Received: 3 May 2019 | Revised: 30 June 2020 | Accepted: 3 August 2020

DOI: 10.1002/hed.26433

WILEY

ORIGINAL ARTICLE

Panendoscopy during follow-up in laryngeal carcinoma patients after radiotherapy

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Section Editor: Steven Chinn

Abstract

Background: Early detection of a recurrent disease remains essential during follow-up to improve outcome and reduce morbidity. The purpose of this study was to evaluate the adequacy of panendoscopy after radiotherapy for recurrent laryngeal carcinoma.

Methods: In this retrospective analysis, 623 patients were included. Clinical and radiological examinations were compared to pathohistological results of panendoscopy and clinical outcome.

Results: In the first 6 months after therapy, a negative histopathological result was significantly higher in patients after radiotherapy (n = 394) compared to patients after surgery (n = 195) alone (odds ratio [OR] 0.4424, 95% confidence interval [CI] 0.2081-0.969, $P = .05$). After radiotherapy, a suspicious radiological result was not significantly linked to recurrence (OR 1.461, 95% CI 0.7126-3.021, $P = .37$). Clinical investigation was the best predictive parameter for detecting recurrent disease after radiation therapy (OR 4.061, 95% CI 2.268-7.113, $P = <.0001$).

Conclusions: Our results suggest that in the first 6 months after radiotherapy, emphasis should be placed on clinical evaluation during follow-up.

KEYWORDS

follow-up, head and neck carcinoma, laryngeal carcinoma, panendoscopy, radiotherapy

1 | INTRODUCTION

Head and neck cancer is the sixth most common carcinoma world-wide and is diagnosed in more than 550 000 patients per year.[1] Head and neck squamous cell carcinoma (HNSCC) accounts for 6% of new cancers worldwide and 5.2% of carcinoma related deaths.[2] Despite new approaches in basic and clinical research, the overall 5-year survival rate for HNSCC remains stable at approximately 55%.[3]

Diagnosis of HNSCC comprises evaluation of the medical history and clinical examination with flexible endoscopy as well as imaging modalities, for example, CT or MRI. If a suspicious lesion is found in the head and neck area, the patient undergoes panendoscopy under general anesthesia. Panendoscopy is regarded as a gold standard for confirming diagnosis, defining tumor extension, treatment planning, and excluding a secondary primary tumor.[4,5] Although different prospective studies and retrospective analyses dispute the relevance of panendoscopy in evaluation for a secondary primary tumor,[5,6] it is undoubtedly essential in evaluation for operability, alongside imaging studies, such as CT and MRI. [7,8] Follow-up of patients with HNSCC is crucial in effective carcinoma management and routine panendoscopy during follow-up has been suggested to improve early diagnosis of recurrent disease.[4,5] However, this is discussed very controversially in the current literature. In particular, strategies such as clinical history

taking, physical examination, and CT have been proposed to be sufficient for tumor follow-up.[9] Yet, patients who were treated with primary radio(chemo)therapy (RT or RCHT) or adjuvant radiotherapy show unspecific chronic inflammation after treatment, as well as post-therapeutic side effects, such as mucositis, dysphagia, and pain.[10] Therefore, it may be difficult to distinguish between these treatment-related signs and symptoms and a residual tumor or recurrence. Even the use of imaging modalities, for example, CT scan and PET/CT, may provide little more information or diagnostic assurance in RT patients, since it can be challenging to discern between chronic inflammation and a neoplasm.[11-13]

Recent studies have suggested that CT scans provide a high sensitivity and specificity for detection of recurrent disease after treatment of HNSCC tumors. These studies included patients irrespectively of the treatment strategy—that is, surgery, chemotherapy, and radiotherapy.[9] In our clinical experience, the effective use of imaging techniques during follow-up is limited to surgical patients. Due to chronic inflammation after radiotherapy, especially in the early phase, a reliable distinction between post-treatment effects and recurrent or residual tumors is rarely possible. Thus, over- as well as under-diagnosis may be common—however, no studies have investigated this issue.

