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LARYNGOLOGY

Magnetic resonance imaging to assess cartilage invasion in recurrent laryngeal carcinoma after transoral laser microsurgery

Il ruolo della risonanza magnetica nell'identificazione dell'invasione cartilaginea nelle recidive di carcinoma laringeo dopo trattamento con microchirurgia laser transorale

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SUMMARY

Objective. To evaluate the diagnostic performance of magnetic resonance (MR) with surface coils in assessing cartilage invasion in recurrent laryngeal carcinoma after carbon dioxide transoral laser microsurgery (CO_2 TOLMS).

Methods. Two expert head and neck radiologists assessed cartilage invasion (infiltrated or non-infiltrated) in submucosal recurrences of laryngeal carcinoma after CO_2 TOLMS: results were compared with histopathological report after salvage laryngectomy.

Results. Thirty patients met the inclusion criteria and 90 cartilages were assessed. Overall sensitivity, specificity, and positive and negative predictive values for cartilage infiltration were 76, 93, 72 and 94%, respectively; for thyroid cartilage, the values were 82, 79, 69 and 88% respectively; for cricoid cartilage, all values were 100%; and for arytenoids, the values were 33, 96, 56 and 93% respectively.

Conclusions. MR with surface coils was able to detect most thyroid and cricoid infiltration in the complex setting of post-CO_2 TOLMS laryngeal carcinoma recurrence. In particular, the optimal performance in assessing cricoid invasion can be valuable in choosing the most appropriate treatment among total laryngectomy, open partial horizontal laryngectomies and non-surgical strategies.

KEY WORDS: transoral laser microsurgery, magnetic resonance, laryngeal cancer, recurrence, cartilage invasion

RIASSUNTO

Obiettivo. *Valutare la capacità diagnostica della risonanza magnetica nell'identificazione di invasione della cartilagine laringea nelle recidive sottomucose di carcinoma laringeo dopo chirurgia laser transorale.*

Metodi. *Due radiologi con anni di esperienza in radiologia testa collo hanno valutato l'infiltrazione cartilaginea (infiltrata o non infiltrata) nelle recidive sottomucose di carcinoma laringeo, i risultati sono stati poi confrontati con il referto istologico dopo laringectomia totale.*

Risultati. *Trenta pazienti rispettavano i criteri di inclusione, 90 cartilagini sono state valutate. La sensibilità, specificità, valore predittivo positivo e negativo sono stati globalmente 76, 93, 72 e 94%; per la cartilagine tiroide erano 82,79,69 e 88% rispettivamente; per la cartilagine cricoide tutti i valori erano 100%.*

Conclusioni. *La risonanza magnetica con bobine di superficie è in grado di identificare la maggior parte delle infiltrazioni cartilaginee della cartilagine tiroide e cricoide in un contesto complesso come quello delle recidive di carcinoma laringeo dopo chirurgia laser transorale. La capacità di predire l'invasione cricoidea potrebbe orientare nella scelta del trattamento adeguato tra laringectomia totale, laringectomia parziale orizzontale e strategie non chirurgiche.*

PAROLE CHIAVE: *microchirurgia laser transorale, risonanza magnetica, cancro laringeo, recidiva, invasione cartilagine laringea*

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Introduction

Carbon dioxide transoral laser microsurgery (CO_2 TOLMS) as defined by the European Laryngological Society (ELS) [1] is a well-established treatment option for early (T1-T2) and selected T3 glottic tumours [2-5]. When compared to open surgery, assessment of tumour margins during and after CO_2 TOLMS is hampered by thermal damage and shrinkage of the small specimens, potentially reaching 29% in its anteroposterior length [6]. For this reason, discrimination between R0 and R1 margins may be a complex task for the pathologist, with some arguing that single close/positive superficial margins can play a secondary role in defining subsequent oncologic outcomes [6,7]. Clearly, the influence of multiple positive superficial and deep margins may be greater, macroscopically reducing the rate of local control of disease. In these patients, because of both the inappropriate surgical margins and the biologically high risk of cancer recurrence, strict follow-up is mandatory for the early detection of tumour relapse [8].

