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HEAD AND NECK

PET/CT prior to salvage surgery in recurrent head and neck squamous cell carcinoma

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Abstract

Purpose The purpose of this study was to assess the use of 18F-FDG PET/CT scans for detecting distant metastases in patients with recurrent head and neck squamous cell carcinoma (HNSCC) and investigate the treatment and survival of patients with recurrence.

Methods In this retrospective study, consecutive head and neck cancer patients referred for FDG PET/CT scan between 2012 and 2014 were included. Patient records were reviewed and only patients with recurrence of HNSCC were enrolled for further analysis. Information on distant metastases, surgery and survival was collected. A Kaplan–Meier analysis was used to report survival.

Results Overall 275 PET/CT scans were performed due to suspected recurrence, and in 166 scans (144 patients), recurrence of HNSCC was confirmed, making them eligible for further analysis. Distant metastases were revealed in 29.8% of the scans ($n=51$) and the proportion of revealed metastases remained constant at approximately 30% each year. Although the number of performed scans increased twofold each year, there was no statistically significant change in the proportion of scans with distant metastasis ($p=0.55$). The distant metastases were most often seen in the lungs ($n=44$) and bone ($n=15$). A few patients had widespread dissemination to other areas. Salvage surgery was performed following 81 of the 166 PET/CT scans. Seven of the patients who underwent salvage surgery had M-site oligo-metastases. Patients who underwent salvage surgery had a median survival of 22 months whereas patients not treated with salvage surgery had a median survival of 6 months. After 5 years, 21% of the patients selected for salvage surgery were alive.

Conclusions Distant metastases occur frequently in patients with recurrent HNSCC disease and the proportion of revealed distant metastases remained the same (30%). Imaging with FDG PET/CT can be recommended in patients with recurrent HNSCC prior to putative salvage surgery.

Keywords Salvage surgery · Squamous cell carcinoma · Recurrence · FDG PET/CT

Introduction

Head and neck cancers represent about 3–4% of all new cancer cases worldwide [1] and more than 90% of these head and neck cancers are squamous cell carcinomas (HNSCC) [2]. The treatment of HNSCC is multidisciplinary and consists of surgery and/or radiotherapy with or without chemotherapy depending on disease stage and anatomical location [3]. Recurrence is experienced by about 40% of the patients, causing severe morbidity and mortality [4, 5]. The prognosis after recurrence is poor and salvage surgery is usually the only option for curative treatment [6]. It is crucial to select the right patients for salvage treatment to avoid

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unnecessary treatment morbidity, especially in cases where salvage proves to be unobtainable [7, 8].

Functional imaging with [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography combined with computed tomography (PET/CT) is increasingly used in the management of HNSCC both in the pre-, per-, and post-treatment setting. In the pre-treatment setting, PET/CT has, in some studies, been shown to improve staging [9, 10] and the diagnostic workup for patients with neck metastasis and unknown primary tumor [11] as well as the detection of distant metastases [12]. In the per-treatment setting, the use of FDG PET/CT reduces the variability in target delineation for radiotherapy [13] and can be used in more advanced experimental radiotherapy planning such as dose painting [14]. In the post-treatment setting, surveillance with PET/CT is non-inferior to planned neck dissections after primary treatment with radiotherapy [15].

The use of PET/CT may potentially help patients avoid unnecessary salvage surgery in case of distant metastases or excessive disease, making it an important factor when deciding treatment modalities. However, studies that have investigated the use of PET/CT in recurrent HNSCC are limited to specific parts of the workup and treatment process. The purposes of the current study are twofold (1) to investigate the use of PET/CT in patients with recurrent HNSCC, prior to salvage surgery by assessing how often distant metastases were revealed and (2) to investigate the survival after recurrence in patients treated with salvage surgery and patients not treated with salvage surgery.