This retrospective analysis of our institution's head and neck carcinoma patient database evaluated the incidence of recurrent or residual laryngeal carcinoma based on the results of (a) panendoscopy, (b) clinical history taking and physical examination, or (c) CT imaging who either were treated with RT or surgery.

2 | METHODS

2.1 | Study population

A single center, retrospective analysis of database records was conducted at the Department of Otolaryngology - Head and Neck Surgery, Medical University of Vienna, Austria. Data of patients with histologically proven laryngeal carcinoma between January 1998 and August 2017 were included in this study. The study protocol was approved by the ethics committee of the Medical University of Vienna (1892/2017).

2.2 | Clinical data

Sociodemographic characteristics of each patient were obtained from the electronic health records of the Vienna General hospital. The data included age, sex, tumor classification (TNM classification, tumor staging, histology, localization), treatment, secondary primary carcinoma, residual or recurrence disease, disease-specific survival, disease-free survival, date of last follow-up visit, and day of death. Tumor staging was performed based on the latest TNM classification. Furthermore, time between end of treatment and dates of follow-up visits, including the date of panendoscopy, results of the clinical or imaging follow-up, the reason for scheduling a panendoscopy, as well as clinical as well as histopathological results of the panendoscopy were retrieved. The first follow-up CT scan was performed 3 months after the end of radiotherapy to evaluate response after treatment. If there was a radiological or clinical suspicion for recurrence or residual disease, a panendoscopy in general anesthesia was scheduled. All patients underwent flexible laryngopharyngoscopy during routine tumor check-ups and any finding, tumor lesions of any kind, functional impairments, or symptoms as pain, dysphonia, or dysphagia represented an indication for panendoscopy. If CT could not clearly differentiate between recurrent disease of post-therapeutic tissue alterations such as inflammation, the CT scan was interpreted as suspicious and control panendoscopy was planned to definitely rule out recurrence. In the case of more than one panendoscopy, all procedures were included for analysis.

2.3 | Statistics

Descriptive statistics were used to evaluate the demographic data. Statistical analysis was performed using SPSS software (version 21.0; IBM SPSS Inc, Chicago, Illinois) and GraphPad Prism (Version 7.03, GraphPad Software Inc, San Diego, California). Clinical data collected during the follow-up (clinical investigation, CT result, and primary therapy) were modeled as predictors and were analyzed by Fisher's exact test. The effects of the resulting models are reported as odds ratios (OR) and the appropriate 95% confidence interval (CI) and *P*-values were calculated to identify statistical significance. A *P*-value of $<.05$ was considered statistically significant. Sensitivity, specificity, and predictive values were calculated for different cut-offs resulting from the model. The methods used to compute CI for OR are Baptista-Pike and for sensitivity, specificity, positive predictive value, and negative predictive value (NPV) Wilson-Brown analysis.

3 | RESULTS

3.1 | Clinical data

Seven hundred fifty-nine patients underwent panendoscopy because of a suspected laryngeal carcinoma. Squamous cell carcinoma was diagnosed in 82.08%

(n = 623), carcinoma in situ in 2.11% (n = 16), leukoplakia in 11.07% (n = 84), other malignant carcinoma in 3.69% (n = 28), and papilloma in 0.53% (n = 4). No histological result was available in 0.53% (n = 4) of patients. Six hundred twenty-three patients with laryngeal squamous cell carcinoma were treated at the General Hospital of Vienna between January 1998 and August 2017. At the time of diagnosis, mean age was 61 ± 9.72 years. There was a male predominance, representing 82.18% (n = 512) of the population (Table 1). The majority of patients had a negative lymph node classification (64.04%, n = 399) and no distant metastases (90.53%, n = 564) (Table 1).