Fibreoptic endoscopy represents the cornerstone of surveillance after CO_2 TOLMS, since it allows early and real-time assessment of new mucosal abnormalities in proximity to or further from the scar tissue, the presence of submucosal bulging and the possible alteration of vocal cord motility. Furthermore, examination with narrow band imaging (NBI) or other bioendoscopic devices provides additional diagnostic value, enabling highly accurate assessment of the neoangiogenetic patterns associated with persistent/recurrent disease [8-10]. At present, follow-up with endoscopy alone after CO_2 TOLMS is considered sufficient for T1 and low-risk T2 tumours. However, recurrences may occur at depth below the post-surgical scar, and may be barely visible during fibreoptic examination. In such scenarios, imaging with computed tomography (CT) or magnetic resonance imaging (MRI) has been shown to be effective in the detection of submucosal recurrences and should be performed periodically during the first few years after transoral surgery for high-risk T2 and T3 tumours, even in the absence of clinical suspicion [11].

According to the literature, MR performed with surface coils may be considered the gold standard for follow-up of these patients, due to its high spatial resolution and the possibility to implement diffusion-weighted imaging (DWI) sequences [12]. In fact, thanks to its optimal contrast resolution, MRI can easily differentiate post-surgical scar tissue (characterised by a low signal on T2-weighted sequences and the absence of restricted diffusion on DWI), oedema/granulation (characterised by a high T2-signal and increased water diffusivity on DWI), and recurrence (typically nodular in shape, and characterised by an intermediate T2-signal and restricted diffusion on DWI) (Fig. 1). Moreover, MRI is not only aimed at identifying submucosal recurrences, but it also provides crucial information about their spatial extent. This information is mandatory for planning the appropriate salvage treatment, both non-surgical (radiotherapy [RT] or chemoradiotherapy [CRT]) and surgical (repeat CO_2 TOLMS, open partial horizontal laryngectomy [OPHL], or total laryngectomy [TL]). In detail, cartilage invasion is one of the crucial aspects governing the choice of the most appropriate rescue treatment. In fact, the frequent presence of cartilage invasion (apart from partial infiltration of the arytenoids) excludes further transoral procedures; purely thyroid cartilage invasion without prelaryngeal muscle involvement is still manageable by OPHL Types II and III [13], while massive cricoid cartilage involvement inevitably leads to TL.

Several studies have already demonstrated the effective performance of MR in assessing cartilage invasion by primary laryngeal tumours [14,15]. In contrast, data regarding the accuracy of MR in evaluating local recurrences of cartilage invasion after CO_2 TOLMS are still lacking. In our opinion, this topic is of outmost importance for both the widespread adoption of transoral approaches, and the difficulty of correctly identifying possible submucosal patterns of recurrence in an already treated anatomic subsite. This is even more true when considering that the spread of deep recurrences may follow different vectors when compared to primary lesions due to the presence of fibrotic barriers, and because the cartilage signal may be altered by iatrogenic inflammation.

The aim of the present study was therefore to evaluate the diagnostic performance of MR with surface coils in assessing cartilage invasion in recurrent laryngeal carcinoma after CO_2 TOLMS.

Materials and methods

Patients

Data from patients who underwent open surgery (OPHLs or TL) for submucosal recurrence after CO_2 TOLMS between January 2008 and September 2021 were retrieved from our institutional electronic database of patient health records. As per internal standard protocol, patients treated with TOLMS underwent flexible videoendoscopy and high-definition NBI bimonthly and MR using surface coils every 6 months in the first 2 years after surgery. Inclusion criteria were: a) availability of an MR study with surface coils performed in our institute less than 1 month before salvage surgery, and b) availability of a definitive histopathological report describing the status of the laryngeal cartilage (invaded *vs* not invaded). Patients with previous radiotherapy on the neck were excluded.

MR technique

Imaging studies were carried out using a 1.5 Tesla scanner (Magnetom Aera, Siemens, Erlangen, Germany), using small loop surface coils applied to the patient's neck. The MRI protocol included turbo spin-echo (TSE) T2- and T1-weighted sequences with slice thickness of 3 mm or less with high matrix number; echo-planar DWI sequences; and volumetric sub-millimetric gradient-echo fat-suppressed T1-weighted sequences (VIBE) after intravenous gadolinium injection. Patients were instructed not to swallow and to breath gently during sequence acquisition; in uncooperative patients, standard sequences were replaced by sequences with radial k-space sampling (BLADE and star-VIBE). Further technical details are described in previous papers [12,16].

