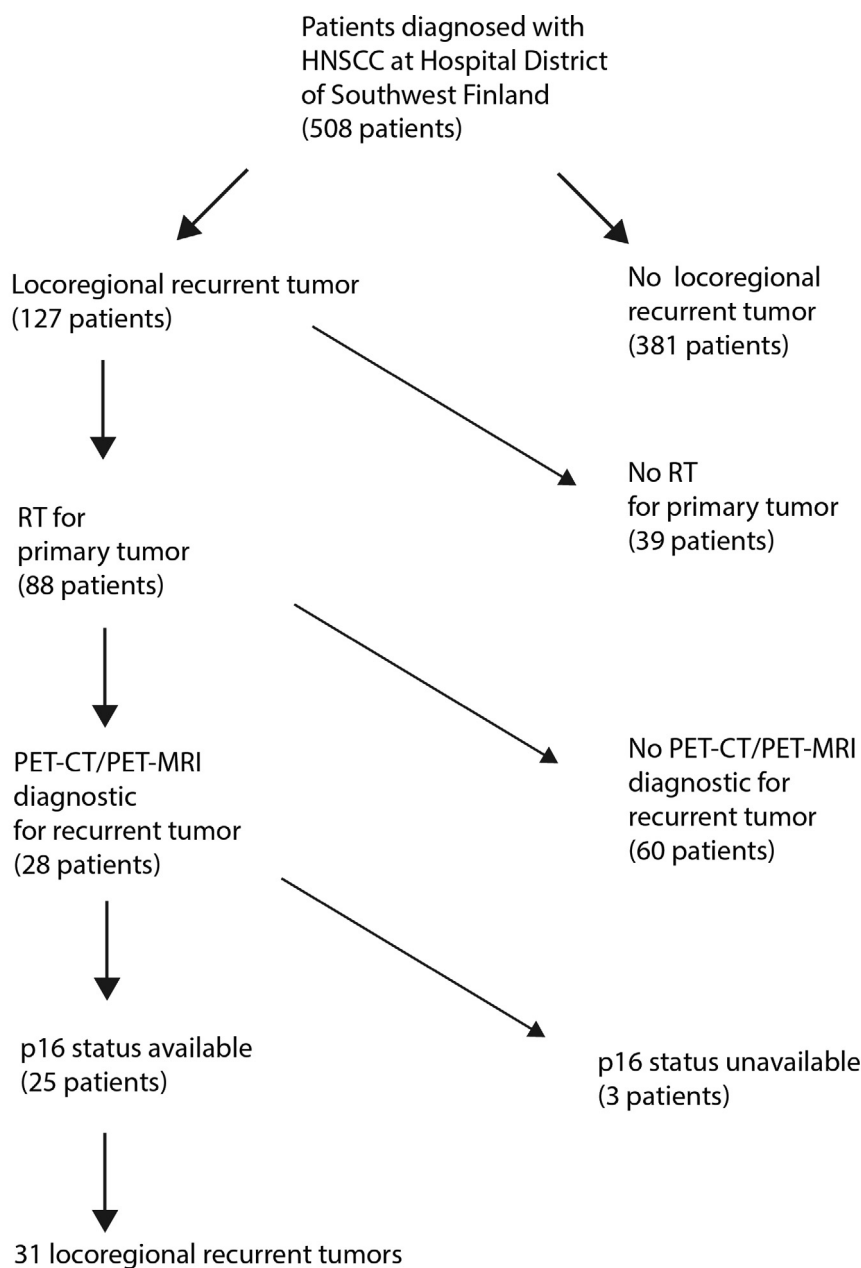


Fig. 1. Process chart of patient selection for detailed analysis. Abbreviations: head and neck squamous cell cancer, HNSCC; magnetic resonance imaging, MRI; positron emission tomography, PET; computed tomography, CT; RT, radiation therapy.

Table 1
Patient characteristics.

