Oral Oncology 94 (2019) 1–7

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Upfront PET/CT affects management decisions in patients with recurrent head and neck squamous cell carcinoma

Max Rohde[a,b,*], Anne L. Nielsen[c], Jørgen Johansen[d], Jens A. Sørensen[b,e], Anabel Diaz[f], Manan Pareek[g], Jon T. Asmussen[f], Oke Gerke[c], Anders Thomassen[c], Niels Gyldenkerne[d], Helle Døssing[a], Kristine Bjørndal[a], Poul Flemming Høilund-Carlsen[b,c], Christian Godballe[a,b]

[a] Department of ORL – Head & Neck Surgery and Audiology, Odense University Hospital, Odense, Denmark
[b] Department of Clinical Research, University of Southern Denmark, Odense, Denmark
[c] Department of Nuclear Medicine, Odense University Hospital, Odense, Denmark
[d] Department of Oncology, Odense University Hospital, Odense, Denmark
[e] Department of Plastic Surgery, Odense University Hospital, Odense, Denmark
[f] Department of Radiology, Odense University Hospital, Odense, Denmark
[g] Department of Cardiology, North Zealand Hospital, Hillerød, Denmark

ARTICLE INFO

Keywords:
Head and neck neoplasms
MDTC
Patient management
PET/CT
Recurrence
Treatment plan

ABSTRACT

Purpose: To compare multidisciplinary team conference (MDTC) decisions regarding treatment intent based on either chest X-ray + MRI of the head and neck (CXR/MRI) or ^{18}F-FDG-PET/CT (PET/CT) in patients with recurrent head and neck squamous cell carcinoma (HNSCC).

Methods: Prospective blinded cohort study based on paired data. Consecutive patients with suspected recurrent HNSCC were invited to participate. All included patients underwent CXR/MRI and PET/CT before diagnostic biopsy. An ordinary MDTC using all available imaging data was conducted as per standard practice. After at least three months (to eliminate recall bias in the team), the first project MDTC, based on either CXR/MRI *or* PET/CT, was conducted, and the tumor board made conclusions regarding treatment. After an additional three months, a second project MDTC was conducted using the complementary imaging strategy. The separate treatment strategies were compared using McNemar's test.

Results: A total of 110 patients (90 males and 20 females, median age 66 years, range 40–87) were included. The initial primary tumor originated from the pharynx in 56 (51%) patients, oral cavity in 17 (15%) patients, and larynx in 37 (34%) patients. Based on CXR/MRI, 87 patients (79%) were recommended curative treatment and 23 (21%) palliative treatment. Based on PET/CT, the MDTC decided that 52 (47%) patients were suitable for curative treatment and 58 (53%) for palliative treatment. The absolute difference of 32% was statistically significant (95% CI: 22–42%, $p < 0.001$).

Conclusions: PET/CT affected MDTC decisions in patients with recurrent HNSCC towards less curative and more palliative treatment.

Introduction

Although the 5-year mortality in patients with head and neck squamous cell carcinoma (HNSCC) has declined during the last decades, relapses within the first three years are frequently encountered [1,2]. Recurrent HNSCC is generally considered to have a poor prognosis [3,4]. Curatively intended surgery is extensive and requires advanced reconstructive procedures, and a substantial proportion of patients with recurrent HNSCC are treated with palliative intent [5]. Therefore, careful evaluation and selection of patients with recurrent disease is imperative.

^{18}F-FDG-PET/CT (PET/CT) appears to be more effective than standard imaging strategies, i.e., head and neck magnetic resonance imaging (MRI) and/or computed tomography (CT), in detecting posttreatment recurrent HNSCC [6,7]. Furthermore, we have already demonstrated in a prior study that PET/CT affects multidisciplinary team conference (MDTC) decisions compared with standard imaging in patients with primary HNSCC, leading to more individualized patient management [8]. However, the effect of such a strategy on treatment decisions in recurrent HNSCC is currently unknown.

* Corresponding author at: Department of ORL – Head & Neck Surgery and Audiology, Odense University Hospital, J. B. Winsløws Vej 4, 5000 Odense C, Denmark.
E-mail address: max.rohde@rsyd.dk (M. Rohde).

https://doi.org/10.1016/j.oraloncology.2019.04.025
Received 14 August 2018; Received in revised form 26 April 2019; Accepted 29 April 2019
Available online 06 May 2019
1368-8375/ © 2019 Elsevier Ltd. All rights reserved.

For suspected recurrences, the European Head & Neck Society and the European Society for Medical Oncology recommend an imaging strategy with head and neck MRI or CT + chest X-ray (CXR/MRI). PET/CT is suggested in the presence of unclear findings [9]. The Danish national guidelines also recommend imaging in case of suspected recurrence, directed towards tumor location, but without a clear choice of imaging modality [10]. The US National Comprehensive Cancer Network (NCCN) does not include specific guidelines for working up recurrent disease. The NCCN recommendations merely relate to standard follow-up with imaging of the primary tumor site within six months of completing treatment using PET/CT or CT and/or MRI with contrast. Further reimaging is indicated based on symptomatology [11].

