

CT-scan prediction of thyroid cartilage invasion for early laryngeal squamous cell carcinoma

Dana M. Hartl · Guillaume Landry ·
François Bidault · Stéphane Hans · Morbize Julieron ·
Gérard Mamelle · François Janot · Daniel F. Brasnu

Received: 19 December 2011 / Accepted: 15 March 2012 / Published online: 30 March 2012
© Springer-Verlag 2012

Abstract Treatment choice for laryngeal cancer may be influenced by the diagnosis of thyroid cartilage invasion on preoperative computed tomography (CT). Our objective was to determine the predictive value of CT for thyroid cartilage invasion in early- to mid-stage laryngeal cancer. Retrospective study (1992–2008) of laryngeal squamous cell carcinoma treated with open partial laryngectomy and resection of at least part of the thyroid cartilage. Previous laser surgery, radiation therapy, chemotherapy and second primaries were excluded. CT prediction of thyroid cartilage invasion was determined by specialized radiologists. Tumor characteristics and pathologic thyroid cartilage invasion were compared to the radiologic assessment. 236 patients were treated by vertical (20 %), supracricoid (67 %) or supraglottic partial laryngectomy (13 %) for tumors staged cT1 (26 %), cT2 (55 %), and cT3 (19 %). The thyroid cartilage was invaded on pathology in 19 cases (8 %). CT's

sensitivity was 10.5 %, specificity 94 %, positive predictive value 13 %, and negative predictive value 92 %. CT correctly predicted thyroid cartilage invasion in only two cases for an overall accuracy of 87 %. Among the false-positive CT's, tumors involving the anterior commissure were significantly over-represented (61.5 % vs. 27 %, $p = .004$). Tumors with decreased vocal fold (VF) mobility were significantly over-represented in the group of false-negatives (41 vs. 13 %, $p = .0035$). Preoperative CT was not effective in predicting thyroid cartilage invasion in these early- to mid-stage lesions, overestimating cartilage invasion for AC lesions and underestimating invasion for lesions with decreased VF mobility.

Keywords Larynx · Cancer · Computed tomography · Thyroid cartilage

Introduction

Suspicion of thyroid cartilage invasion by laryngeal squamous cell carcinoma has a major impact on treatment choice. In open conservation laryngeal surgery and in total laryngectomy, resection of all or part of the thyroid cartilage is performed, whereas in transoral laser surgery, the thyroid cartilage is generally spared or removed in a more limited fashion. Major thyroid cartilage invasion with extralaryngeal spread is generally considered a contraindication for conservation laryngeal surgery, whereas minor cartilage invasion is not. Invasion through the thyroid cartilage, with infiltration of the outer cortex may be considered a relative contra-indication for radiation therapy or non-surgical organ preservation approaches, whereas minor inner cortex erosion may be amenable to radiation therapy. The choice between a surgical approach or radiation therapy

Abstract accepted for oral presentation at the American Laryngological Association spring meeting, April 27, 2011.

D. M. Hartl (✉) · M. Julieron · G. Mamelle · F. Janot
Department of Head and Neck Oncology,
Institut Gustave Roussy, 114 rue Edouard Vaillant,
94805 Villejuif Cedex, France
e-mail: dana.hartl@igr.fr

G. Landry · S. Hans · D. F. Brasnu
Voice, Biomaterials and Head and Neck Oncology Research
Laboratory, Department of Otolaryngology Head and Neck
Surgery, CNRS UMR 7018, European Hospital Georges
Pompidou, University Paris Descartes, AP-HP,
20 rue Leblanc, 75908 Paris Cedex 15, France

F. Bidault
Department of Radiology, Institut Gustave Roussy,
114 rue Edouard Vaillant, 94805 Villejuif Cedex, France

may be influenced by the extent of thyroid cartilage invasion seen on preoperative imaging.

The aim of this study was to determine the predictive value of computed tomography (CT) for inner cortex thyroid cartilage invasion (tumors staged pT3) [1] in early- to mid-stage laryngeal tumors treated with open partial laryngectomy, in order to determine the sensitivity and specificity of this imaging modality and the clinical factors involved in over- or underestimation of thyroid cartilage invasion. This is a follow-up study to our previously published report showing a low incidence of thyroid cartilage invasion by tumors treated with open partial laryngectomy [2].

Patients and methods

A retrospective bi-institutional study, in two tertiary care centers specialized in head and neck cancer (one university hospital and one cancer center), was conducted on files of patients from 1992 to 2008, all treated for laryngeal squamous cell carcinoma with open partial laryngectomy and resection of at least part of the thyroid cartilage. Patients having previously received laser surgery, radiation therapy or chemotherapy were excluded, as were laryngeal second primary tumors.