Characteristic	p16 negative N	p16 positive N
Median age	62 (33–74)	56 (44–68)
Sex		
Female	8	2
Male	10	5
Primary site		
Oral cavity	9	1
Oropharynx	2	5
Nasopharynx	2	0
Hypopharynx	1	0
Larynx	4	1
Initial treatment		
Definitive CRT	5	4
Preoperative CRT	1	2
Postoperative CRT	12	1
Concurrent systemic therapy		
Cisplatin	17	6
Cetuximab	1	1
Excessive use of alcohol		
Current	5	1
Previous	3	1
None	10	5
Smoking status		
Smoker	11	1
Ex-smoker	5	1
Never-smoker	2	5
Stage		
I	1	0
II	2	1
III	3	2
IV a	11	3
IV b	1	1

tumor, iii) diagnosis of local and/or regional recurrence at hybrid positron emission tomography (PET)/computed tomography (CT) and/or magnetic resonance imaging (MRI) that was technically possible to co-register with radiotherapy dose plans iv) known p16 status. All patients had treatment plans based on PET/CT imaging with ¹⁸F-fluorodeoxyglucose (FDG) and intensity modulated radiotherapy (IMRT) was used for irradiation [8].

The patients' follow-up schedule has been described in detail by Kytö et al. [9]. In brief, clinical and radiological assessment of

patients after multimodality treatment was the responsibility of the head and neck surgeon and during study period no systematic radiological imaging protocol was included in the schedule. The follow-up PET/CT performed three months after the end of treatment became a routine first in 2016 [10]. Therefore, imaging without a clinical suspicion of recurrence was performed only occasionally. Recurrence of study patients was detected in PET/CT or PET/MRI referred to by the head and neck surgeon and subsequently confirmed by biopsy.

2.2. Image registration and overlap definition

Eclipse 15.6 (Varian Medical Systems, Paolo Alto, CA) was used to fuse the RT treatment planning CTs with the PET/CT or PET/MRI images obtained at the time of relapse. Normal tissue regions deemed stable were utilized to achieve optimal image co-registration. Rigid registration was adequate for the paired image sets of 22 patients. Deformable image registration was necessary for the remaining 3 patients who had experienced major changes in tissue structures caused by combined modality treatment. The recurrent tumor volume was derived from the 50% SUV_{max} (maximum standardized uptake volume) threshold obtained 60 min from injection of FDG [8]. After the recurrent tumor volume was copied on the planning CT, the dose of radiation received by the recurrent tumor volume was calculated using dose-volume histograms. Overlap volume of the recurrence and high-risk treatment volume was then determined. The high-risk treatment volume was defined as 95% isodose volume of the mean dose of the high-risk planning target volume. Delineation of high-risk treatment volume is described in more detail in Ref. [8].

The recurrence volumes were classified as in-field (95% or more of recurrence volume encompassing the 95% isodose), marginal miss (20%–95% of recurrence volume encompassing the 95% isodose), or true miss (less than 20% of recurrence encompassing the 95% isodose) [11]. In 5 patients more than one recurrent tumor was identified, thereby multiple recurrence volumes were delineated and analyzed independently.

2.3. Statistical analysis

Overall survival and disease-free survival were calculated using Kaplan-Meier method.