The objective of this study was to compare MDTC decisions reached with respect to treatment intent based on either CXR/MRI or PET/CT in patients with recurrent HNSCC.

Methods

We conducted a blinded prospective cohort study based on paired data. The setting and methods have been described previously [8]. We considered patients with suspected recurrent oral, pharyngeal, or laryngeal carcinoma referred to the Head and Neck Cancer Center, Odense University Hospital, from September 2013 to March 2016.

Inclusion criteria were; histologically verified recurrence in previous treated HNSCC patients, without distant metastasis in the diagnostic work up of the initial disease, and with a minimum time interval of four months from primary treatment. We defined a primary site recurrence as squamous cell carcinoma within five years in the same anatomical site (i.e., oral cavity, pharynx, or larynx). Exclusion criteria included allergy or intolerance toward iodine contrast, use of high-dose systemic corticosteroids (equivalent to > 50 mg prednisolone daily), impaired renal function (plasma creatinine > 90 micromol/L for women and > 105 micromol/L for men or previously diagnosed kidney disease), inability to cooperate, or blood glucose > 8 mmol/L (slightly elevated blood glucose levels were acceptable).

All patients underwent upfront (prior to biopsy) CXR/MRI and PET/CT on the same day, upfront imaging being the standard procedure for all patients in the Danish head and neck cancer fast-track program [12]. Patients with histologically verified recurrent HNSCC constituted the final study population and their data were used to compare the overall treatment decision reached by the MDTC, based on either PET/CT or CXR/MRI.

Multidisciplinary team conference

The MDTC was a collaborative effort among the Departments of Oto-Rhino-Laryngology (Head & Neck Surgery), Plastic Surgery, Oncology, Nuclear Medicine, and Radiology, who were all represented by experienced specialists participating in MDTC conferences as part of their daily clinical practice. Pathologists and neurosurgeons were invited to participate as needed.

All patients participated in an ordinary MDTC that included all available imaging in order to ensure that they received full benefit of the examinations performed as part of their workup for recurrent HNSCC and subsequent treatment (Fig. 1). As part of the study, a project MDTC based on CXR/MRI or PET/CT was undertaken after at least three months. The delay was introduced to eliminate recall bias in the tumor board of evaluators. After an additional three months, a second project MDTC was carried out based on the complementary imaging strategy only. All patients were thus evaluated twice in a blinded and paired setup, in which the only difference was the available imaging strategy and the corresponding imaging team. No fixed method was used (nor randomization) for selection between CXR/MRI and PET/CT as the first imaging strategy during project MDTC sessions.

The PET/CT imaging team included nuclear medicine specialists and radiologists, while the CXR/MRI team consisted of radiologists only. All were experienced chief physicians. The individual imaging team members were allocated to only one team, and no overlap or interchange between teams was allowed.

Project MDTC sessions were held once a week and included approximately fifteen patients at each session. A representative from the PET/CT team joined the MDTC every other week, and equivalently, one from the CXR/MRI team the other week. At each project session, the pre-diagnostic patient history was briefly presented by the lead author MR (who was not a member of the tumor board), and the scans were evaluated and discussed. Both patient history and the reviewed imaging was anonymized. All imaging studies were evaluated by the tumor board, and registration forms comprising variables about treatment strategy, intent, and modality were completed and filed in separate, sealed envelopes [8].