Materials and methods

Patient population

The current retrospective study included all consecutive patients referred to PET/CT scans, after primary treatment, from the Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet from 2012 to 2014. Only patients with HNSCC in the oral cavity, nasopharynx, oropharynx, hypopharynx, larynx or from unknown primary tumors (all SCC) were included. Rigshospitalet is a public university hospital treating all cancer patients from a catchment area population of 2.6 million people. The Danish healthcare system provides the population with free access to all diagnostics and treatments from general practitioners to hospitals, financed by general taxes [16]. This means that the treatment was initiated when indicated, irrespective of e.g., patient economy and insurance. Patient records were reviewed and all patients with a PET/CT scan and a new local, regional or distant recurrence of HNSCC were included. Thus, patients with other histology than squamous cell carcinoma and patients with previously known distant metastasis were excluded upfront. If a patient experienced more than one recurrence and had a PET/CT performed for each new recurrence, each of those PET/CT scans were included as separate scans.

Clinical information was retrieved from patient records and included pathology, date of recurrence, age, sex, TNM staging, tumor subsite, primary treatment, imaging description, recurrence site (local, regional or distant), location of distant metastasis (lung, bone, liver, etc.), possible salvage surgery, and date of death or last follow-up. Ethics approval was not required for this study under Danish law, but the data collection was approved by the Danish Data Protection agency.

Imaging acquisition

All patients had a whole-body PET/CT scan performed with an integrated PET/CT scanner (Biograph 40 True-Point 40 HD-PET; Siemens Medical Solution, Malvern PA; Biograph 64 True-Point HD-PET, Siemens Medical Solutions; or Biograph 64 mCT, Siemens Medical Solutions). Patients were instructed to fast for at least 6 h before intravenous administration of FDG (4 MBq/kg, max. 400 MBq) and were scanned 1 h after injection. The diagnostic CT scans were acquired at 120 to 140 kVp and at a maximum of 225 mAs modulated. The latter was adjusted according to body size and intravenous contrast was given unless contraindicated. The PET scans were performed after the CT with a scan duration of 3 min per bed position. All PET scans were reconstructed iteratively using a point spread function with 2-mm Gauss filter.

The descriptions of all PET/CT scans were reviewed, and for every patient with recurrence or suspected recurrence, the patient record was reviewed including pathology reports to verify the M-site recurrence either by pathology report or by imaging with multiple metastases.

Statistical analysis

Statistical analyses were performed using SPSS version 22 and R version 3.2.3. In the survival analysis, follow-up time was calculated from the date of the first PET/CT scan to time of death or last follow-up. Survival curves were plotted with the Kaplan–Meier method. A p value ≤ 0.05 was considered statistically significant.

Results

PET/CT scans and patients

HNSCC recurrence was confirmed in 166 out of 275 PET/CT scans. Figure 1 illustrates a flowchart of inclusion and

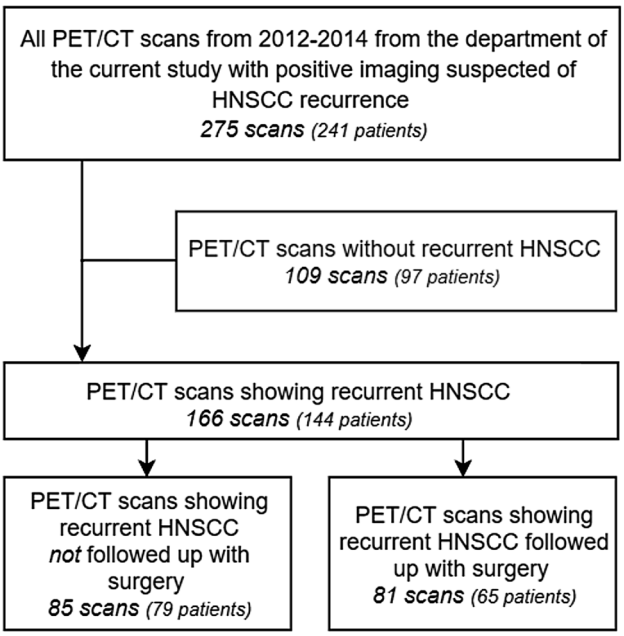

Fig. 1 Flowchart illustrating inclusion and exclusion of PET/CT scans. Number of patients in parentheses

