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Original Research Article

Post-therapeutic detection of local tumor persistence of head and neck cancer: the value of routine control endoscopy with biopsy and medical imaging

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ABSTRACT

Background: Insufficient local tumor control is the main cause of treatment failure in head and neck cancer (HNC). Re-staging HNC is challenging because of post-therapeutic tissue distortion. We investigate whether medical imaging and biopsy is more sensitive in identifying tumor persistence.
Methods: In our clinic a re-staging with a control endoscopy and medical imaging is performed 3 months after therapy for some HNC patients. In this retrospective study, we compare the accuracy of imaging to the histology (gold standard). Imaging reports were classified according to 3 scales and re-assessed by 2 neuroradiologists. Furthermore, we evaluate recurrence rates and disease-free survival.
Results: 100 cases were evaluated. 14 patients presented with positive histology at the re-staging. Biopsy detected malignancy in 7 patients with inconspicuous imaging. Disease-free survival during the first 2 years was generally low (n=55). The accuracy of the RECIST scale was 0.74 with a sensitivity of 0.50 and a specificity of 0.78. Imaging reports reviewed according to the Lee-scale and a self-developed scale presented an accuracy of 0.47 and 0.51. Re-assessment of imaging by 2 neuroradiologists showed an accuracy of 0.87.
Conclusions: Medical imaging alone serves as a moderate diagnostic tool to diagnose local persistence of HNC 3 months after therapy. Radiologic misdiagnosing can be addressed by control endoscopy. Our results indicate a benefit of routine biopsies since reliance on imaging may fail to notice tumor persistence. A binary classification of imaging showed a higher accuracy than conventional imaging scales and may help to predict tumor recurrence within 24 months after re-staging.

Keywords: Follow-up, HNC, Imaging, Re-staging

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the 7th most common cancer worldwide and refers to a group of malignancies involving the upper aerodigestive tract. According to the latest GLOBOCAN estimates (2020), HNSCC globally accounts for an estimated 890,000 new cases and 450,000 deaths per year.[1]

These patients raise many diagnostic and therapeutic challenges. Their disease course is often complicated by recurrent disease, regional lymphatic spread, synchronous primary tumors, and distant metastases. Insufficient local tumor control is the main cause of treatment failure. However, tissue distortion from radiation and surgery can obscure early detection of lesions. Thus, endoscopy with biopsy is often needed to investigate potential tumor persistence. The aim of this analysis is to investigate the

data of re-staging findings of patients who underwent both an endoscopy with biopsy, as well as medical imaging to assess tumor persistence. The hypothesis is that this method is more sensitive in identifying tumor persistence.

METHODS

In the department of otolaryngology (ORL), head and neck surgery of the Kantonsspital Aarau, a planned re-staging consisting of a routine control endoscopy in addition to cross-sectional imaging is performed at 3 months after treatment for selected head and neck cancer (HNC) patients, especially after primary radio(chemo)therapy and surgery. In this retrospective study of patient records, we compare the diagnostic accuracy of imaging to histology (gold standard). The primary objective is to calculate the sensitivity and specificity of both methods. Finally, we describe the recurrence rate and disease-free survival in our cohort.

Population

The sampling technique was performed as follows. ISMed-eOPPS (KSA) was used to identify all ORL endoscopy procedures in the operation room (OR) schedule in our clinic between 01 January 2011 and 31 December 2019. To be eligible for this study, cases must have a diagnosed HNC, that was restaged with operative control endoscopy and biopsy in addition to medical imaging (CT or MRI) approximately three months after completion of therapy. The medical records of these patients were retrospectively reviewed using KISIM version 5.1.0.3 to collect basic health information, such as sex, tumor location, primary therapy, along with initial TNM-stage, and date of initial diagnosis, date of birth, date of control endoscopy and date of imaging scan.

All patients were staged according to the American Joint Committee on Cancer Guidelines and discussed at our tumor board. Imaging reports were obtained from centricity universal viewer zero footprint version 6.0 SP9.0.1.2.[2,3] The software used for the descriptive statistical analysis is “R” (version 4.2.1).