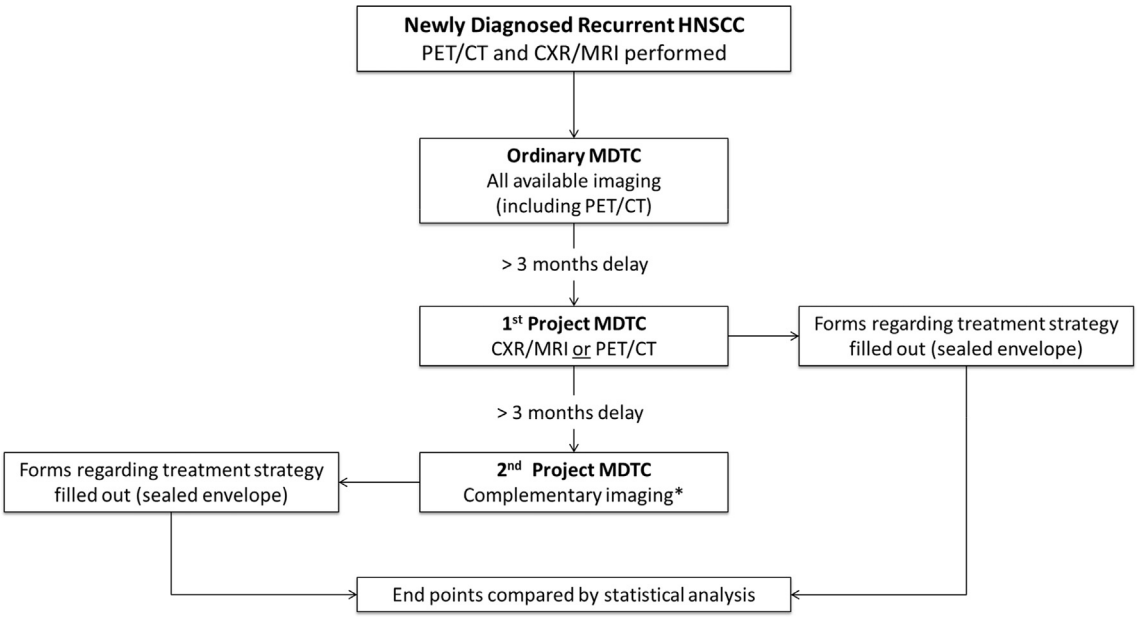


Fig. 1. Diagram of the multidisciplinary team conferences (MDTC). CXR = chest X-ray, HNSCC = head and neck squamous cell carcinoma, MRI = magnetic resonance imaging of the head and neck, PET/CT = ^{18}F-FDG-PET/CT. *CXR/MRI if PET/CT was used first during the first project MDTC and vice versa.

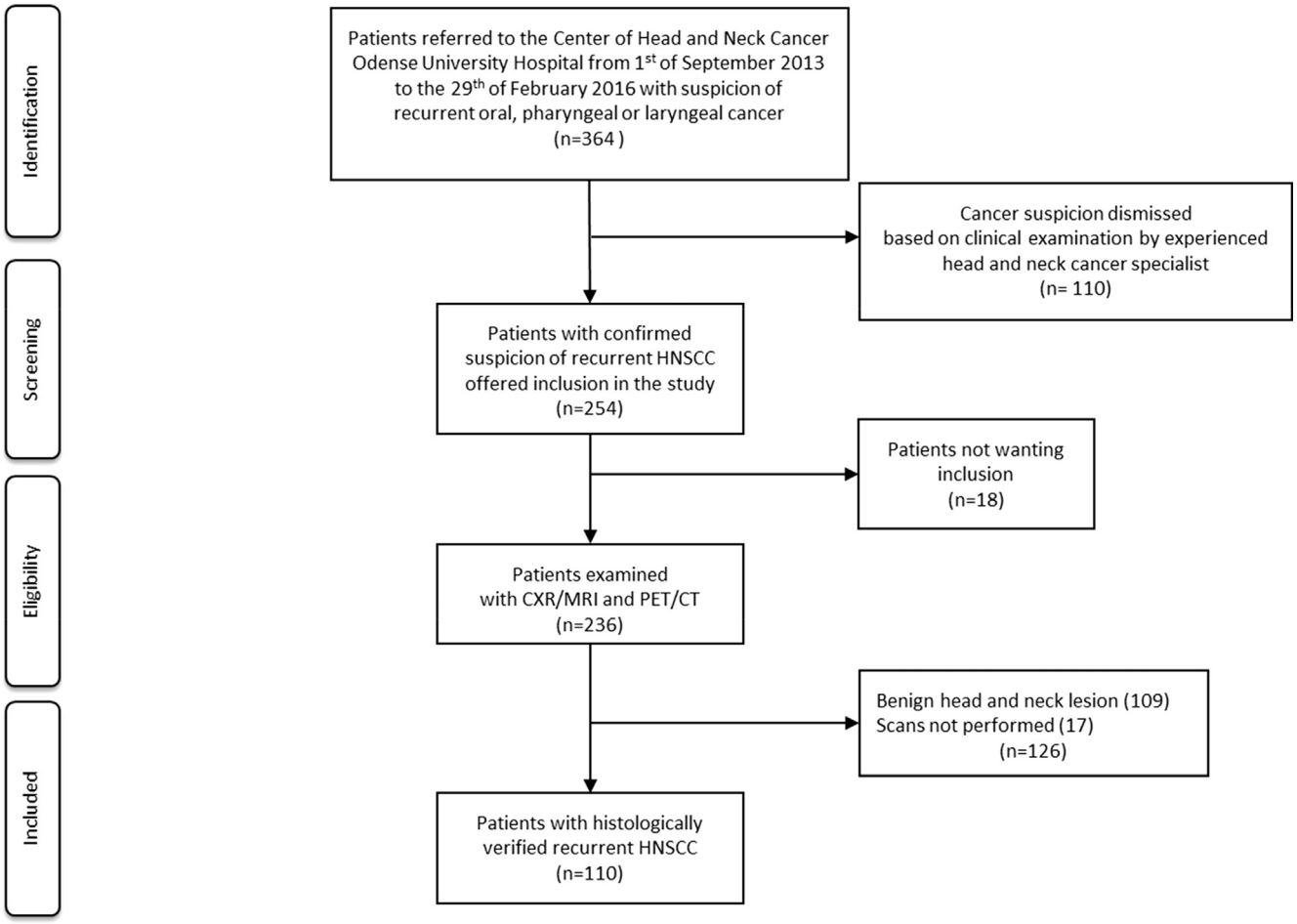


Fig. 2. Flowchart of patient selection. CCT = chest computed tomography, CXR = chest X-ray, HNSCC = Head and neck squamous cell carcinoma, MRI = magnetic resonance imaging of the head and neck, PET/CT = ^{18}F-FDG-PET/CT.