Table 1 General patient information

Median age in years (range)	64 (39–88)	
	Number (*n*)	Percent (%)
General patient information		
Sex		
Male	118	82
Female	26	18
Sites of primary tumors		
Oral cavity	43	29.9
Larynx	37	25.7
Oropharynx	27	18.8
Hypopharynx	21	14.6
Nasopharynx	11	7.6
Unknown primary tumor	5	3.5
Primary treatment		
Radiotherapy	55	38.2
Chemoradiotherapy	37	25.7
Surgery and radiotherapy	24	16.7
Surgery	20	13.9
Surgery and chemoradiotherapy	8	5.6

The 166 included scans were performed on 144 patients as 17 patients were scanned more than once. Only scans with a new recurrence were included

exclusion in the study. The 166 scans were performed in 144 patients. Specifically, 13 patients contributed with 2 recurrence scans, 3 patients contributed with 3 recurrence scans and 1 patient with 4 recurrence scans. In all cases, each separate PET/CT scan for a new verified recurrence was included and as such each scan is counted separately when analyzing scans regarding HNSCC recurrence and surgery. The most common primary tumor sites were the oral cavity ($n=43$), larynx ($n=37$), and oropharynx ($n=27$), and the majority of the patients ($n=92$) received radiotherapy with or without concomitant cisplatin as primary treatment. Table 1 depicts the patient characteristics.

PET/CT scans and recurrence

Distant metastases were revealed in 29.8% ($n=51$) of the 171 scans with HNSCC recurrence. These 51 scans were performed on 51 different patients. All 51 patients with M-site failure were clinically assessed as having distant metastases from their primary HNSCC. Seventeen (33%) of the distant metastases were verified with biopsy, 8 were reassessed with subsequent re-imaging, confirming the continuous presence of metastases, and the remaining 26 had multiple metastases and were not verified with biopsy or re-imaging. Biopsies of the first recurrence were routinely performed also if the patient only had distant metastasis. In two patients with distant metastases, this was not possible, and these two patients were followed with re-imaging which revealed disease progression. In the remaining 12 of the 17 patients, the biopsies were CT-guided lung biopsies to ensure that the patient did not have a new primary lung tumor since this would change patient treatment.

The distant metastases were most often seen in the lungs ($n=44$), bone ($n=15$), thoracic wall tissue ($n=6$) and liver ($n=5$). A few patients had widespread dissemination to other areas; one patient had lung, colon, and prostate metastasis, one patient had lung and kidney metastasis, and one patient had lung, bone, and brain metastasis. Of the 51 scans with distant metastases, 10 scans showed recurrence in both T- and M-site, 18 scans showed recurrence in N- and M-site and 16 scans showed simultaneous recurrence in all 3 sites. The remaining seven scans showed solely distant metastases and could potentially represent new primary tumors. However, five were biopsy verified as metastases from their primary HNSCC, and the last two scans revealed multiple metastases and were clinically judged as recurrence from their primary HNSCC. Figure 2 illustrates the distribution of recurrences in all 144 patients.