CT scan prediction of thyroid cartilage invasion was determined by specialized radiologists in each center (three different specialized radiologists in each center) but the initial radiology report was used for our study (no re-evaluation or collegial evaluation of the images was performed). Before 2005, contrast-enhanced spiral CT was performed with single row technology. After 2005, spiral CT employed 64 row technology. At the level of the larynx, 1-mm thick slices were made and viewed with soft-tissue and bone window settings. The pathological evaluation was performed by pathologists specialized in head and neck tumors. Each specimen was decalcified and analyzed after serial section of the entire specimen.

Tumor stage, anterior commissure involvement, vocal fold (VF) mobility and pathologic thyroid cartilage invasion were compared to the radiologic assessment.

Results

Two hundred and thirty-six patients (211 males, 25 females, average age 59 years, range 36–81 years) were treated by vertical partial laryngectomy ($n = 47$, 20 %), supracricoid ($n = 157$, 67 %) or supraglottic partial laryngectomy ($n = 32$, 13 %) for tumors staged cT1 ($n = 61$, 26 %) cT2 ($n = 131$, 55 %) and cT3 ($n = 44$, 19 %). Analysis of the operating specimens showed inner cortex thyroid cartilage

Table 1 Sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and overall accuracy (ACC) of CT scan evaluation for thyroid cartilage invasion according to the type of partial laryngectomy performed

| | <i>n</i> | Se (%) | Sp (%) | PPV (%) | NPV (%) | ACC (%) |
|-----------------------------------|----------|--------|--------|---------|---------|---------|
| Vertical partial laryngectomy | 47 | 0 | 93 | 0 | 95 | 89 |
| Supracricoid partial laryngectomy | 157 | 12 | 94 | 18 | 90 | 85 |
| Supraglottic laryngectomy | 32 | 0 | 97 | 0 | 97 | 94 |
| Overall | 236 | 10.5 | 94 | 13 | 92 | 87 |

invasion in 19 cases (8 %). There were no cases of outer cortex invasion (no patients classified as pT4a).

Table 1 shows the sensitivity, specificity, positive and negative predictive values and the accuracy of CT according to the different surgical techniques used to treat these tumors. CT scan prediction had a sensitivity of 10.5 %, a specificity of 94 %, a positive predictive value of 13 % and a negative predictive value of 92 %. The CT scan correctly predicted the presence of thyroid cartilage invasion in only two cases and the absence of thyroid cartilage invasion in 204 cases, for an overall accuracy of 87 %.

Among the false-positive CT scans (13 cases), tumors involving the anterior commissure were significantly over-represented (61.5 vs. 27 %, Fisher's exact test $p = .004$) (Fig. 1). Tumors with decreased vocal fold mobility were significantly over-represented in the group of 17 cases of false-negative CT scans (41 vs. 13 %, Fisher's exact test $p = .0035$) (Fig. 2).

Discussion

Radiologic criteria for CT diagnosis of cartilage invasion include sclerosis (increased density of the cartilage or high attenuation), lysis, erosion, and extralaryngeal tumor spread (cartilage discontinuity with tumor extending through both the inner and outer cortices) [3, 4]. Using these major criteria, reported sensitivities of CT for laryngeal tumors range from 46 to 94 %, with specificity ranging from 41 to 94 % [3–6]. The most specific radiologic sign of cartilage invasion is a thorough-and-through tumor extension with extralaryngeal spread, and the least specific sign is thyroid cartilage sclerosis [3].

In our series of tumors treated with conservation laryngeal surgery, we only observed invasion of the inner cortex on pathology. There were no tumors staged pT4a, and thus the criteria of outer cortex invasion or extralaryngeal spread could not be employed for this group of

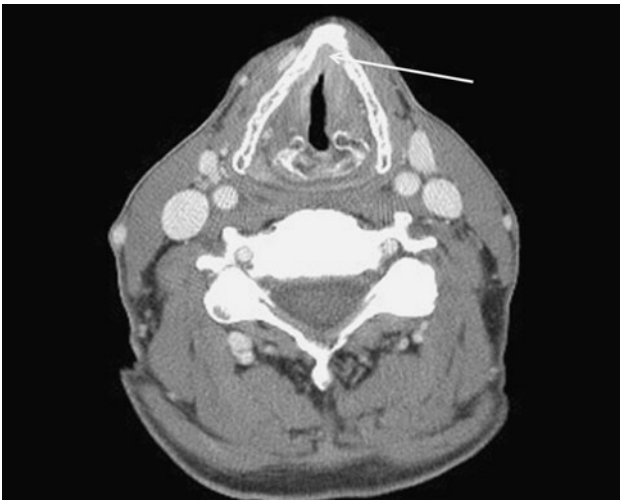


Fig. 1 Example of a false-positive CT reading for a tumor involving the anterior commissure (*white arrow*). The high attenuation of the cartilage at the level of the anterior commissure was diagnosed as sclerosis