Patients were excluded from the study if the data sets were incomplete, an endoscopy was performed without biopsy, re-staging was performed without imaging or if PET/CT was used as the primary imaging method. Furthermore, patients were excluded if their age was <18 years, tumor persistence was detected prior to re-staging, or the index tumor was a malignancy of other regions of the head and neck, such as the thyroid gland, paranasal sinuses, skin, salivary glands, or lymphoma.

The study was conducted in full accordance with the Declaration of Helsinki and was approved by the institutional Swiss ethics committee (Ethikkommission Nordwest- und Zentralschweiz, EKNZ, project-ID 2019-01134).

RESULTS

A total of 100 patients (80 males, 20 females) with HNC were evaluated. The average age was 62.2 years. Oropharyngeal cancer was the most common diagnosis. The demographic data and details of the tumor characteristics are shown in Tables 1 and 2.

Table 1: Demographic data of the patients; overall (n=100).

Sex	Percentage (%)
Male (n=80)	80
Female (n=20)	20
Average Age (years)	62.2

Table 2: Overview of the tumor characteristics; overall (n=100).

Characteristics	N
Tumor location	
Oral cavity	5
Oropharynx	48
Nasopharynx	4
Hypopharynx	20
Larynx	21
CUP-syndrome	2
T-classification	
Early stage (T1, T2)	43
Advanced stage (T3, T4)	55
CUP-syndrome	2
N-classification	
Positive (N+)	64
Negative (N-)	36
Primary treatment	
Radiotherapy	17
Surgical resection	43
Radiochemo/-immunotherapy	40

For post-therapeutic re-staging, all patients underwent control endoscopy with biopsy in addition to medical imaging. Median time between the end of the treatment and endoscopic examination was 3.14 months (IQR: 2–6). In the re-staging 86 cases (86%) presented no signs of malignancy. 14 patients (14%) presented with positive histological findings (local tumor persistence), which was referred to as the gold standard (Table 3).

Table 3: Imaging results compared to histology.

Imaging scale	Histology+	Histology-
Recist+	7	19
Recist-	7	66
Lee+	13	52
Lee-	1	34
Engert+	10	37
Engert-	2	31

Medical imaging reports predominantly obtained from CT-scans (n=85; 85%) in addition to fewer MRI-scans (n=15; 15%) were classified according to the internationally applied RECIST imaging scale, as well as a scale by Lee et al and a self-developed Engert-scale (Table 4).[4,5] Diagnostic accuracy was determined as shown in Table 5.

Table 4: Overview of the imaging scales.

Imaging scale and radiologic interpretation	N
Recist	
Complete remission	29
Partial remission	44
Stable disease	9
Progression	17
Lee	
Very probable	16
Somewhat probable	29
Somewhat unlikely	20
Unlikely	35
Engert	
Complete remission	48
Partial response	29
No differentiation possible	5
Suspicious for malignancy	10
Persistence/progression	8

Table 5: Diagnostic accuracy of the three imaging scales when compared to histology.

Imaging scale	Sensitivity	Specificity	Accuracy
Recist	0.50 [0.27, 0.73]	0.78 [0.68, 0.85]	0.74 [0.68, 0.85]
Lee	0.93 [0.69, 0.99]	0.40 [0.3, 0.5]	0.47 [0.38, 0.57]
Engert	0.83 [0.55, 0.95]	0.46 [0.34, 0.57]	0.51 [0.4, 0.62]

Imaging reports assigned to the RECIST scale showed a positive re-staging result in 26 cases, although histology only presented malignancy in 7 of these cases. An important implication for clinical practice is that 7 patients with tumor persistence in the histological re-staging had a negative imaging report according to the RECIST scale.

Based on the numbers above, the accuracy of the RECIST scale with the corresponding 95% Wilson confidence interval was 0.74 [0.64, 0.81] with a sensitivity of 0.50 [0.27, 0.73] and a specificity of 0.78 [0.68, 0.85]. Imaging reports reviewed according to the Lee-scale presented a lower accuracy of 0.47 [0.38, 0.57] with a sensitivity of 0.93 [0.69, 0.99] and a specificity of 0.40 [0.3, 0.5]. Due to its high proportion of positive classifications (65%) most true positive cases were correctly identified as such, but the low specificity (40%) is also proof for a high number of false positives.