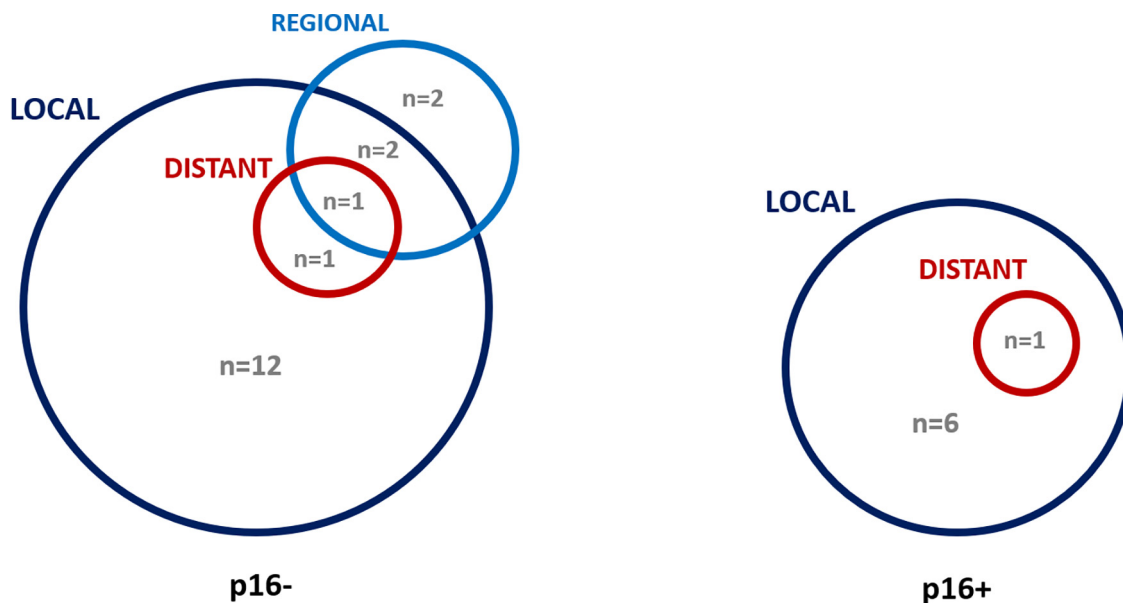


Fig. 2. Breakdown for combination of recurrence sites in 25 patients according to their p16 status. None of the p16 positive cases relapsed in neck.

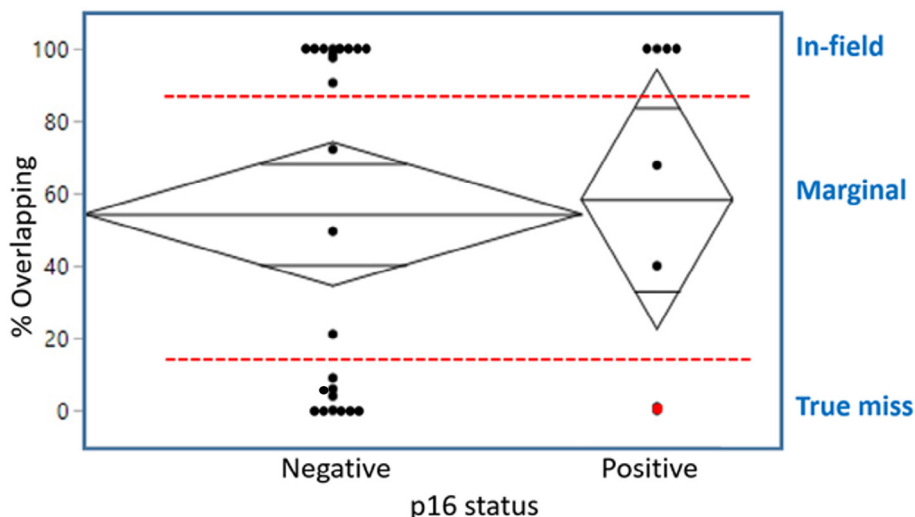


Fig. 3. Overlap % of high-risk planning target volume (95% isodose) and recurrent tumor volume in p16 negative and positive patients. Recurrence classes are separated by dashed lines and indicated in blue. The recurrence of the only true miss among originally p16 positive tumors was p16 negative (red dot, see Fig. 4). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.4. Ethics

All necessary approvals were obtained before the study was conducted. The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland and use of biologic information such as p16 status was granted by permissions from National Supervisory Authority for Welfare and Health (License No. V47408/4017 and V47856/2018) and Auria Biobank (License No. AB17-8403).

3. Results

3.1. Survival and recurrence

Of the 508 patients in our dataset p16 status was known for 72 patients. The 5-year overall survival (OS) rates were 47% and 71%, and the 5-year disease-free survival (DFS) rates were 48% and 82% in p16 negative and positive patients, respectively. 25 patients fulfilled all study inclusion criteria and general characteristics of these patients are detailed in Table 1. We detected 31 PET/CT or PET/MRI positive lesions representing locoregional recurrences out of which 7 (23%) were p16 positive and 24 (77%) were p16 negative in this subset of 25 patients. The number of locoregional tumors per patient at the timepoint when recurrence was first detected was one in 21, two in 3 and four in 1 patient, respectively. Eighteen patients (72%) had local recurrence only and two patients (8%) had neck recurrence only. The remaining five patients (20%) had a combination of local and neck recurrences, and distant metastases as shown in Fig. 2. No relapses in neck were found among p16 positive patients. Distant metastasis was not found to be associated with any clinical or pathological variable (Supplementary Table A1).