Scan protocols

This study followed the imaging protocols previously described [8]. PET/CT scans were performed with by a hybrid PET/CT scanner (GE Discovery 690, 710, VCT, or RX) and extended from the vertex to the upper thighs. Images from all four PET/CT systems had a slice thickness of 3.27 mm. A diagnostic quality CT scan with intravenous contrast medium (Ultravist®) was acquired after the PET scan.

MRI was performed on Philips Achieva, Achieva dStream or Ingenia 1.5T. The exam protocol was kept unchanged for the duration of the study and consisted of STIR, TSE-T2 and -T1 with and without contrast enhancement, in axial or coronal planes with coverage from skull base to aortic arch using 5 mm slices. CXR was performed to departmental standards in full inspiration anteroposterior and lateral projections.

Image evaluation

Discrimination of recurrent disease from benign post-treatment sequelae was evaluated at the primary site, regional lymph nodes, and distant metastases. In general, morphological changes, altered signal intensity, contrast enhancement, changes in diffusion and metabolic information on FDG avidity by PET were evaluated. A fixed threshold of standard uptake value was not used to determine whether a lesion was malignant or not. Presence of post-surgical and/or radiation-induced edema and inflammation was thoroughly assessed for all imaging modalities. In particular, increased metabolism of the oral cavity after resection and/or irradiation was thoughtfully recognized. If available, prior scans were used to help distinguish a recurrence from benign post-treatment changes. For instance, the visual intensity of FDG uptake in terms of lesion to background difference was compared with that of the primary tumor in previous scan(s) to help discrimination of recurrence from benign post-treatment effects.

Endpoints

The primary outcome measure was change of treatment intent (i.e., curative versus palliative) decided by the multidisciplinary tumor board, based on a PET/CT-based imaging strategy versus a CXR/MRI-based strategy. Cancer-specific mortality (from diagnosis of recurrent disease) was applied as the event for the net reclassification improvement (NRI) analysis. Follow-up data on mortality were obtained from the patients' medical records at least 6 months (August 31, 2016) after termination of inclusion. Our electronic record system is linked to the Danish Cause of Death Registry [8].

Statistical methods

Continuous variables are presented as medians and ranges (minimum and maximum values), and categorical variables as counts and corresponding percentages. We conducted a head-to-head comparison of MDTC decisions on patients assigned to curative or palliative treatment, based on either PET/CT or CXR/MRI, using 2 × 2 tables and McNemar's test. Moreover, the ability of PET/CT to improve the MDTC decision regarding treatment intent, in terms of predicted survival, was tested using categorical NRI [13,14]. NRI calculates the improvement in risk prediction obtained by a new model (as compared to an older

one) by measuring the ability of the new model to reclassify subjects (into a higher or lower risk category) either properly or improperly. NRI is a relatively new statistical method of risk prediction that has gained wide attention. C-statistics and area under the curve have been the standard approach of measuring improvements, but may not have clinical applicability and can be challenging to interpret in case of small-scale changes [8,14].

The significance level was 5%. All analyses were performed with Stata/IC 15.1 (StataCorp LP, College Station, Texas, USA).

Ethics and disclosures

The study was conducted in accordance with the Declaration of Helsinki. Permission was granted from the Regional Ethics Committee (Project ID: S_20120217), and written informed consent was obtained from all included patients. The project was implemented without the involvement of private organizations or companies.

Results

Three-hundred-and-sixty-four patients were referred to our institution with suspected recurrent HNSCC. Of these, a total of 110 patients had histologically verified relapse and were included in the study (Fig. 2); 90 (82%) were men and 20 (18%) women with a median age of 66 years (range 40–87). The initial primary tumor originated in the pharynx in 56 (51%) patients, oral cavity in 17 (15%) patients, and larynx in 37 (34%) patients. Median follow-up from diagnosis of recurrent disease was 491 days (range 13–1505 days). At study termination, the overall cancer-specific mortality rate was 57% (63/110) (Table 1).

Table 1
Basic clinical characteristics of head and neck squamous cell carcinoma patients (n = 110).

Clinical characteristics	Patients	%
Age, years		
Median (range)	66 (40–87)	
Sex		
Male/female	90/20	82/18
Initial primary tumor site		
• Oral cavity	17	15
• Pharynx	56	51
• Larynx	37	34
Primary stage		
• I	15	14
• II	20	18
• III	19	17
• IVA	44	40
• IVB	12	11
• IVC	0	0
Primary N-classification		
• N0	60	55
• N+	50	45
Primary treatment		
• Surgery	8	7
• Surgery + Radiotherapy	10	9
• Radiotherapy	68	62
• Chemoradiotherapy	24	22
Follow-up*		
• Days (median)	491	
• Range	13–1505	
Cancer-specific mortality		
Overall	**63/110**	**57**
• Oral Cavity	9/17	53
• Pharynx	35/56	63
• Larynx	19/37	51

* From diagnosis of recurrence.

Table 2
Site of recurrence for 110 patients with recurrent head and neck squamous cell carcinoma (HNSCC).