Image analysis

MRI studies were retrospectively reviewed by two head and neck radiologists (operators 1 and 2, with 10 and 20 years of experience, respectively), blinded to patient identity and histopathological reports in order to assess their inter-observer variability. Image quality was assessed with a 5-point Likert scale (1, non-diagnostic; 5, optimal). Radiologists were asked to assign one of two choices (invaded *vs* not invaded) for each cartilage (thyroid, arytenoid, cricoid) relying on multi-sequence evaluation: discontinuity of cortical lining in ossified cartilage and disruption of the normal intracartilaginous signal (in ossified and non-ossified cartilage) by a tumour-like signal (intermediate intensity in T2, low intensity in T1, enhancement after gadolinium and restricted water diffusivity in DWI) were considered to be signs of invasion; an inflammatory signal (a combination of T1 hypointensity, T2 hyperintensity and increased water diffusivity in DWI sequences) within cartilage was discretionally considered on a case-by-case basis as an indirect sign of infiltration or a non-neoplastic change combining this information with a number of other observations such as the presence of adjacent healthy scar tissue, the sharpness of the interface between tumour and cartilage, and the extent of the contact between tumour and cartilage (Fig. 1).

Statistical analysis

Inter- and intra-observer agreements were tested with the Cohen's k coefficient: 0.4-0.6, 0.6-0.8, and 0.8-1 k values were interpreted as fair, good and optimal concordance, respectively. Diagnostic performance was evaluated using 2x2 tables for each cartilage and overall.

Results

Patients

Thirty patients met the above-mentioned inclusion criteria. Ninety cartilages (30 thyroid, 30 cricoid, and 30 arytenoid) were evaluated. Thyroid and arytenoid cartilages were assessed on the tumour side only. At the final histopathological evaluation, overall, 18 (20%) cartilages were found to be infiltrated. Of these, the distribution of cartilaginous involvement was: 13/30 thyroid, 3/30 cricoid and 2/30 arytenoid cartilages.

Image quality evaluation

The mean image quality evaluated using the 5-point Likert scale was 3.5 (standard deviation, 0.97). None of the studies were scored 1. In three cases MRI was integrated with CT.

Inter-observer agreement

Cohen's k value demonstrated good concordance between the two radiologists in assessing all cartilages (k = 0.61, 95 CI 0.4-0.82), thyroid laminae (k = 0.7, 95 CI 0.43-0.97) and cricoid cartilages (k= 0.78, 95 CI 0.37-1), while poor agreement was found with regards to arytenoids (k = 0.3, 95 CI -0.1 to 0.7).

Diagnostic performance

Overall, the number of true positives were 13/90, true negatives were 68/90, false positives were 4/90 and false negatives were 5/90. Overall sensitivity (Se), specificity (Sp), positive (PPV), and negative predictive values (NPV) were 72% (95% CI 52-86%), 94% (95 CI 88-98%), 76% (95% CI 50-93%), and 93% (95% CI 85-98%), respectively. Se, Sp, PPV and NPV for thyroid cartilage infiltration were 82% (95% CI 48-98%), 79% (95% CI 54-94%), 69% (95% CI 47-85%) and 88% (95% CI 68-96%), respectively. Se, Sp, PPV, and NPV for cricoid cartilage infiltration were 100% (95% CI 29-100%), 100% (95% CI 87-100%), 100%, and 100%, respectively. Se, Sp, PPV, and NPV for arytenoid infiltration were 33% (95% CI 1-91%), 96% (95% CI 81-100%), 56% (95% CI 8-92%), and 93% (95% CI 73-98%), respectively. Figures 2-4 show a false negative, a false positive and a true positive case, respectively.