Furthermore, the self-developed Engert-scale was created, since 20 cases were unclassifiable. It showed a positive radiologic re-staging in 10 of the 16 histologically confirmed cases of tumor persistence. 2 cases with positive histology were missed and classified as negative imaging. This leads to comparable results with an accuracy of 0.51 [0.4, 0.62], sensitivity of 0.83 [0.55, 0.95] and specificity of 0.46 [0.34, 0.57]. The concordance of the 3 imaging scales was assessed using McNemar tests and showed little agreement as follows: p value <0.001 (RECIST versus Lee), p value <0.001 (RECIST versus Engert-scale) and p value 0.019 (Engert-scale versus Lee).

Re-assessment of imaging

A radiologic differentiation between malignancy and post-therapeutic sequelae by medical imaging is often difficult, which leads to a high number of false-positive imaging scans. The RECIST-scale did only identify half of the true positives, which results in a low sensitivity (50%). Post-therapeutic tissue changes lead to ambiguous imaging reports and did not allow a binary classification in many cases. To tackle this issue, imaging scans were additionally re-assessed by 2 neuroradiologists independently and classified into “tumor persistence” or “no tumor persistence”. The results were subsequently compared to the histological findings. The 2 radiologists disagreed regarding 13 patients and 24 patients were evaluated as positive for tumor persistence by both examiners. The diagnostic accuracy of the classification by radiologist 1 compared to radiologist 2 was 0.87 [0.79, 0.92] with a sensitivity of 0.71 [0.54, 0.83] and a specificity of 0.95 [0.87, 0.98]. When compared to histology (gold standard) the accuracy of imaging assessment of neuroradiologist 1 showed to be 0.77 [0.68, 0.84] with a sensitivity of 0.64 [0.39, 0.84] and specificity of 0.79 [0.69, 0.86]. For neuroradiologist 2, these results were 0.70 [0.6, 0.78], 0.64 [0.39, 0.84] and 0.71 [0.61, 0.79]. The contingency table and binary imaging classification of the 2 neuroradiologists compared to histology is shown in Tables 6 and 7.

Table 6: Contingency table of classification by neuroradiologist 1 and 2.

Parameters	Radiologist 2 +	Radiologist 2-	Col-sum
Radiologist 1 +	24	3	27
Radiologist 1 -	10	63	73
Row-sum	34	66	100

Tumor control

Tumor persistence was confirmed in 14 cases. Among patients with negative biopsy in the control endoscopy, only 55 patients (55%) remained disease-free during a follow-up of 2 years. The disease-free survival by

re-staging findings according to histology and the 3 different imaging scales is shown in Figure 1.

Table 7: Binary imaging classification of neuroradiologists 1 and 2 compared to histology.

Parameters	Histology +	Histology -	Col-sum
Radiologist 1 +	9	18	27
Radiologist 1 -	5	68	73
Row-sum	14	86	100
Radiologist 2 +	9	25	34
Radiologist 2 -	5	61	66
Row-sum	14	86	100

Patients with early-stage disease (T1/T2) showed tumor recurrence in 30.2% [18.602, 45.105] versus 41.8% [29.738, 54.967] in advanced-stage disease (T3/T4). Primary radiotherapy and primary radiochemo-/radioimmunotherapy showed a comparable recurrence rate of 41.8% [29.738, 54.967] and 42.5% [28.509, 57.805]. This rate was lower 30.2% [18.602, 45.105] in patients receiving primary surgery. Tumor recurrence occurred most common in the hypopharynx 65.0%, followed by the oral cavity 60.0% and oropharynx 31.2%.

When histology showed no signs of malignancy in the re-staging, the likelihood of tumor recurrence during 2 years of follow-up was 27.9% [19.529, 38.175]. Negative results in the imaging scans according to the scales of RECIST, Lee and Engert presented with a recurrence rate of 35.6% [25.605, 47.067], 28.6% [16.327, 45.055] and 27.3% [15.067, 44.218]. The tumor recurrence rate (%) within 24 months by imaging re-staging in patients with negative histological results is shown in Table 8.