3.2. Recurrence in relation to high-risk treatment volume

Among 31 locoregional recurrences, 14 (45%) were classified as in-field, 5 (16%) as marginal miss, and 12 (39%) as true miss (Fig. 3). As per calculations based on co-registered hybrid PET-scans and treatment planning CTs we estimated mean radiation doses previously received by the volume of recurrence to be 67 Gy (range

62–71 Gy); 61 Gy (range 58–66); and 47 Gy (16–56 Gy), respectively, for in-field, marginal, and true miss recurrences. Among p16 positive patients 4 in-field, 2 marginal, and 1 true miss recurrences were found. This recurrent tumor classified as true miss was p16 negative in contrast to the original neck tumor (Fig. 4). By contrast, p16 negative patients had 10 in-field, 3 marginal, and 11 true miss recurrences. The mean \pm 95% confidence intervals for overlap percentages of high-risk treatment volume and recurrence volume were 58 (16–100)% in p16 positive and 52 (33–72)% in p16 negative patients. Individual overlap percentages in p16 positive and negative patients are illustrated in Fig. 3.

3.3. Timepoint of recurrence

The median time from end of RT to the PET/CT or PET/MRI scan diagnostic for local or locoregional recurrence was 9 months for p16 negative patients and 14 months for p16 positive patients. The median time for p16 negative in-field recurrences was 6 months compared to that of 9 months for p16 positive in-field recurrences.

3.4. Recurrence in relation to treatment characteristics and modality

Out of 14 in-field recurrences 7 had received definitive CRT, 2 had received preoperative CRT, and 5 had received postoperative CRT. Proportions of different primary treatments in each recurrence class are shown in Table 2. There was no clear association between modality of primary treatment (definitive or combined CRT and surgery) and recurrence class (Table 2). Twenty-three patients received weekly low dose (40 mg/m²) cisplatin and two patients who could not receive cisplatin because of intercurrent morbidity received weekly cetuximab (250 mg/m²) [12]. Median cumulative dose of cisplatin was 240 mg/m² (range, 120–240). The cumulative dose was 1900 mg/m² for both two patients who received cetuximab. One patient who received cetuximab was p16 positive and one p16 negative. Median amount of RT fractions was 33 (range 30–35). Median number of fractions did not differ between p16 subgroups. Median duration of RT was 46 days (range 43–53) in the p16 positive group and 48 days (range 43–60) in the p16 negative group. Specific patterns of recurrence are pre-