The number of PET/CT scans performed in patients with HNSCC recurrence increased yearly, but surprisingly the proportion of scans with distant metastases remained at approximately 30%. In 2012, 8 out of 24 patients had distant metastasis (33.3%); in 2013, 17 out of 51 had distant metastasis (33.3%); and in 2014, 26 out of 91 had distant metastasis (28.6%) (Fig. 3). A Chi-Squared test of equal proportions showed no statistically significant difference

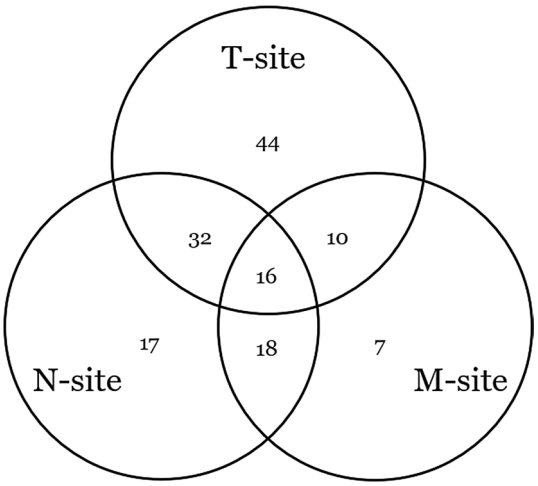

Fig. 2 Scans of patients with HNSCC recurrence performed each year with the proportion revealing distant metastasis

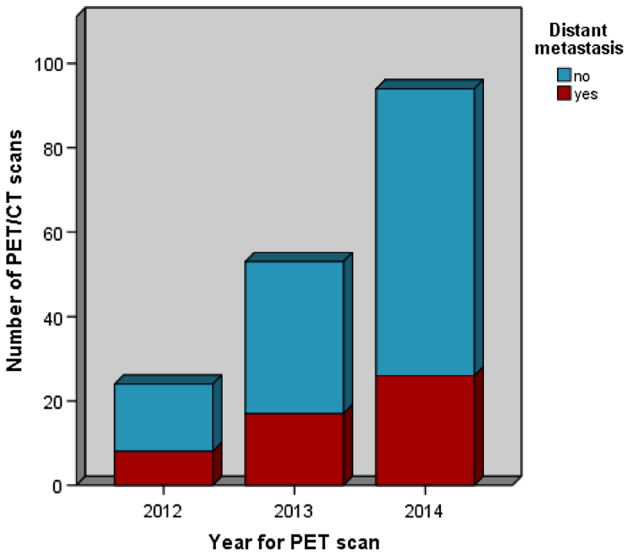

Fig. 3 The distribution of recurrences specified on T-, N- and/or M-site

in the proportions of distant metastases that were revealed each year ($p = 0.55$).

Approximately half ($n = 81$) of the 166 scans were followed up with surgery (Fig. 1). Seven patients who had a distant metastasis was revealed on PET/CT and were treated with salvage surgery because they were assessed curable also at the M-site. All seven patients had oligometastasis such as a single lung lesion. Thirty-five of the patients without distant metastases were inoperable due to either tumor encasement of the carotid artery, involvement of the skull base, involvement of prevertebral fascia, too extensive disease or comorbidity in general.

Survival after recurrence

The survival after recurrence was poor with a median overall survival of 9 months (95% CI 7–10 months). Figure 4 illustrates the survival stratified by salvage surgery. Patients selected for salvage surgery had a significantly better survival ($p < 0.001$, tested with log-rank) with a median survival of 22 months whereas patients not undergoing salvage surgery had a median survival of 6 months. After 5 years, 21% of the patients treated with salvage surgery were alive. Figure 5 depicts the survival stratified for both surgery and distant metastases. Patients *without* distant metastases who underwent surgery had a significantly better survival compared to patients who did not undergo surgery ($p = 0.006$, tested with log-rank). Regarding patients with distant metastasis, there was no significant difference in survival between the few who underwent surgery and those who did not ($p = 0.9$). Of note, very few patients with M-site recurrence underwent surgery.