Interestingly, patients with a negative histology in the re-staging displayed similar tumor recurrence rates, independent from the results of their re-staging imaging scans. The combination of a negative biopsy with a negative imaging scan led to tumor recurrence in 28.8% (RECIST-scale), 26.5% (Lee-scale) and 22.6% (Engert-scale). In the same setting, a positive imaging scan led to tumor recurrence in 26.3%, 28.8% and 32.4%. However, the "binary classification" by the 2 radiologists showed, that even in cases with negative histology, the tumor recurrence rate within 24 months was higher in cases, which were classified as positive imaging (44.4% and 44.0%) compared to negative imaging (23.5% and 21.3%).

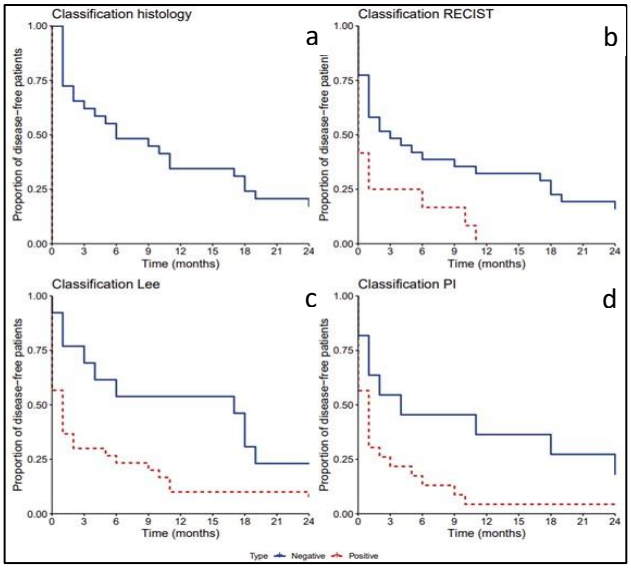

Figure 1 (a-d): Disease-free survival by re-staging findings according to histology and the three different imaging scales.

Table 8: Tumor recurrence rate (%) within 24 months by imaging re-staging in patients with negative histological results.

Method and classification	N	Estimate (%)	CI
Recist scale			
Positive	5	26.3	[11.806, 48.792]
Negative	19	28.8	[19.272, 40.637]
Lee scale			
Positive	15	28.8	[18.33, 42.273]
Negative	9	26.5	[14.601, 43.117]
Engert scale			
Positive	12	32.4	[19.633, 48.536]
Negative	7	22.6	[11.395, 39.812]
Radiologist 1			
Positive	8	44.4	[24.56, 66.284]
Negative	16	23.5	[15.034, 34.855]
Radiologist 2			
Positive	11	44.0	[26.666, 62.933]
Negative	13	21.3	[12.9, 33.122]

DISCUSSION

To this date, there is no internationally validated evidence-based surveillance protocol for survivors of HNC after treatment. The recommended time intervals, duration of follow-up and specific components of screening examinations are not uniformly defined.[6] Since approximately 80-90% of all tumor recurrences occur within the first 2-4 years, the follow-up intensity is generally higher during this time.[7] The lack of evidence continues to challenge clinicians in making practice decisions in the follow-up.[8] The evaluation of therapy success in most clinics is primarily based CT-/MRI-scans and a fiberoptic endoscopy. However, these approaches are often inadequate to discriminate between post-actinic tissue changes and tumor persistence and often require histological confirmation by biopsy.[9,10]

By performing medical imaging and a biopsy in our hospital, we were able to compare the results of both examinations and state an approximation of sensitivity and specificity.