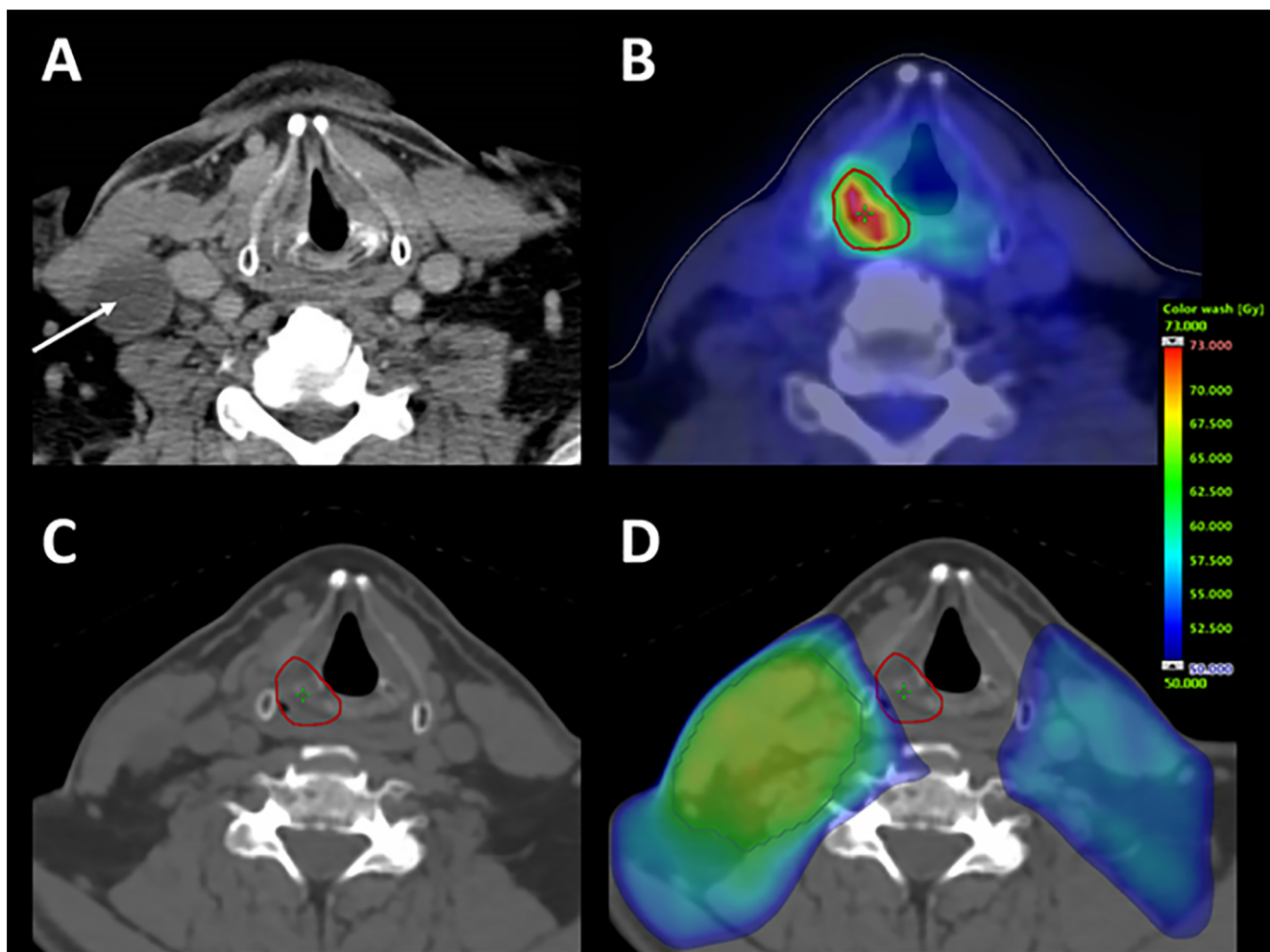


Fig. 4. This 48-year man with a history of 30 pack-years smoking and increased alcohol use presented with a right neck lump originally regarded as a cervical cyst. In biopsy a moderately differentiated squamous cell carcinoma positively staining for p16 was found. Neck and chest CT showed four cystic nodal metastases in right level III (A, arrow) while all diagnostic work-up including panendoscopy and right tonsillectomy and biopsy from base of tongue were negative for primary tumor. The patient received CRT with 5 weekly doses of cisplatin to total dose of 66 Gy in high-risk area. Two years and 9 months after CRT PET/CT (B) showed recurrent tumor in right pyriform sinus. C and D illustrate PET-finding (red contour) superimposed on treatment planning CT with dose wash in D locating recurrence outside of original high-risk treatment volume (dark contour). Following recurrence, the patient had pharyngolaryngectomy and subsequently died 4 years and 9 months after CRT. This patient had the only p16 positive tumor classified as true miss in our study (red dot in Fig. 3). A second primary rather than recurrence of first cancer could not be ruled out, since p16 staining of tumor cells in B was negative in contrast to the p16 positive lymph node in A. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Primary treatment modalities of 31 recurrent tumors in 25 patients in each three recurrence classes.

Treatment	In field		Marginal miss		True miss	
	N	column %	N	column %	N	column %
Definitive CRT	7	50%	3	40%	2	25%
Preoperative CRT	2	14%	1	20%	0	0%
Postoperative CRT	5	36%	2	40%	8	75%

sented in [Supplementary Table A1](#). Examples of patients with in-field and true miss recurrences with their accompanying RT plans are depicted in [Figs. 4–6](#).

4. Discussion

Current literature has not studied in-depth the location of recurrent tumors in relation to radiation fields. This information could have an impact on optimization of dose planning of de-escalated or highly conformal CRT protocols. In this study we

retrospectively investigated patterns of HNSCC recurrence in and outside of high-risk treatment volume planning target volumes. We had an additional interest to detect putative differences in p16 positive and p16 negative tumors based on the higher radiosensitivity and tendency to present with extensive nodal involvement in neck of the former. Although p16 positivity does not directly translate to HPV positivity the former is widely accepted as a biomarker of HPV infection and used in clinical practice guidelines where p16 positive oropharyngeal cancers have distinct TNM classification [13].