Discussion

PET/CT is increasingly used in the management of HNSCC and implemented in different guidelines [17, 18]. In the current study, we investigated the impact of PET/CT to detect distant metastasis in patients with recurrent HNSCC, prior to salvage surgery. All scans referred from the Department of Otorhinolaryngology, Head and Neck Surgery and Audiology between 2012 and 2014 were initially reviewed and only those eligible with recurrent HNSCC were included for further analysis (Fig. 1). Compared to primary HNSCC, distant metastases occur more frequently in recurrent HNSCC, and in this study, distant metastases were revealed in 29.8%. The number of performed PET/CT scans approximately doubled each year, but despite the large increase in scans, the proportion of scans revealing distant metastasis remained close to 30% (Fig. 2), which is comparable with other studies [19, 20]. In 2012, FDG PET/CT was primarily used at our institution for patients undergoing major salvage surgery. However, during the following years, the indications expanded and patients with recurrence were scanned before less comprehensive surgery and this should be recognized as a limitation. One might expect that scanning more patients with less excessive disease would reduce the proportion of scans revealing distant metastases. The proportion of revealed distant metastases that were revealed was reduced from 33% in 2012 to 28% in 2014. However, there was no statistically significant difference in the proportion of distant metastases that were revealed each year ($p = 0.55$). Within the last few years, it has become a standard practice to perform a PET/CT scan of patients with recurrent HNSCC before salvage surgery at our institution. This practice intuitively seems