Primary therapy was surgery in 315 patients (50.56%). The following types of surgery were performed as primary therapy: total laryngectomy in 72 (22.86%), hemilaryngectomy in 45 (14.29%) and microlaryngoscopy (MLS) with tumor resection or laser resection in 204 patients (62.86%). Radiotherapy with or without concomitant systemic treatment was the primary therapy in 288 patients (46.22%). All patients included in this study that were treated with radiotherapy received external beam photon irradiation. The systemic treatment concomitant to radiotherapy was cisplatin in 72 of 129 patients (55.81%), taxotere in 2 (1.55%), and cetuximab in 45 (34.88%) patients. No data concerning the systemic treatment agent were noted in 10 patients (7.75%). All in all, 195 patients were treated with surgery alone and 411 patients received either primary R(CH)T or adjuvant RT (Table 2). Primary therapy according tumor stage was as followed; patients with stage I tumors received MLS or laser resection in 114 cases and primary radiotherapy in 54 cases. Stage II tumors were treated with surgery in 66 cases, in detail total laryngectomy, hemilaryngectomy and MLS/laser resection in 6, 3, and 21 cases, respectively. Fifty-seven patients were treated with primary radiotherapy for stage II carcinomas. Stage III tumors received surgery in 45 cases and radiotherapy with concomitant systemic treatment in 51 cases. Surgery for stage III tumors consisted of total laryngectomy, hemilaryngectomy and MLS/laser resection in 18, 12, and 15 cases, respectively. Patients with stage IVa tumors underwent surgery in 78 cases: total laryngectomy, hemilaryngectomy and MLS/laser resection in 42, 6, and 27 cases, respectively, and radiotherapy with concomitant systemic treatment in 104 cases. Primary therapy in patients with stage IVb (n = 7) and stage IVc (n = 15) was solely radiotherapy with concomitant systemic treatment.

Residual tumor was clinically and radiologically suspected in 87 and 117 cases, respectively. In 174 cases, there was a clinical and radiological suspicion for residual or recurrent carcinoma. Three hundred fifteen patients (52.24%) underwent at least one panendoscopy, 141 (23.38%) at least two and 63 (10.44%) more than two panendoscopy at our department during follow-up (Table 2).

During follow-up with panendoscopy, residual tumor was detected in 39 patients, a recurrence was found in 173 patients and in addition 57 patients had a secondary primary carcinoma of the head and neck. Out of 315 patients who underwent primary surgery, 86 patients (27.3%) developed recurrent disease. Recurrence at the primary tumor site occurred in 73 patients (85.88%) out of 86 patients, nodal recurrence in 5 (5.81%) out of 86 patients and distant metastasis in 8 (9.30%) out of

TABLE 1 Patient clinical parameter (n = 623)

Clinical parameter	Number of patients (%)
Gender (n = 623)	
Male	512 (82.18)
Female	111 (17.82)
Age at diagnosis	
Mean	61.92
Median	62
Range	35-86
T classification	
T1	179 (28.73)
T2	166 (26.65)
T3	144 (23. 11)
T4	105 (16.85)
Tx	33 (4.65)
N classification	
N0	399 (64.04)
N1	30 (4.82)
N2	156 (25.04)
N3	3 (0.48)
Nx	35 (7.06)
M classification	
M0	564 (90.53)
M1	15 (2.41)
Mx	44 (7.06)
Tumor stage	
I	168 (26.79)
II	123 (19.62)
III	99 (15.79)
IVa	182 (29.03)
IVb	7 (1.12)
IVc	15 (2.39)
Missing data	33 (5.26)

TABLE 2 Therapy and panendoscopy

Characteristics	Number of patients (%)
Primary therapy	
Surgery	315 (50.56)
RT	165 (26.48)
RCHT	81 (13)
RIT	42 (6.74)
No data	20 (3.21)
Adjuvant therapy	
None	461 (74)
RT	105 (16.85)
RCHT	18 (2.89)
CHT	3 (0.48)
Surgery	9 (1.44)
No data	27 (4.33)
RT total	411 (65.97)
Control panendoscopy during follow-up	519

Abbreviations: CHT, chemotherapy; MLS, microlaryngoscopy; RCHT, radio-chemotherapy; RIT, radio-immunotherapy; RT, radiotherapy.