Discussion

Tumour recurrences after CO_2 TOLMS occur in a significant number of patients and may represent both a diagnostic and a treatment challenge [11,17,18]. The ensuing selection of salvage treatment is based on several patient- and tumuor-related factors, e.g. local and loco-regional extent of disease, vocal cord motility, history of previous (C)RT, patient comorbidities, status and compliance. Among the tumour variables that may greatly impact the therapeutic choice, cartilage infiltration is one of the most influential; however,

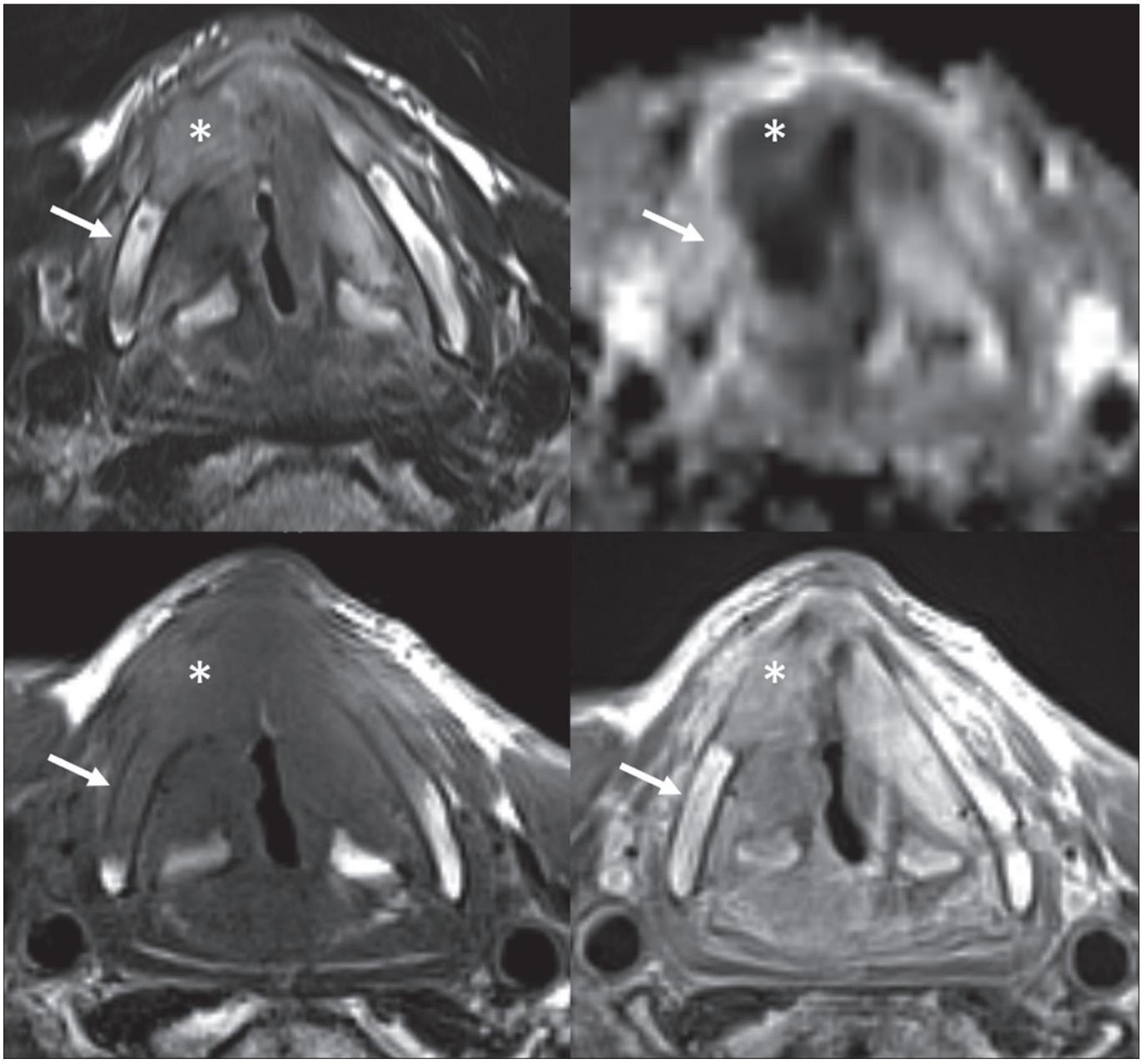

Figure 1. T2-weighted image (left top), apparent diffusion coefficient (ADC) map (right top), unhenhanced T1-weighted (left bottom), contrast-enhanced T1-weighted (right bottom). Images show a submucosal recurrence infiltrating thyroid laminae (asterisks). The signal pattern of cartilage-infiltrating tumour includes T2 intermediate signal, low ADC value, low T1 signal before contrast injection and contrast-enhancement. Arrows show a part of right thyroid lamina with a signal pattern consistent with chondritis: T2 hyperintensity, high ADC value, low T1 signal before contrast and intense contrast-enhancement.