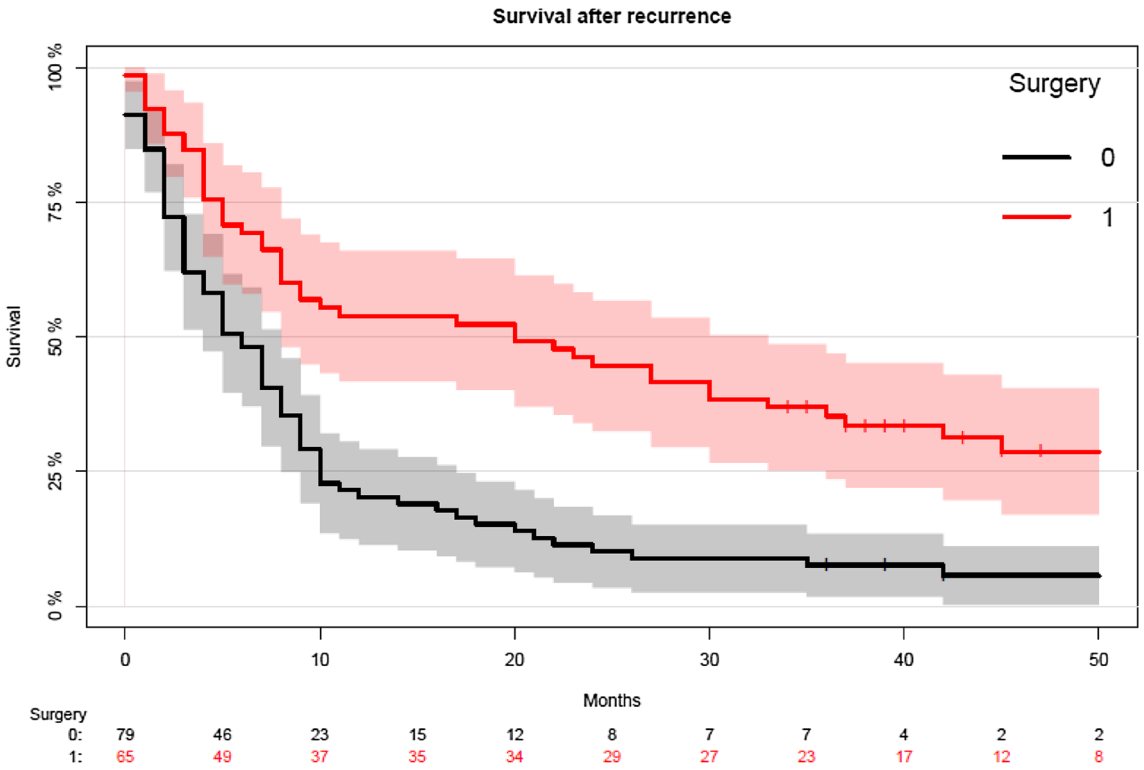

Fig. 4 Survival after recurrence PET/CT scan stratified by salvage surgery

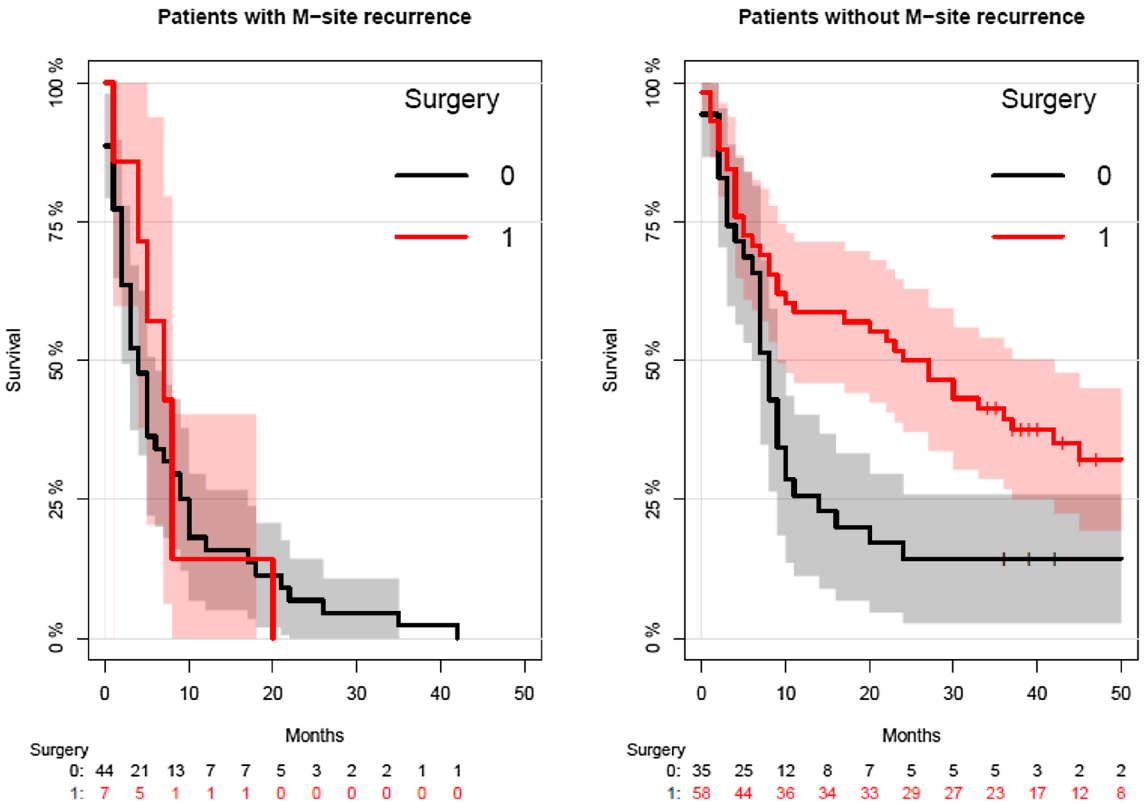

Fig. 5 Survival after recurrence PET/CT scan stratified by salvage surgery and M-site recurrence

rational and seems to be supported by the data presented here. On the other hand, it is not possible to conclude if PET/CT is a better way to select patients for salvage surgery from these data. Patients without distant metastases on PET/CT might still not benefit from salvage surgery, and even though distant metastases were revealed in 30% of the scans, this current study does not provide evidence as to whether those patients would benefit from salvage surgery or not, regardless of distant metastases. This evidence can only come from randomized clinical trials which would be difficult to design and ethically problematic. The high mortality and morbidity after recurrence justify thorough examination and imaging with PET/CT, which potentially can spare patients from unnecessary risk and morbidity from salvage surgery in case of distant metastases. The present-day approach at the institution of the current study includes informed consent, a general evaluation of patient status, rehabilitation assessment and possibly post-operative rehabilitation. Patients who were considered unlikely to benefit from often extensive surgery receive non-surgical treatment. More detailed knowledge about prognosis enables patients and their surgeons to make this decision.