86 patients after primary surgery. After total laryngectomy, recurrence was detected in 12 (16.66%) out of 72 patients. In particular, 7 local, 3 nodal, and 2 distant metastases were detected during the clinical follow-up. All seven recurrences at the primary tumor site were found as well as mucosal as submucosal. In addition, all were found to be radiologically and clinically suspicious for recurrent disease. After hemilaryngectomy only local recurrent disease was found in 6 (13.33%) out of 45 patients. All patients with mucosal and submucosal lesions were radiologically and clinically suspicious for recurrent disease. Separate submucosal lesions were solely detected by computed tomography. Tumor recurrence occurred in 68 (33.33%) out of 204 patients after MLS with tumor resection with or without laser resection. In particular, 60 patients suffered from local, 2 from regional, and 6 from distant metastatic disease. Recurrences in the mucosa (n = 28) were found to be radiologically suspicious in 11 cases and clinically suspicious in 24 cases. Submucosal lesions (n = 3) were detected by both radiological imaging and clinical examination. Mucosal with coexistent submucosal tumors (n = 29) were identified by radiological imaging in 21 cases and by clinical examination in 24 cases.

After primary radiotherapy, 87 (30.21%) out of 288 patients developed recurrent disease. The pattern of recurrence in patients after primary radiotherapy was recurrent disease at the primary tumor site, nodal, and distant metastasis in 69 (79.31%), 13 (14.94%), and 5 patients (5.75%) out of 87 patients, respectively. Detailed results are listed in Table 3.

After primary surgery, recurrent disease occurred significantly more often as mucosal rather than submucosal recurrence compared to patients after primary radiotherapy ($P = .007$, OR 4.421, 95% CI 1.458-13.72, sensitivity 0.8235, specificity 0.4865).

Computed tomography identified recurrent disease in 142 patients, of which 134 (94.37%) were at the primary tumor site and 8 (5.63%) nodal recurrences. At the primary tumor site, recurrence was located at the mucosa, submucosal, and both mucosal and submucosal in 21, 21, and 72 patients, respectively. Twenty-six recurrences were not detected by CT. All of these undetected recurrences were mucosal carcinomas at the primary tumor site. After primary radiotherapy, 48 patients with recurrent disease were identified by CT. The recurrence was located mucosal, submucosal, and both mucosal and submucosal in 7, 13, and 24 patients, respectively. Submucosal recurrences are significantly more frequent detected by CT than solely mucosal recurrences ($P = .0004$, OR 24, 95% CI 2.99-266.4, sensitivity 0.9375, specificity 0.6154). Mucosal recurrences are more securely detected by clinical examination than submucosal lesions ($P = .007$, OR 16, 95% CI 1.842-189.3, sensitivity 0.96, specificity 0.4).

Several distinct clinical findings were observed in panendoscopy in patients with biopsy proven recurrent disease. An overt tumor was noted in 86 patients (51.43%), altered mucosal tissue, granulations, thickened tissue, or bleeding after manipulation was found in 24 patients (14.29%). Leukoplakia-like mucosa alterations, edema, erythema, ulcerations, and scar tissue were documented in 14 (8.57%), 14 (8.57%), 10 (5.71%), and 3 patients (2.8%), respectively. Panendoscopy was without pathological findings in 5 patients (2.86%) with recurrent disease.