Current guidelines

The idea of post-treatment surveillance is based on 2 assumptions. It is beneficial for patients to detect disease before self-referral and early detection in the asymptomatic patient improves the outcome. For both premises there is no strong evidence. Up to this date, there are no randomized trials that have compared 2 different surveillance strategies or a follow-up protocol without surveillance, partly due to ethical reasons. This leads to frequent examinations every 1-3 months at the beginning, which gradually decline each year to annual appointments after 5 years.[11] In 2016, the American Cancer Society developed guideline recommendations for HNC survivorship care for primary care clinicians.[12] When evaluating the guideline, the expert panel realized the limited evidence for many of the recommendations and emphasized the importance of team-based, multispecialty, multidisciplinary, collaborative care.[8]

A critical review of the follow-up protocol for HNC patients with 456 subjects was published in 2019 and showed a tumor relapse in 22% (n=94) during a 5-year follow-up period. 90% of recurrences were found within the first 3 years. Patients with tumor recurrence showed to have symptoms in 56%. Since recurrent disease after 3 years only occurred in 2% of the patients, a routine follow-up thereafter was rated as questionable.[13]

Some authors generally recommend surveillance beyond 5 years, because late recurrences are occasionally observed, and the risk of a second primary malignancy remains elevated for at least 10 years' post-therapy.[14] Of note, more intensified surveillance is often performed in patients, who initially are diagnosed with advanced disease. While in these cases, recurrences are indeed more frequent than, they are less likely to be successfully salvaged.[15,16]

Imaging

Most international HNC societies recommend cross-sectional imaging 8-12 weeks' post-therapy using CT, MRI, and/or PET scan.[17] However, this is mainly based on expert consensus. Other guidelines recommend imaging at least once during the first 6 months after curative-intent surgery to create a baseline for future scans.[18] Subsequent imaging is only obtained in symptomatic patients or when there is clinical suspicion for tumor recurrence.[19] Although CT and MRI are the mainstays of surveillance, ultrasonography is universally available, cheap and holds the benefit of lacking radiation exposure.[20] Various publications show that combined with fine needle aspiration, it is superior to CT in detecting lymph node metastasis.[21]

Despite being expensive and not universally available yet, the importance of PET/CT is rising in more developed countries. Besides evaluating the primary tumor site, it helps to detect locoregional and distant metastatic disease. Supported by the results of the UK PET-neck randomized controlled trial study, it is recommended for the assessment of response 3 months post-chemoradiotherapy, especially in patients with advanced nodal disease.[22] The high negative predictive value suggests that salvage surgery can be avoided in many cases.[23] Furthermore, results confirm the high effectiveness of PET/CT in the assessment of HNC recurrence and suggest that it is more accurate than conventional follow-up in the assessment of recurrence and could be proposed systematically at 12 month of the usual follow-up.[10] However, invasive procedures may still be necessary in a considerable number (11.8%, n=8) of patients.[24]

Even for experienced neuroradiologists, the interpretation of imaging is challenging and often leads to vague and ambiguous formulations. These reports do not allow a categorization of imaging into "tumor persistence" or "complete remission" in the routine clinical setting. Besides the internationally applied RECIST-scale, a similar categorization was created by Lee et al when interpreting conventional MRI scans for the detection of tumor recurrence.[5] Due to the retrospective nature of our study we had to add further groups to allocate imaging reports, where no differentiation was possible and created the Engert-scale. The authors believe that imaging reports tend to keep a backdoor for uncertainty to evade possible (legal) consequences. For this reason, imaging reports frequently include phrases such as "ultimately malignancy cannot be excluded". In fact, imaging reports tend to state possible tumor persistence rather than ruling it out, which ultimately leads to a higher rate of false positive imaging reports. We were able to show this, when 2 neuroradiologists independently re-assessed all imaging scans. Interobserver agreement was high with an accuracy of 0.87 and when compared to histology, the accuracy was 0.70 and 0.77. In this setting, the only choice for the examiner was "tumor" or "no tumor", which was only possible due to the retrospective nature of this study

without any clinical implications for the further treatment. However, this "gut feeling" expressed as an additional "binary scale" off the record could be helpful to lead doctors in the follow-up. In all cases with negative histology, the tumor recurrence rate within 24 months was 44.4% and 44.0 % in the imaging group re-assessed as "tumor persistence" compared to 23.5% and 21.3% in the "no tumor" imaging group. These results demonstrated to be more accurate than any of the other 3 imaging scales.

A greater risk is harbored by false negative imaging studies, because in most clinics no biopsies are performed, if these patients are asymptomatic. Patients with inconspicuous imaging scans (RECIST negative, n=73) were seen to have malignancy in the control endoscopy in 7 (9.59%) cases. Of all 14 patients with malignant histology in the control endoscopy, only 7 (50%) showed rather suspicious or highly suspicious imaging scans (category 4 and 5). If only these 7 patients had received re-staging with biopsy, 7 (50%) cases of tumor persistence would have been missed.