Seven of the 51 patients with DM did not have lung metastasis, and as such, the DM may not have been revealed with conventional CT of the thorax. The performance of PET/CT compared to other imaging modalities reported in the literature is divergent. Some studies report PET/CT scans to be more sensitive than conventional CT scans [21, 22]. Another study compared PET/CT to 3 T whole-body MRI scans and found their diagnostic capabilities similar [23]. There is a high risk of distant metastases in recurrent HNSCC, e.g., 23% [24] and 27% [25], compared to the relatively low risk of distant metastases at the primary diagnosis, e.g., 6% [26] and 7.4% [27]. Since PET/CT has a high sensitivity and specificity for detecting distant metastases [28–30], this argues for the use of PET/CT in recurrent HNSCC. Nevertheless, the retrospective design should be recognized as a limitation. In the present study, not all the distant metastases were biopsied although this could be interesting for academic purposes. At out institution, a biopsy from the first recurrence is routinely performed. A biopsy from subsequent or simultaneously distant metastasis is only performed if it has clinical relevance, i.e., a consequence for the following treatment. This practice may change in the future with more targeted therapy becoming available. This discussion, however, is beyond the scope of this article. Another limitation is that this study does not compare PET/CT with other imaging modalities and a systematic comparison in a prospective study would be preferable to estimate a clinically significant advantage of PET/CT in recurrent HNSCC.

The importance of selecting the right patients for salvage surgery is illustrated by the poor survival after recurrence. Not surprisingly the survival curve in Fig. 4 shows a statistically significant ($p < 0.001$) better overall survival (OS) for patients who were selected for surgery. Previous studies reported 5-year OS to be about 27% after salvage surgery [8, 31]. One other study reported salvage surgery to be independently associated with an improved OS compared to non-surgical treatment (3-year OS 61.8% vs. 24.1%) [32]. In the current study, 21% of the patients treated with salvage surgery were alive after 5 years and they had a significantly better overall survival than patients who were not found suitable for and treated with salvage surgery. Non-salvageable patients received differentiated variations of palliative treatments and best supportive care possible. In general, patients are treated with palliative chemotherapy if tolerated and bone metastasis is treated with palliative radiotherapy. However, rather than the surgery itself, the difference in survival is more likely to reflect that patients who did not receive surgery had a more advanced disease and/or comorbidity and, consequentially, a worse prognosis. Likewise, patients who managed with salvage surgery were carefully selected and, therefore, already more likely to have a better prognosis, and patients without distant metastases who underwent surgery had a significantly better survival ($p = 0.006$) compared to patients who did not undergo surgery (Fig. 5). Patients with distant metastases undergoing surgery were too few (7 of 51) to provide sufficient data for thorough analysis and no survival difference was shown ($p = 0.9$) (Fig. 5). The low number of patients with distant metastases who underwent salvage surgery emphasizes that patients with distant metastases generally are not considered as candidates for salvage treatment. It is possible that more than seven patients would have undergone futile salvage surgery if a PET/CT was not performed; however, the number of patients, their characteristics as well as potential outcome remain a matter of speculation. With the possible toxicity from salvage surgery in mind, it is reassuring that almost half of the patients who received surgery were alive 2 years after recurrence.

To conclude, distant metastases occur frequently in patients with recurrent HNSCC disease. The proportion of patients with distant metastases remained the same (30%), even though more patients with less extensive disease were scanned. Imaging with FDG PET/CT can be recommended in patients with recurrent HNSCC, prior to salvage surgery.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent is not required for this study under Danish law, but the data collection was approved by the Danish Data Protection agency.

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