as a result of the post-surgical anatomic and histopathological changes to the larynx, it is not always easily identifiable, even using state-of-the-art imaging techniques [19,20]. When occurring in deep visceral (paraglottic and preepiglottic) spaces, especially when already treated, tumour recurrences may rapidly invade critical anatomic structures, such as the cartilaginous laryngeal framework, before becoming clinically evident. Neoplastic thyroid cartilage infiltration automatically defines a recurrent lesion as a rcT3-4 cancer not amenable to CO_2 TOLMS due to its well-known suboptimal capability to control intra-cartilaginous margins under such circumstances [21]. In contrast, a rcT3-4 with thyroid cartilage infiltration can be favourably managed using OPHL [22] or TL based on tumour location, vocal fold motility and pa-

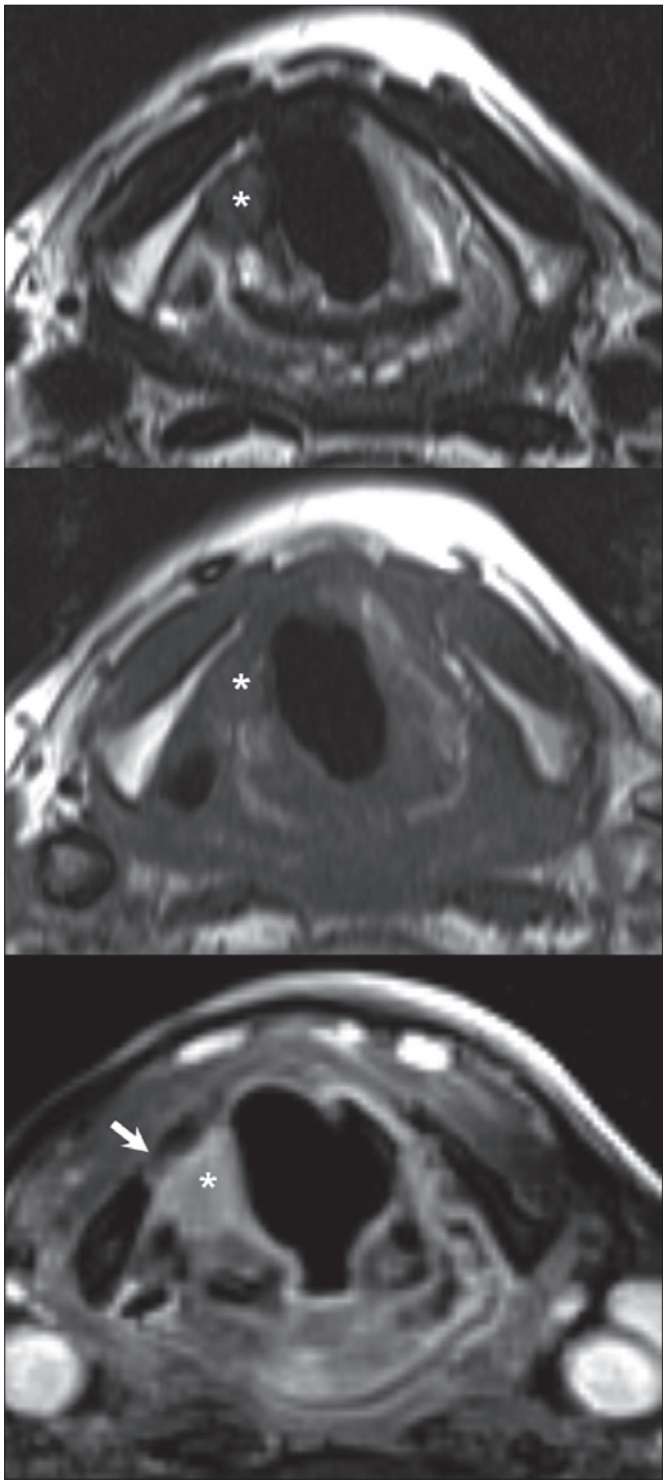

Figure 2. False negative. Images show a submucosal nodule (asterisk) in contact with the right thyroid lamina. Relying on top and middle images (T2-weighted and unenhanced T1-weighted, respectively), showing a sharp interface between tumour and cartilage, without abnormal signal of the medullary component, the cartilage was judged as non-invaded by both readers. Nevertheless, contrast-enhanced VIBE (bottom image) shows a focal faint enhancement within the cartilage (white thick arrow), which might be consistent with partial infiltration. Histology confirmed invasion.