Control endoscopy

Histological confirmation is often crucial for the induction of salvage therapy. Currently, it is undertaken to confirm disease or when imaging does not deliver sufficient interpretation in most clinics. The 2019 AWMF S3-guidelines for laryngeal carcinoma recommend a control endoscopy only when there is suspicion for tumor recurrence, close tumor margins, or after partial laryngectomy.[25] There are no recommendations for routine post-therapeutic control endoscopies in asymptomatic patients with HNC of other locations. A study recommends a routine endoscopy within 2 years of treatment for optimum detection of second primaries in HNC patients.[26] This is obviously too late to screen for residual local disease. A study group by Zbären et al showed that post-therapeutic staging of laryngeal and hypopharyngeal carcinomas by medical imaging was underestimated and underclassified in most cases when compared to histology.[27]

It is of note, that early-stage (secondary) malignancies cannot be detected on imaging scans, but can be visualized and sampled during control endoscopies.[28] In our investigation 8% of patients presented with a secondary malignancy in the head and neck region. In the literature the incidence varies between 4.7-24% for metachronous tumors and 0.3-14% for synchronous secondary carcinomas.[29,30]

The optimal timing of re-staging is still subject of discussion. In our study the re-staging was performed 3.14 months after treatment and revealed 14 patients (14%) with residual disease. Thus, a timely identification is critical to allow a prompt salvage treatment. The time to treatment initiation independently affects survival. A study demonstrated that an interval of greater than 46-52 days introduced an increased risk of death.[31] Nevertheless, performing a re-staging too early is not reasonable either, as some tumor residuum may not be clonogenic and radiation-induced biologic effects may continue after treatment completion.[32] There is a "re-staging window of opportunity" for early salvage surgical procedures 4-8 weeks after radiotherapy. The window of opportunity begins when acute inflammatory response begins to wane and ends before long-term tissue damage is maximal (Figure 2).

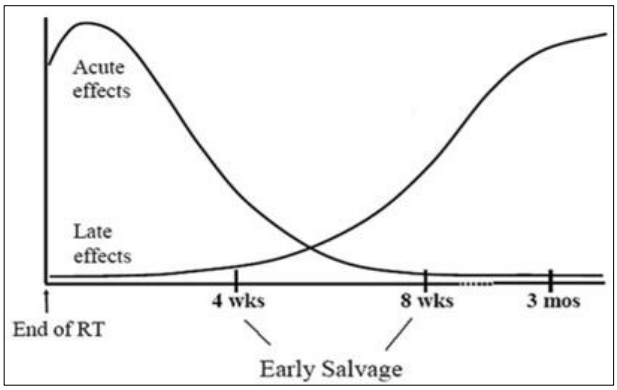

Figure 2: The re-staging window of opportunity, when acute inflammatory response begins to wane and before long-term soft tissue damage is maximal.

Biomarkers

There are currently no commercially available biomarkers, that are recommended for the routine surveillance or screening of HNC.[6] However, with HPV associated tumors, viral elements have demonstrated to be promising and in nasopharyngeal cancer EBV DNA monitoring may be considered.[33,34] Furthermore, there is ongoing research in the field of liquid biopsies by analysing exosomes, ctDNA and CTCs. Approaches to follow-up HNC may not replace medical imaging and biopsies, because it is still essential to know where the tumor is located, but it might lead to early detection and avoidance of unnecessary procedures.[35,36]

No follow-up

A close follow-up is generally strongly recommended, despite a lack of data. There is only weak evidence of improved outcome resulting from a salvage therapy of tumor recurrences detected at routine follow-up visits when compared with those detected at self-referral.[37] Other studies have not observed a survival benefit from detecting asymptomatic recurrences.[7,38] The importance of intensive surveillance is further undercut by the fact that most of the tumor recurrences (56-85%) are symptomatic and may lead to a self-referral.[16,39,40] It is important not to confuse routine follow-up with self-referral of symptomatic patients. The latter corresponds with a no-follow-up approach and can overestimate the effect of follow-up.[37]

Limitations

The primary limitation of this study was its retrospective design. Due to the nature of our inclusion and exclusion criteria, the study population cannot be compared to the HNC patient population in general. This study is limited by the exclusion of many early-stage laryngeal cancers where re-staging is often performed without cross-sectional imaging, as well as the exclusion of patients who had a PET-CT scan. However, when comparing the cohort of our study to similar studies, it was found to be a representative sample.