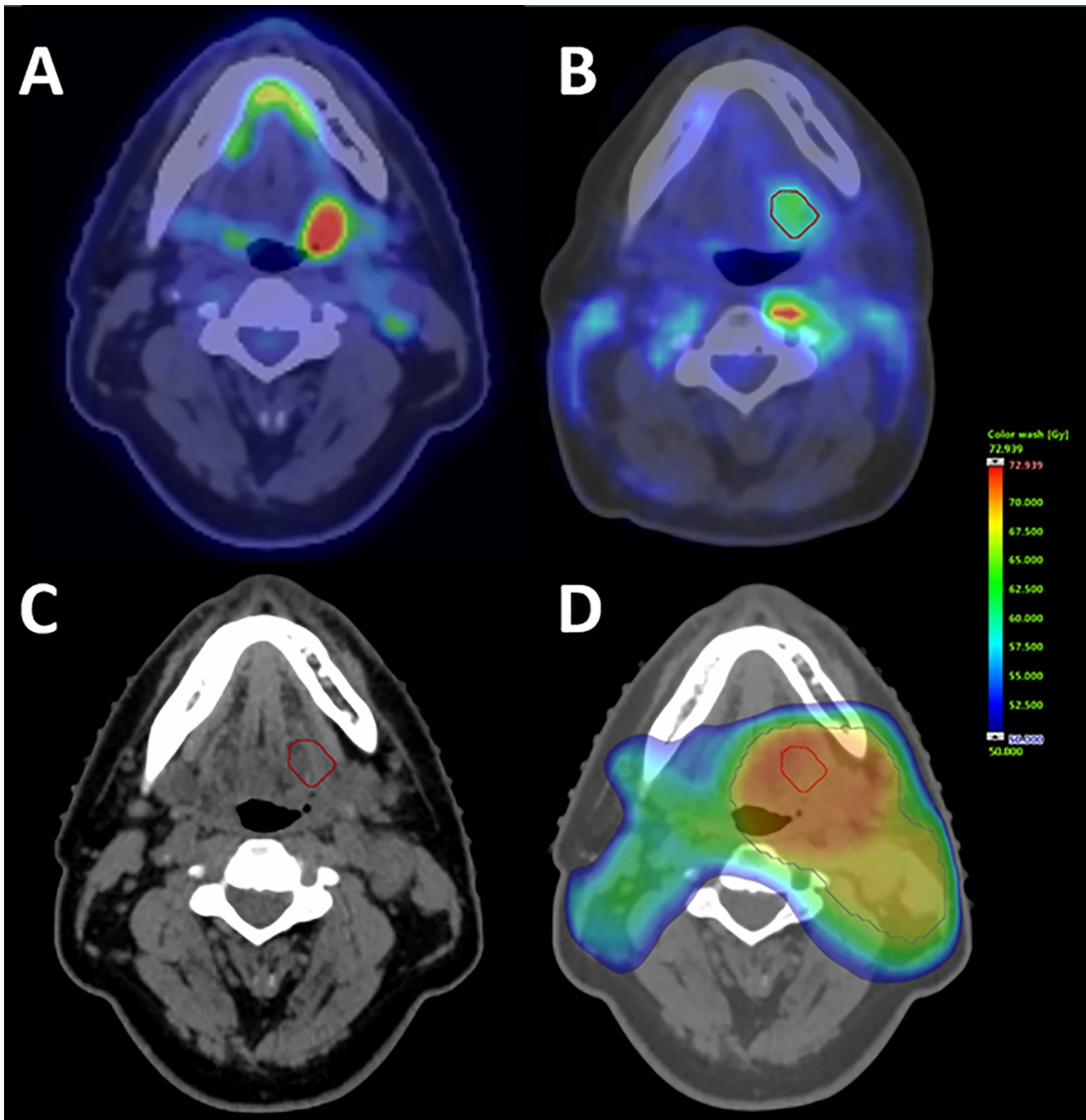


Fig. 5. A 51-year man with a history of 30 pack-years smoking and intermittently heavy alcohol use was referred to hospital after suffering 2–3 months from sore throat and pain radiating into left ear. Diagnostic work-up showed biopsy confirmed p16 negative left tonsillar carcinoma and multiple ipsilateral nodal metastases in neck. Primary tumor is depicted on PET/CT (A). Multimodality treatment included 70 Gy RT in high-risk area, 6 weekly doses of cisplatin and planned selective left neck dissection to levels I–V where residual necrotic cancer was seen in two lymph nodes. Only four months from surgery follow-up PET/CT was positive in original tumor area and retropharyngeal space (B) and lung and bone where metastases had developed. The recurrent cancer in original area is superimposed as red contour on treatment planning CT (C) and the same axial slice with dose wash (D) demonstrates both in-field recurrences within original high-risk treatment volume (dark contour). Because of rapid deterioration of general health, the patient could be offered only palliative treatment. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Four of the patients in our study had a multifocal recurrence pattern previously described also by Geretschläger et al. [14]. Recurrent tumors in the current study were classified as in-field (45%), marginal miss (16%), and true miss (39%). Proportion of in-field recurrences was fairly similar to those presented by Chen et al (40%, 41%, and 18% respectively) in their study on tumor recurrence in 50 patients with HPV-positive oropharyngeal squa-

mous cell cancer [15]. The higher amount of true miss recurrences in our study could be explained by the larger variety of primary tumor sites of our study and inclusion of p16 negative cases. Considering both our and patients studied by Chen et al [15] together one could argue that a notable portion of patients with p16 positive recurrent tumors relapse in-field or as marginal misses in relation to the high-risk volume (Fig. 3). A high proportion of