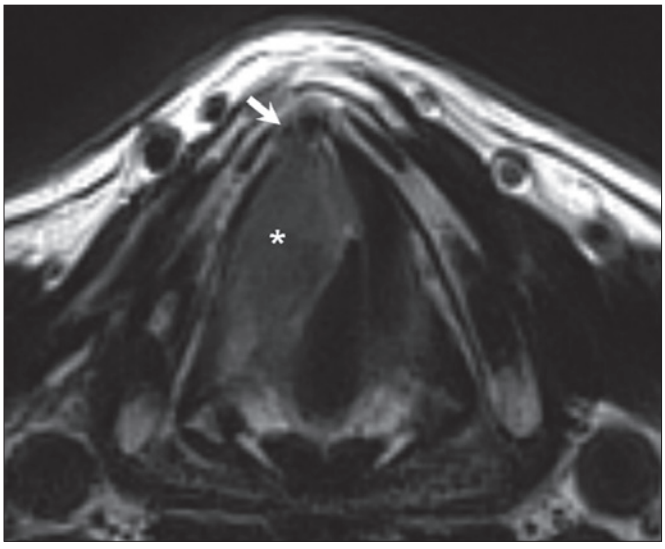

Figure 3. False positive. In this T2-weighted image, a submucosal recurrence is shown (asterisk), in contact with the anterior inner aspect of the thyroid lamina, whose cortex signal seems to be focally effaced (thick white arrow). The cartilage was considered invaded by both the readers, while histology excluded infiltration. MRI findings might be the result of a partial volume effect due to intrinsically insufficient spatial resolution.

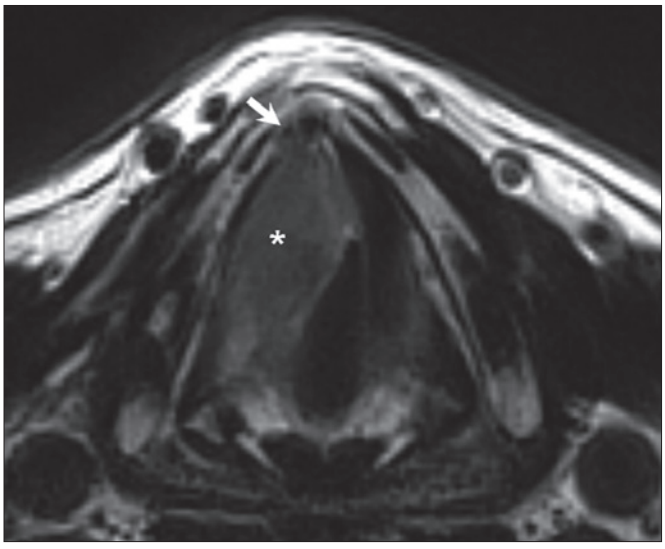

Figure 4. True positive. Images (from top to the bottom T2-weighted, unenhanced T1-weighted and contrast enhanced VIBE sequences) show an anterior commissural submucosal recurrence, which encroach the anterior extremity of both thyroid laminae. Cortical signal is effaced, and focal abnormal signal is seen within the whole thickness of the cartilage (thick white arrow). Both readers considered these findings as indicative of cartilage invasion, which was confirmed by histology.

tient-related factors. Massive laryngeal cartilage invasion is at present considered to be a poor prognostic factor for CRT response, while massive cricoid involvement represents a contraindication for OPHL, even when applying the most extended technique of OPHL Type III [22].