Main symptoms of patients with biopsy proven recurrent disease at the time of panendoscopy were dysphonia, dyspnea, dysphagia or odynophagia and no symptoms in 46 (27.47%), 22 (13.19%), 22 (13.19%), and 11 (6.59%), respectively. No data concerning symptoms were available in 66 patients (39.56%). Main symptoms of patients at the time of panendoscopy with biopsy proven recurrent or residual disease and patients with a negative histopathological result are listed in Table 4. Patients with symptoms at the time of control panendoscopy had a significant higher risk for recurrence compared to patients without symptoms ($P < .0001$, OR 7.933, 95% CI 3.445-17.68, sensitivity 0.4304, specificity 0.913).

TABLE 3 Pattern of recurrence

Primary surgery			Primary radiotherapy	
Type of recurrences		Number of patients (%)	Type of recurrences	Number of patients (%)
Primary tumor site		73 (85.88)	Primary tumor site	69 (79.31)
Mucosal	Total	28	Mucosal	21
	Laryngectomy	0		
	Hemilaryngectomy	0		
	MLS	28		
Submucosal	Total	6	Submucosal	20
	Laryngectomy	0		
	Hemilaryngectomy	3		
	MLS	3		
Mucosal and submucosal	Total	39	Mucosal and submucosal	28
	Laryngectomy	7		
	Hemilaryngectomy	3		
	MLS	29		
Nodal		5 (5.81)	Nodal	13 (14.94)
Distant metastasis		8 (9.30)	Distant metastasis	5 (5.75)

Abbreviation: MLS, microlaryngoscopy with tumor resection or laser resection.

TABLE 4 Symptoms at the time of control panendoscopy

Main symptoms	Biopsy proven recurrent or residual disease (%)[a]	Negative histopathological result in panendoscopy (%)[a]	*P*-values
Dysphonia, hoarseness	46 (22.33)	96 (35.56)	.002
Dyspnea	25 (12.14)	18 (6.67)	.63
Dysphagia, odynophagia	34 (16.50)	3 (1.11)	≤.0001
Pain	12 (5.83)	9 (3.33)	.26
Bleeding	0 (0.00)	3 (1.11)	.25
No symptoms	17 (8.25)	63 (23.22)	≤.0001
No data	72 (34.95)	78 (28.89)	—

[a]Number of patients (%).

3.2 | Regression results

We found that patient characteristics like sex, age, tumor stage, and time since diagnosis had no significant influence on the detection of a recurrent or residual disease. Only clinical investigation and CT were statistically strong predictors for the detection of a recurrent laryngeal tumor.

In the analysis of all patients combined, regardless of whether treated by radiotherapy or surgery, multivariate analysis revealed that a suspicious CT finding increased the odds of detecting a recurrence nearly 7-fold (OR 6.714, 95% CI 4.022-11.33, $P \leq .0001$) and a suspicious clinical examination approximately 4-fold (OR 3.787, 95% CI 2.413-5.878, $P \leq .0001$).

Sensitivity and specificity of CT in patients treated with surgery ranged between 80% and 90%. In contrast, the specificity of CT in patients after radiotherapy dropped significantly to 21.3%, whereas specificity of clinical examination in patients after radiotherapy was twice as high (48.57%; Table 5).

In patients after radiotherapy, panendoscopy did not significantly impact detection of recurrent disease in patients with suspicious compared to unsuspicious CT results (OR 1.461, 95% CI 0.7126-3.021, $P = .37$). In clear contrast, clinical examination with finding of a suspicious tissue was a statistically significant predictor of recurrence. Here we observed a 4-fold increase of risk (OR 4.061, 95% CI 2.268-7.113, $P \leq .0001$) after clinical examination with flexible nasopharyngoscopy.

TABLE 5 Positive predictive values and negative predictive values for clinical parameters

Cutoffs	Sensitivity (%)	Specificity (%)	Negative predictive value (NPV) (%)	Positive predictive value (PPV) (%)
Clinical examination (all)	81.36	46.46	47.56	80.70
Clinical examination (surgery)	84.00	31.03	69.23	51.22
Clinical examination (RT)	81.13	48.57	80.95	48.86
Suspicious CT (all)	87.04	50.00	85.42	53.42
Suspicious CT (surgery)	80.95	83.33	78.95	85.00
Suspicious CT (RT)	84.38	21.30	60.53	48.80

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; RT, patients after radiotherapy.