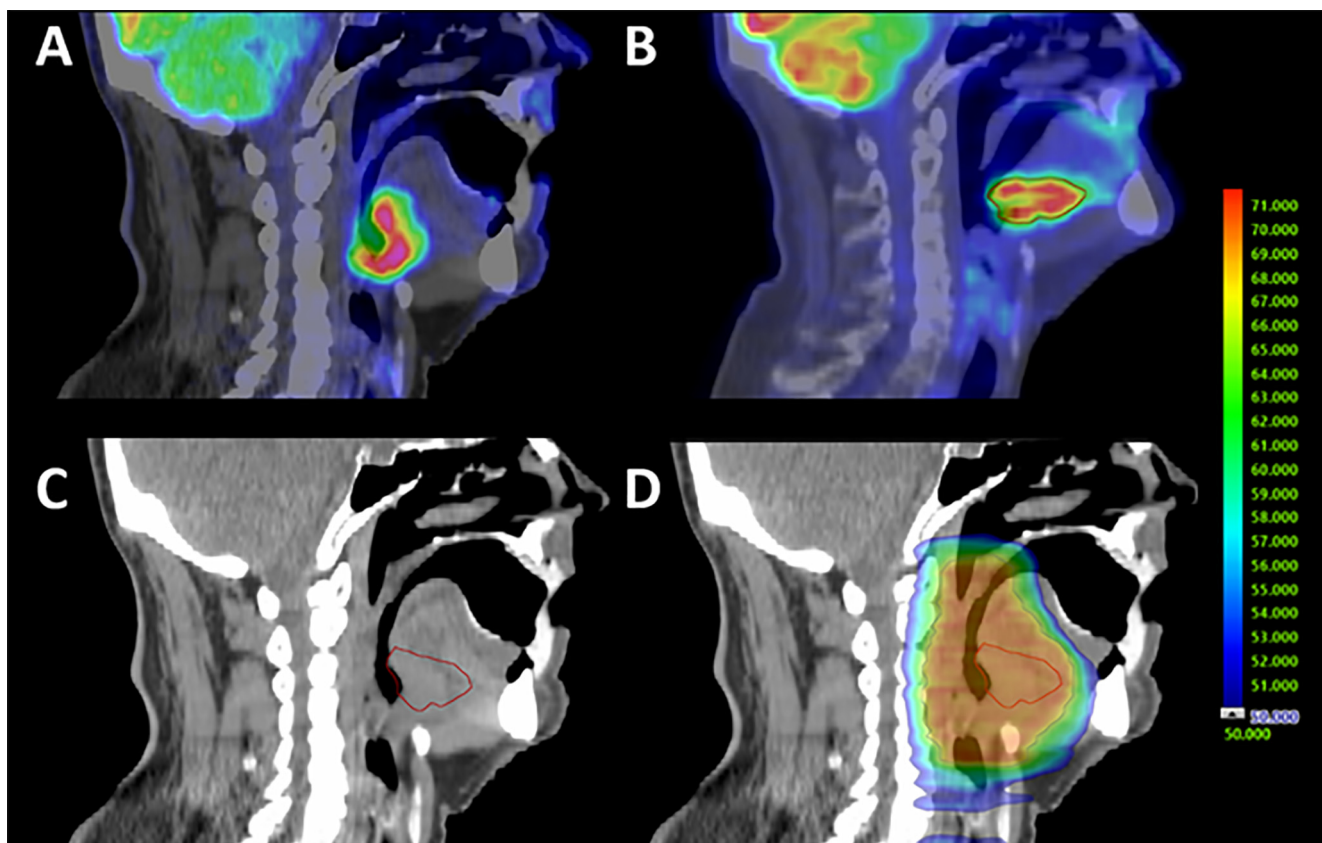


Fig. 6. A 63-year non-smoking abstinent man had radical prostatectomy and RT to prostate bed because of pT3N0 Gleason 6 prostate cancer 5 years before presenting with a large left p16 and polymerase chain reaction confirmed HPV 16 positive tonsillar squamous cell carcinoma which infiltrated to base of tongue but revealed no lymph node metastases on treatment planning PET/CT (A). On audiometry bilateral high frequency hearing loss at 2–8 kHz was found and he therefore received instead of cisplatin cetuximab-enhanced RT to 70 Gy in high-risk area. Two years after end of bio-RT PET/CT showed local recurrence in base of tongue (B) and multiple lung metastases. C and D illustrate PET-finding (red contour) superimposed on treatment planning CT with dose wash in D locating tumor within original high-risk treatment volume (dark contour) consistent of in-field recurrence. Please note the different position of mobile tongue in B compared to A, C and D because of use of mouthpiece in RT. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

recurrences occurring marginally or outside of the high-risk treatment volumes (10 out of 12 patients) was reported by Geretschläger et al. [14]. They had only 2 recurrences in the high-risk treatment volume and did not report p16 status but since no oropharyngeal cancers were included it is likely that the majority if not all tumors were p16 negative. Although half of our patients who had an in-field recurrence had received definitive CRT as a primary treatment, no significant relation was observed between primary treatment modality and recurrence class. This result is similar to the findings of Johansen et al. [16] who did not include information about p16 status in their findings but based on tumor sites included mostly p16 negative patients.

Our 5-year overall and disease-free survival data in 71 patients show better overall prognosis (OS and DFS) for p16 positive HNSCC which is in line with existing literature [3]. However, we also describe a p16 positive subpopulation whose disease recurred rapidly in a median of 9 months within the high-risk treatment volume. This compares similarly with time interval of 10 months reported by Chen et al. [15] in their study of p16 positive oropharyngeal cancer. Four out of seven p16 