Recurrent site#	Patients
Local (T-site)*	**80 (73%)**
• Oral cavity (n = 17)	13 (71%)
• Pharynx (n = 56)	38 (68%)
• Larynx (n = 37)	29 (78%)
Regional (N-site)**	**60 (55%)**
• Oral cavity (n = 17)	11 (65%)
• Pharynx (n = 56)	34 (61%)
• Larynx (n = 37)	15 (40%)
Metastatic (M-site)***	**33 (30%)**
• Oral cavity (n = 17)	5 (29%)
• Pharynx (n = 56)	20 (36%)
• Larynx (n = 37)	8 (22%)

Each patient had recurrence at one or several sites.
* Histology was the reference standard.
** Histology or cytology was the reference standard.
*** Based on ordinary MDTC decision with all available imaging as reference standard (CXR/MRI + PET/CT).

Table 2 presents the site(s) of recurrence; 80 (73%) patients had local failure, 60 (55%) patients had regional failure, and 33 (30%) had distant failure. The distribution of localized (stage I-II), locally advanced (stages III, IVA, or IVB), and metastatic (stage IVC) disease, categorized by CXR/MRI and PET/CT, respectively, is presented in Table 3 [15]. CXR/MRI categorized 40% as localized, 54% as locally advanced, and 6% as distant metastatic disease, whereas PET/CT categorized 21% as having localized disease, 45% as locally advanced, and 34% as metastatic disease ($p < 0.001$). Supplemental Table 1 displays the anatomical location of the distant metastases among the 33 patients diagnosed with disseminated disease.

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.oraloncology.2019.04.025.

Five (5%) patients were upstaged from localized disease by CXR/MRI to metastatic disease based on PET/CT, whereas 26 (24%) patients were upstaged from locally advanced to metastatic disease. One patient was downstaged from metastatic disease to locally advanced based on PET/CT.

The discrepant rate of distant metastasis in Tables 2 and 3 (i.e., 30% vs. 34%) is due to the use of differing reference standards. Metastatic disease in Table 2 was clinical reasoned, i.e., based on the ordinary MDTC decision with all available imaging as reference standard (CXR/MRI + PET/CT), while Table 3 was based on PET/CT findings alone.

Management decisions

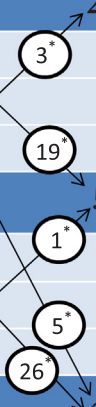
MDTC decisions based on CXR/MRI recommended treatment with curative intent for 87 (79%), and palliative treatment for 23 (21%) patients. PET/CT-based decisions found 52 (47%) patients suitable for curative treatment, and 58 (53%) for palliative treatment (Tables 4 and 5). The resulting absolute difference of 32% was statistically significant (95% CI: 22–42%, $p < 0.001$).

Reclassification

NRI analysis showed that the use of PET/CT was associated with a significant improvement in determining the appropriate treatment intent as compared with CXR/MRI, from a prognostic perspective (NRI = 48%, 95% CI: 29–67%, $p < 0.001$). Cancer-specific mortality was chosen as the event for reclassifying subjects, and the *net* reclassification was obtained by subtracting the 2/47 (4%) patients in the non-event group who were apparently *incorrectly* reclassified to palliative treatment from the 33/63 (52%) patients in the event group

Table 3
Distribution of Union for International Cancer Control (UICC) equivalent relapse stages: localized (stages I or II), locally advanced (stages III, IVA, or IVB), and metastatic (stage IVC) disease according to upfront imaging strategy, including specific upstaging and downstaging based on CXR/MRI vs. PET/CT.

Patients (n=110)	CXR/MRI	PET/CT
Localized	**44 (40%)**	**23 (21%)**
• Stage 0**	6 (5%)	1 (1%)
• Stage I	22 (20%)	14 (13%)
• Stage II	16 (15%)	8 (7%)
Locally Advanced	**59 (54%)**	**50 (45%)**
• Stage III	20 (18%)	13 (12%)
• Stage IVA	35 (32%)	32 (29%)
• Stage IVB	4 (4%)	5 (4%)
Metastatic	**7 (6%)**	**37 (34%)**
• Stage IVC		



CXR = chest X-ray, HNSCC = head and neck squamous cell carcinoma, MRI = magnetic resonance imaging of the head and neck, PET/CT = ^{18}F-FDG-PET/CT.
*Number of patients upstaged and downstaged based on CXR/MRI vs. PET/CT.
**Based on upfront imaging, but subsequently histologically verified as HNSCC.
Adapted with permission from Journal of Nuclear Medicine [15].

Table 4
Distribution of treatment intent according to initial primary tumor site, as decided by the multidisciplinary team conference for 110 patients with recurrent head and neck squamous cell carcinoma (HNSCC) and based on either chest X-ray + MRI of the head and neck (CXR/MRI) or ^{18}F-FDG-PET/CT (PET/CT).