In the cohort of patients that were treated with surgery alone, a suspicious CT scan indicated a 21-fold higher frequency of recurrence (OR 21.25, 95% CI 8.308-54.4, $P \leq .0001$) and a suspicious clinical finding appeared to be a significant predictor for recurrent disease (OR 2.366, 95% CI 8.308-54.41, $P \leq .03$).

In addition, if panendoscopy was performed within the first 6 months after end of therapy, patients after radiotherapy had a 2.26-fold higher incidence of a histopathological negative result (OR 0.4424, 95% CI 0.2081-0.969; reciprocal OR 2.26, 95% CI 1.032-4.805, $P = .05$). However, in the entire follow-up period, there was no difference concerning the likelihood of recurrence detected by panendoscopy in patients treated with irradiation compared to patients treated with surgery alone (OR 1.074, 95% CI 0.7228-1.614, $P = .76$; Figure 1).

4 | DISCUSSION

This retrospective data analysis demonstrated that in the first 6 months after the end of primary treatment for laryngeal carcinoma, patients who received RT had a 2.26-fold higher frequency for histopathological negative result after control panendoscopy compared to patients undergoing only surgery. Subsequently, almost 2/3 of all patients after RT underwent panendoscopy under general anesthesia due to radiological suspected tumor recurrence without having a recurrent or residual carcinoma.

In the entire cohort, both clinical investigation and suspicious CT findings had significance on the likelihood of detecting a recurrence by panendoscopy. However, after irradiation CT scans had no significant predictive value on finding a recurrent or residual carcinoma in control panendoscopy, whereas clinical examination remained a significant predictor. Patients who were treated with surgery solely, clinical, and radiological examination consistently had a high sensitivity and specificity in detection of a recurrence. Furthermore, all patients with recurrent disease after total laryngectomy presented with suspicious clinical findings. Recurrences after MLS or laser resection did not show reliable suspicious clinical findings in all patients compared to patients after laryngectomy. Nevertheless, clinical examination indicated recurrent disease more often than radiological imaging.

Despite advances in basic and clinical research, the overall survival rate for patients with HNSCC remains low.[3] Therefore, optimizing therapeutic strategies and individualized follow-up regimens is essential for patient management. Early detection of primary tumors and recurrence is very important to reduce comorbidity and increase quality of life in patients with HNSCC. Routine control panendoscopy during follow-up has already been widely abandoned in clinical routine.14 The introduction of easily available or highly sensitive imaging modalities such as CT scan and MRI reduced the indication for follow-up panendoscopy. Many studies proposed that routine panendoscopy during follow-up could be abandoned as long the clinical evaluation and imaging results remained without suspicious findings. Parker and Hill found that only 1.9% of panendoscopies detected tumors that were not identified by clinical examination or imaging modalities.[15] Münscher et al[9] did not perform routine panendoscopy during follow-up after introducing radiological control (CT/MRI) on a regular basis. In summary, their findings suggest that patient anamnesis and suspicious CT findings had a high sensitivity and specificity concerning detection of recurrence, a finding which is in line with our results.