In a retrospective series of 15 patients treated by salvage TL for recurrences after CO_2 TOLMS, Horwich et al. [23] found a high prevalence of cartilage invasion (at the level of the thyroid and cricoid in 66% and 60% of patients, respectively), probably reflecting the three most frequent areas of failure of tumour control by transoral surgery, i.e. the anterior commissure (especially in the presence of transcommissural tumours), the subglottis, and the posterior paraglottic space [5,23]. In our series, the rate of invaded cartilages was much lower, presumably indicating that recurrences had been detected earlier, thanks to our proactive policy of systematic imaging follow-up in high-risk T2-T3 glottic cancers [11]. Supporting such a close radiological follow-up protocol, Marchi et al. showed that improved detection of submucosal recurrences by imaging techniques in patients with an *a priori* high risk of recurrence closed the gap in terms of oncological outcomes in low-risk patients and allowed salvage CO_2 TOLMS in half of the patients due to the prevention of cartilaginous tumour infiltration.

The low rate of cartilage invasion in our group of patients may be responsible for the low statistical power of this study. However, it should be underlined that all cricoid infiltrations were correctly identified by both radiologists. As rule of thumb, signal abnormalities in the cricoid lamina, even though consistent on their own with inflammation, must be considered as indirect signs of infiltration. On the other hand, chondritis in the thyroid laminae may be present even in the absence of infiltration and generally should not be considered as an indirect sign of partial infiltration [28]. In our study, such signal abnormalities in thyroid laminae have been evaluated case-by-case by each radiologist considering for example the extent of contact between the recurrent tumour and lamina. The specificity in assessing thyroid laminae infiltration was suboptimal (79%), given the presence of multiple false positive cases. In contrast, the reported sensitivity of 82% can be judged as a good result, especially considering that the presence of false negative cases might be due to microscopic infiltration, which is far from being detectable by the spatial resolution of MR sequences. Finally, a lower performance rate of MR in evaluating arytenoid infiltration was demonstrated. Even if must be considered that this result could be affected by the low rate of arytenoid infiltration (arytenoid invasion occurred in only two cases), it could be conceived that very low sensitivity might be related to the difficulty in identifying the elastic cartilage of the arytenoid vocal processes. However, this is by far the least impacting element on the choice of rescue treatment.

As far as we know, there are no papers in literature dealing with this clinical scenario not only for MRI, but also when considering other techniques, such as CT (which seems to have a worse performance compared to MRI in cartilage infiltration by primary tumours), ultrasound (which is affected by the acoustic barrage in ossified cartilages) and PET-CT (which does not have enough spatial resolution to depict focal erosions).

As mentioned above, the low number of cases, which influenced the statistical power of our results, represented the main limitation of this study. However, such a drawback appeared acceptable in order to maintain as homogeneous as possible the study cohort (the same surgical and radiological teams), thus limiting treatment and diagnostic biases to a minimum. Furthermore, the entity of cartilaginous infiltration was not graded, and therefore a minimal erosion was counted equally to full-thickness invasion.

Conclusions

MR with surface coils was able to detect most thyroid and cricoid infiltrations in the complex setting of post-CO_2 TOLMS recurrence. In particular, the optimal performance in assessing cricoid invasion could be valuable for choosing the most appropriate treatment among TL, OPHL and non-surgical strategies. Signal changes in thyroid laminae should be carefully considered on a case-by-case basis, given that even minimal infiltration represents a contraindication for salvage transoral procedures.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

MR: study design, image analysis and paper writing; DL: paper writing; RM: supervision and paper corrections; AP: paper writing, surgery and post-surgical follow-up; PR: paper editing, relationship with the ethic committee; SB: histopathological reporting; LA: histopathological reporting; MV: statistical analysis; FDB: surgery and post-surgical follow-up; DF: supervision and paper corrections; CP: supervision and paper corrections.

Ethical consideration

This study was approved by the Institutional Ethics Committee (CEB Comitato Etico Brescia) (approval numberNP-4267).

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

Written informed consent was obtained from each participant/patient for study participation and data publication.

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