Treatment intent of recurrent HNSCC (n = 110)	CXR/MRI	PET/CT
Curative	**87 (79%)**	**52 (47%)**
Oral cavity (n = 17)	14 (82%)	11 (65%)
Pharynx (n = 56)	42 (75%)	20 (36%)
Larynx (n = 37)	31 (84%)	21 (57%)
Palliative	**23 (21%)**	**58 (53%)**
Oral cavity (n = 17)	3 (18%)	6 (35%)
Pharynx (n = 56)	14 (25%)	36 (64%)
Larynx (n = 37)	6 (16%)	16 (43%)

Table 5
Distribution of treatment intent according to treatment modality, as decided by the multidisciplinary team conference for 110 patients with recurrent head and neck squamous cell carcinoma (HNSCC) and based on either chest X-ray + MRI of the head and neck (CXR/MRI) or ^{18}F-FDG-PET/CT (PET/CT) (PET/CT).

Treatment intent of recurrent HNSCC (n = 110)	CXR/MRI	PET/CT
Curative*	**87 (79%)**	**52 (47%)**
● Surgery	58 (53%)	39 (35%)
● Radiotherapy (primary and postoperative)	13 (12%)	7 (6%)
● Chemotherapy	6 (5%)	5 (5%)
Palliative	**23 (21%)**	**58 (53%)**
● Surgery	0 (0%)	1 (1%)
● Radiotherapy	0 (0%)	3 (3%)
● Chemotherapy	16 (15%)	45 (41%)
● Best supportive care	7 (6%)	9 (8%)

* Each patient could receive none, one or several treatment modalities.

Table 6
The net reclassification index (NRI) of the multidisciplinary team conference conclusion for ^{18}F-FDG-PET/CT (PET/CT) compared with chest X-ray + MRI of the head and neck (CXR/MRI) with cancer-specific mortality as endpoint.

	PET/CT treatment intent				
CXR/MRI treatment intent	Number of patients		Reclassified (%)		
	Curative	Palliative	Palliation	Curation	Net correctly classified
Patients alive (n = 47)					
Curative	44	2	2 (4.3%)	0 (0%)	−4.3%
Palliative	0	1			
Patients died (n = 63)					
Curative	7	34	34 (54.0%)	1 (1.6%)	52.4%
Palliative	1	21			
NRI (95% CI)					**48.1% (29.4–66.8%)**
p-value					**< 0.001**

who, based on PET/CT, were *correctly* reclassified from curative to palliative treatment (Table 6).

Discussion

Our results show that a PET/CT-based imaging strategy changed MDTC decisions regarding treatment intent in almost one-third of patients with recurrent HNSCC when compared directly with CXR/MRI. Furthermore, in terms of cancer-specific survival, a significantly greater share of patients was correctly assigned palliative intended treatment by PET/CT.

Prior studies have demonstrated the superiority of PET/CT to standard imaging strategies for detection of relapse in treated HNSCC, including both loco-regional recurrence and distant disease [6,16,17].

In most cases, metastatic disease precludes definitive treatment and may change the MDTC decision from curative to palliative intent [18]. Despite the relatively low propensity for metastatic spread in untreated

HNSCC (~6%) [19], we have previously demonstrated that upfront PET/CT significantly impacts MDTC decisions in the primary setting (~8%) [8]. In line with our results, existing literature has reported metastatic rates of up to 32% in patients with recurrent HNSCC [20,21]. Accordingly, it seems rational that PET/CT may also influence management decisions in recurrent HNSCC. Our results show that PET/CT-based staging differed significantly compared with CXR/MRI, particularly due to undetected distant spread. Further, the majority of patients with PET/CT-detected distant metastases, not appreciable with CXR/MRI, were upstaged from locally advanced disease based on CXR/MRI.

A retrospective study by Paidpally et al. [22] showed that PET/CT may bring additional value to routine clinical assessment of disease relapse in cases with clinical suspicion or uncertainty. The investigators also found that PET/CT may serve as a prognostic marker of overall survival. Kostakoglu et al. [23] retrospectively investigated how PET/CT versus neck-CT affected management decisions in recurrent HNSCC. The study included 99 patients who were followed after HNSCC treatment. Relapse occurred in 19 patients. PET/CT altered the management decision in 6/19 (32%) compared with neck-CT. Of note, 4/19 (21%) patients with verified distant site recurrences detected by PET/CT were excluded from the analysis, since these sites could not possibly be detected by neck-CT. Although this latter study was small and only dealt with loco-regional recurrences, it showed obvious differences favoring PET/CT.

Our direct comparison of treatment decisions based on PET/CT versus CXR/MRI allowed us to assess the relative impact of each imaging strategy on patient management. This has not previously been done in studies investigating recurrent HNSCC. Furthermore, we demonstrated for the first time that PET/CT pushes MDTC decisions towards more proper selection of appropriate treatments when compared with imaging strategies recommended by current European and American guidelines [9,11]. Conclusively, PET/CT may ensure successful management for a larger share of patients with recurrent HNSCC.

Strengths and limitations

Pros and cons of a paired study design versus a randomized controlled design for diagnostic studies have been well described [24–27]. Our study is a level 4 (therapeutic efficacy) study according to the six-tiered model of Fryback and Thornbury [28]. We chose a paired design for several reasons: A paired data design excludes the risk of confounding and the need for stratification and further allows early unblinding of results at the individual level. In our paired, prospective design, each patient acted as her/his own control. Patients were consecutively included over a 2.5-year period. Other strengths included upfront imaging (i.e., prior to biopsy and histological evaluation) with state-of-the-art technology on the same day. Moreover, all interpretations were done by experienced experts blinded to the results of the complementary imaging strategy.