positive patients in our study had a recurrent tumor with 95% or more of the recurrence volume overlapping with the high-risk treatment volume. Furthermore, the hypopharyngeal tumor representing the only true miss of these seven cases had turned p16 negative (Fig. 4). Our findings implicate heterogenous treatment response among a group of diseases that are generally considered curable by RT. Although p16 positive

patients consumed less tobacco and alcohol compared to their p16 negative counterparts (Table 1) we are not able to address the oxygenation status of these treatment failures since hypoxia-associated gene signatures of the tumors were not analyzed.

Limitations of this study include retrospective design, small size, and heterogeneity of the patient cohort and treatment modalities. The proportion of p16 positive patients is unfortunately small since p16 was not routinely analyzed during study period in 2010–2015. Finally, not all patients had then PET/CT or PET/MRI as part of their diagnostic work-up in follow-up phase and co-registration of 3D-imaging sets acquired several months or years apart is prone to compromised spatial accuracy. On the other hand, metabolic imaging for treatment planning, IMRT and concurrent cisplatin/cetuximab were standard approaches in all patients [8] rendering our findings applicable for current practice. While true miss in adequately planned and treated p16 positive patients seems to be rare, focus should now be on early assessment of local resistance and introduction of adaptive or radiosensitizing approaches during CRT.

We conclude that HNSCCs respond heterogeneously to RT and a small subset of p16 positive diseases relapse within the high-risk treatment volume despite the common view of their high radiosensitivity. Many true and marginal misses among p16 negative tumors in current study suggest that meticulous treatment planning with multimodality imaging may fail to detect all clinically significant disease. Therefore, we encourage validation of

new imaging protocols in addition to FDG PET/CT/MRI to define gross tumor volume or radioresistant subvolumes especially in the setting of highly conformal irradiation techniques.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctro.2021.01.013>.

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