Most patients (96%) were diagnosed with HNSCC, but we also included one case of adenoid cystic carcinoma and 3 lymphoepithelial nasopharyngeal cancers as well as 2 cases of CUP-syndrome. Histology was used as a reference, although there is a possibility for false negative control endoscopies when biopsies are taken at the wrong site or too superficially. The surveillance over at least one year allowed us to estimate the number of false negative biopsies at around 3% (n=3), which was included to validate the results.

For this study, we did not distinguish whether imaging data derived from CT- or MRI-scans, because they show comparable accuracy regarding our key questions. The allocation of imaging reports to the imaging scales left little leeway but showed to be reproducible. The majority of re-stagings was performed after primary therapy, but few cases represented re-stagings after salvage therapy, since our main goal was to compare the results of imaging with biopsy

CONCLUSION

Medical imaging alone only serves as a moderate diagnostic tool to diagnose local persistence of HNC 3 months after therapy, since post-therapeutic tissue distortion reduces the accuracy of cross-sectional imaging.

The issue of radiologic misdiagnosing can be addressed by control endoscopy with biopsy, which was used as a reference in this study. We aimed to review and optimize the surveillance quality during the establishment of a certified Head and Neck Tumor Center in our clinic and evaluate current follow-up protocols. Our results indicate a potential benefit of performing a routine control endoscopy in addition to medical imaging for re-staging, since reliance on imaging alone leads to a high number of false-positive cases and may fail to notice some cases of tumor persistence. Namely in this cohort, control endoscopy helped to detect malignancy in 7 patients with inconspicuous (RECIST negative) imaging.

Furthermore, a new binary classification of medical imaging into “tumor” or “no tumor” was established by 2 experienced neuroradiologists and resulted in a higher accuracy than conventional imaging scales as well as a self-developed imaging scale. Applying this method additionally to the current protocols may help to predict the tumor recurrence rate in patients with negative histology in the re-staging.

Irrespective of the above, control endoscopy with biopsy remains a relevant diagnostic test especially in advanced cases of oro- and hypopharyngeal cancer since imaging has very limited reliability in these cases.

To conclude, we recommend a re-staging with cross-sectional medical imaging as well as a control endoscopy with biopsy 3 months after the completion of therapy in patients with HNC. This study showed that reliance on imaging alone will fail to identify all cases of tumor persistence. We did not experience any major complications in all 100 cases and concluded that routine endoscopy with biopsy is a safe procedure, that can improve the quality of re-staging both in our clinic and beyond. We will continue to do so and try to advance knowledge and understanding in this field. Furthermore, a binary classification of imaging showed a higher accuracy than conventional imaging scales and may help to predict tumor recurrence within 24 months after re-staging.

Recommendations

In the future the key question to address is whether available data sufficiently endorse intensive follow-up protocols or whether we can pursue less intensive approaches to reduce the economic and resource burden without harming our patients. This dilemma can be addressed by a possible personalization of surveillance based on disease subsite, biological characteristics, patient risk factors as well as routine use of molecular biomarkers. Advances in medical imaging accuracy as well as optical technology for office procedures, such as high-definition images and narrow band imaging, may also help to detect early lesions. We have great expectations about the currently ongoing SURVEILL’ORL (NCT03519048) trial aiming to randomly assign over 1000 participants between conventional and intensified surveillance strategies after curative therapy of HNC with a primary outcome measure of overall survival and cost-effectiveness.

Nevertheless, survivors are a heterogeneous group at increased risk of death from numerous socioeconomic, lifestyle, health, disease, and treatment factors and the complex character advocates frequent consultations to address the diverse issues these patients face.

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