The study was performed at a single institution which may limit its generalizability to some degree. It was conducted in agreement with the Danish head and neck fast-track program including MDTCs which has been running successfully for more than ten years [12]. This program ensures uniform workup of all patients with suspected HNSCC, including pre-booked slots for all diagnostic and treatment elements (i.e., clinical examination, imaging, surgery, radiotherapy, etc.). This provides an unusually standardized platform for comparisons of this type, potentially assuring greater transfer of such evidence from one to several centers. To some, it may seem unfair to compare a regional radiological modality with a whole-body examination like PET/CT. In addition, since most of the patients with metastatic spread had dissemination to the thoracic region, a comparison with chest-CT vs. PET/CT would have been preferable, rather than CXR vs. PET/CT. However, the purpose of our study was to compare PET/CT with contemporary clinical imaging strategies used in most European head and neck cancer centers.

A generally accepted definition of a HNSCC recurrence does not exist, other than reappearance of cancer disease after definitive treatment [29]. Distinction between a new primary carcinoma from a recurrence is therefore difficult. Furthermore, distinction of residual disease from recurrence is not clearly defined either.

We included patients with a minimum four-month disease-free interval from primary treatment, and arbitrarily defined primary site recurrences as squamous cell carcinoma occurring at the primary site and same anatomical site (i.e., oral cavity, pharynx or larynx) within five years.

Finally, the appropriateness of using disease-specific death as the event type in our NRI analysis may be discussed. We believe that an endpoint related to mortality was both clinically relevant and feasible due to ease of its recovery from registries. A death endpoint also requires less or no assessment of validity. However, the NRI statistic in a setting like ours depends on the occurrence of death within a specific timeframe. This does not necessarily prove that a PET/CT-based MDTC decision of curative therapy for a patient who was alive when events were captured was the correct conclusion, only that the patient survived to the end of follow-up and accordingly, was more likely to have disease of an extent that would be compatible with receipt of curative therapy.

Conclusions

PET/CT significantly affected MDTC decisions in patients with recurrent HNSCC towards fewer curatively intended, and more palliative, treatments. The value of PET/CT appeared strongly related to detection of distant metastases that were not appreciable with CXR/MRI.

Declaration of Competing Interest

None declared.

Acknowledgement

This study was financially supported by the University of Southern Denmark, the Danish Cancer Society, and the Region of Southern Denmark.

References

[1] Ang KK, Trotti A, Brown BW, Garden AS, Foote RL, Morrison WH, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;51:571–8.
[2] Torre Lindsey A, Bray Freddie, Siegel Rebecca L, Ferlay Jacques, Lortet-Tieulent Joannie, Jemal Ahmedin. Global cancer statistics, 2012: Global Cancer Statistics, 2012. CA Cancer J Clin 2015;65(2):87–108. https://doi.org/10.3322/caac.21262.
[3] Wong RJ, Lin DT, Schoder H, Patel SG, Gonen M, Wolden S, et al. Diagnostic and prognostic value of [(18)F]fluorodeoxyglucose positron emission tomography for recurrent head and neck squamous cell carcinoma. J Clin Oncol Off J Am Soc Clin Oncol 2002;20:4199–208.
[4] Yao M, Smith RB, Hoffman HT, Funk GF, Lu M, Menda Y, et al. Clinical significance of postradiotherapy [18F]-fluorodeoxyglucose positron emission tomography imaging in management of head-and-neck cancer-a long-term outcome report. Int J Radiat Oncol Biol Phys 2009;74:9–14.
[5] Mehanna H, Kong A, Ahmed SK. Recurrent head and neck cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol 2016;130:S181–90.
[6] Ichpujani VK, Rao SA, Chaturvedi AK, Dewan AK, Choudhary PS. Positron emission tomography-computed tomography: a superior and one-stop shop modality for treated head and neck carcinoma compared with conventional tomography. J Oral Maxillof Surg Off J Am Assoc Oral Maxillof Surg 2014;72:2319–32.
[7] Gourin CG, Williams HT, Seabolt WN, Herdman AV, Howington JW, Terris DJ. Utility of positron emission tomography-computed tomography in identification of residual nodal disease after chemoradiation for advanced head and neck cancer. Laryngoscope 2006;116:705–10.
[8] Rohde M, Nielsen AL, Johansen J, Sorensen JA, Diaz A, Asmussen JT, et al. Up-front PET/CT changes treatment intent in patients with head and neck squamous cell carcinoma. Eur J Nucl Med Mol Imag 2018;45:613–21.
[9] Gregoire V, Lefebvre JL, Licitra L, Felip E. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and