In this retrospective study, we focused on patients after radiotherapy. Numerous studies demonstrate that for example PET-CT performed approximately 3 months after RT has a high NPV (>90%), but it performs poorly at differentiating between true recurrence and post-therapeutic inflammation, and thus suffers from a rather high rate of false-positive results.[11,13,16] Our results also suggest that during the first 6 months of follow-up after

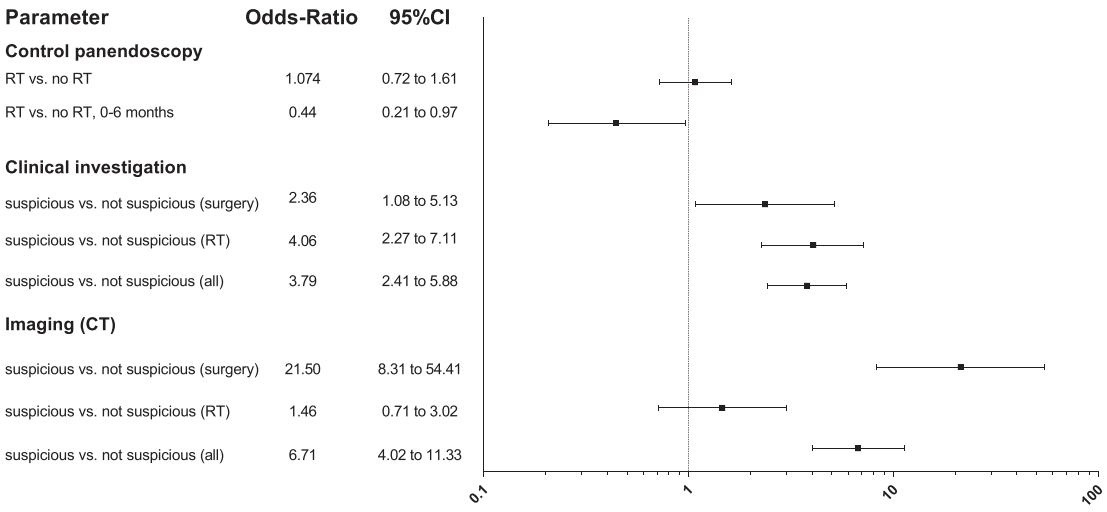

FIGURE 1 Odds ratios. all, patients after RT or surgery; CT, computed tomography; RT, patients after radiotherapy

irradiation, CT scan is less accurate than clinical examination to differentiate between inflammation and neoplasm. Specificity of CT during follow-up in patients after RT was very low (21.3%) compared to patients treated with surgery (83.33%). This high false-positive rate may explain the high percentage of patients after RT, who underwent panendoscopy without detection of a recurrent disease. If this proves to be accurate in prospective trials, it may be possible to avoid panendoscopy in the first 6 months after treatment if there is no clinical suspicion of recurrence. This follow-up strategy may be beneficial in this specific patient group and is associated with less stress, side effects of general anesthesia and postoperative complications. Although the incidence of postoperative complications after panendoscopy in the literature is very low,[5,16,17] rare complications have been reported,[18,19] and there are no high-quality data regarding complications of panendoscopy in RT patients.

Another issue to consider is the cost effectiveness, but unfortunately there are very few published studies addressing this issue. Davidson et al calculated that the omission of routine panendoscopy is certainly more cost-effective.[20]

Our findings suggest, in accordance with previous studies, a follow-up strategy without routine panendoscopy in patients with HNSCC of the larynx.[9] In patients who were treated with RT, especially shortly after treatment, it may be advisable to give priority to findings of clinical examination, due to the low specificity of CT scans in this population. Nonetheless, panendoscopy should be performed when there is reasonable clinical suspicion for a recurrence.

In conclusion, our data suggest that panendoscopy in the first 6 months after RT can possibly be neglected if there are no clinical signs of recurrence. However, these patients should be monitored at close intervals. Early detection of a recurrent disease remains essential during follow-up to improve outcome and reduce tumor and therapy associated morbidity. Furthermore, individualized treatment and follow-up strategies are key to further improve outcome and quality of life.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

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How to cite this article: Stanisz I, Janik S, Grasl MC, Erovic BM. Panendoscopy during follow-up in laryngeal carcinoma patients after radiotherapy. *Head & Neck*. 2020;42:3601–3608. https://doi.org/10.1002/hed.26433