follow-up. Ann Oncol Off J Eur Soc Med Oncol ESMO 2010;21(Suppl. 5):v184–6.
[10] Opfølgningsprogram for Hoved– og Halskræft. Danish Health and Medicines Authority; 2015.
[11] Pfister DG, Spencer S, Adelstein D, et al. Head and neck cancers, Version 1.2016. Clinical practice guidelines in oncology. < wwwNCCN.org > [15-02-2017].
[12] Roennegaard AB, Rosenberg T, Bjorndal K, Sorensen JA, Johansen J, Godballe C. The Danish Head and Neck Cancer fast-track program: a tertiary cancer centre experience. Eur J Cancer (Oxford, England: 1990) 2018(90):133–9.
[13] Greenland P. Comments on 'Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond' by M. J. Pencina, R. B. D'Agostino Sr, R. B. D'Agostino Jr, R. S. Vasan, Statistics in Medicine (DOI: 10.1002/sim.2929). Stat Med 2008;27:188–90.
[14] Pencina MJ, D'Agostino Sr. RB, D'Agostino Jr. RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–72. [discussion 207–12].
[15] Rohde M, Nielsen AL, Pareek M, Johansen J, Sorensen JA, Diaz A, et al. PET/CT versus standard imaging for prediction of survival in patients with recurrent head and neck squamous cell carcinoma. J Nucl Med 2019;60(5):592–9. https://doi.org/10.2967/jnumed.118.217976. Epub 2018 Oct 12.
[16] Ng SH, Chan SC, Yen TC, Liao CT, Lin CY, Tung-Chieh Chang J, et al. PET/CT and 3-T whole-body MRI in the detection of malignancy in treated oropharyngeal and hypopharyngeal carcinoma. Eur J Nucl Med Mol Imag 2011;38:996–1008.
[17] Suenaga Y, Kitajima K, Ishihara T, Sasaki R, Otsuki N, Nibu K, et al. FDG-PET/contrast-enhanced CT as a post-treatment tool in head and neck squamous cell carcinoma: comparison with FDG-PET/non-contrast-enhanced CT and contrast-enhanced CT. Eur Radiol 2016;26:1018–30.
[18] Scott AM, Gunawardana DH, Bartholomeusz D, Ramshaw JE, Lin P. PET changes management and improves prognostic stratification in patients with head and neck cancer: results of a multicenter prospective study. J Nucl Med Off Publ Soc Nucl Med 2008;49:1593–600.
[19] Rohde M, Nielsen AL, Johansen J, Sorensen JA, Nguyen N, Diaz A, et al. Head-to-head comparison of chest X-Ray/head and neck MRI, chest CT/head and neck MRI, and (18)F-FDG PET/CT for detection of distant metastases and synchronous cancer in oral, pharyngeal, and laryngeal cancer. J Nucl Med Off Publ Soc Nucl Med 2017;58:1919–24.
[20] Chen YK, Su CT, Ding HJ, Chi KH, Liang JA, Shen YY, et al. Clinical usefulness of fused PET/CT compared with PET alone or CT alone in nasopharyngeal carcinoma patients. Anticanc Res 2006;26:1471–7.
[21] Gao S, Li S, Yang X, Tang Q. FDG PET-CT for distant metastases in patients with recurrent head and neck cancer after definitive treatment. A meta-analysis. Oral Oncol 2014;50(3):163–7. https://doi.org/10.1016/j.oraloncology.2013.12.002. Epub 2013 Dec 22.
[22] Paidpally V, Tahari AK, Lam S, Alluri K, Marur S, Koch W, et al. Addition of 18F-FDG PET/CT to clinical assessment predicts overall survival in HNSCC: a retrospective analysis with follow-up for 12 years. J Nucl Med 2013;54(12):2039–45. https://doi.org/10.2967/jnumed.113.121285. Epub 2013 Oct 7.
[23] Kostakoglu L, Fardanesh R, Posner M, Som P, Rao S, Park E, et al. Early detection of recurrent disease by FDG-PET/CT leads to management changes in patients with squamous cell cancer of the head and neck. Oncologist 2013;18:1108–17.
[24] Gerke O, Hoilund-Carlsen PF, Poulsen MH, Vach W. Interim analyses in diagnostic versus treatment studies: differences and similarities. Am J Nucl Med Mol Imag 2012;2:344–52.
[25] Siepe B, Hoilund-Carlsen PF, Gerke O, Weber WA, Motschall E, Vach W. The move from accuracy studies to randomized trials in PET: current status and future directions. J Nucl Med Off Publ Soc Nucl Med 2014;55:1228–34.
[26] Vach W, Hoilund-Carlsen PF, Gerke O, Weber WA. Generating evidence for clinical benefit of PET/CT in diagnosing cancer patients. J Nucl Med Off Publ Soc Nucl Med 2011;52(Suppl. 2):77S–85S.
[27] Gerke O, Hoilund-Carlsen PF, Vach W. Analyzing paired diagnostic studies by estimating the expected benefit. Biom J 2015;57:395–409.
[28] Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. Med Decis Mak Int J Soc Med Decis Mak 1991;11:88–94.
[29] Halperin ECPC, Wazer DE. Perez & Brady's principles and practice of radiation oncology. 6th ed. Lippincott Williams and Wilkins; 2013.