Fig. 2 Example of a false-negative CT reading for a tumor with decreased vocal fold mobility (*gray arrow*). The high density of the cartilage at the level of the inferior border of the thyroid cartilage was diagnosed as physiological ossification

tumors. Our radiologists were only able to rely principally on sclerosis and less on lysis or erosion as signs of thyroid cartilage invasion. Several studies, like the present study, have shown that CT has a low-positive predictive value for prediction of microscopic invasion of the inner cortex of the thyroid cartilage represented by cartilage sclerosis [3–8].

Even for higher-stage tumors, the predictive value of CT scan thyroid cartilage sclerosis for predicting pathological thyroid cartilage invasion is reported to be as low as 15 % [7]. The consequences of erroneous CT diagnosis of thyroid cartilage invasion can be serious, with overtreatment (total laryngectomy) for false positives, and undertreatment, with a risk of lower local control, for false negatives

[5, 7, 9]. Organ preservation with chemoradiation may still be legitimate for patients with inner cortex invasion and cartilage sclerosis classified as T3 [7, 10]. Murakami et al. [11] found that tumors adjacent to the thyroid cartilage had a lower rate of local control with radiation therapy (42 %) than tumors separated from the thyroid cartilage (95 %), but this study did not evaluate the effect of vocal fold mobility on local control, which, as the authors noted, may be an independent prognostic factor. As regards surgical treatment, we and others have previously shown that inner cortex erosion is not a risk factor for lower local control in patients treated by open partial laryngectomy [2, 8].

Progressive physiologic ossification of the thyroid cartilage, which increases with age and may sometimes be asymmetric, means that sclerosis is difficult to distinguish from normal ossification and that spaces where the cartilage has not ossified may be mistaken for regions of lysis or erosion [12, 13]. Cartilage sclerosis may also be a local reaction to the presence of tumor with increased osteoblastic activity even before the tumor invades the cartilage [3]. The low-predictive value of CT for these mid-stage lesions is probably due to the microscopic nature of the involvement of the inner cortex of the thyroid cartilage; CT cannot be expected to be sensitive on a microscopic level [6]. As in our study, Kaskayasi et al. [14] found, in a CT-pathology correlation study of 22 cases, that microscopic invasion by tumors adjacent to the thyroid cartilage was missed by CT.

From a statistical standpoint, the positive predictive value of a test is related to the overall incidence of the disease in question. For CT, the positive predictive value reported in the literature is in part determined by the make-up of the cohort and the actual rate of pathological thyroid cartilage invasion observed. Sensitivity and specificity, however, are calculated independently of the incidence of the disease, and thus, for CT, are not affected by the incidence of thyroid cartilage invasion in the cohort studied. In the present study, we found thyroid cartilage invasion in only 8 % of the cases, which contributed to a low-positive predictive value, but the sensitivity in our study, not affected by the incidence of cartilage invasion, was also low.

The majority of the tumors in our study were treated with supracricoid partial laryngectomy. These were tumors that involved both the glottic and supraglottic levels of the larynx to varying degrees and at various subsites. It was not possible, therefore, to calculate the sensitivity and specificity of CT according to the exact tumor site. However, one may deduce from the data concerning tumors treated with supraglottic laryngectomy (Table 1) that the specificity and accuracy of CT for thyroid cartilage invasion in these tumors amenable to this type of surgery was slightly better than for glottic tumors (treated with a vertical partial laryngectomy) or for the more extensive glottic-supraglottic lesions treated with supracricoid laryngectomy.

We found that cartilage invasion was overestimated for AC tumors. AC tumors include a wide variety of macroscopic lesions, ranging from a superficial unilateral involvement of the AC from an adjacent VF tumor to an ulcerating lesion arising at the AC with impaired VF mobility. These tumors involve a small subsite of the larynx which is difficult to analyze radiologically, and the thyroid cartilage at the AC undergoes early ossification, which may be mistaken for cartilage sclerosis, leading to overestimation of cartilage invasion [13, 15, 16]. For AC tumors, Barbosa et al. [17] have described radiologic criteria for diagnosis of tumor at the anterior commissure, termed “gross radiologic anterior commissure involvement” or GRACI, that includes anterior commissure soft tissue thickening, and tumor spreading upward to the epiglottis, downward toward the cricoid cartilage or anteriorly to the thyroid cartilage. In our series, AC tumors were generally superficial lesions, with limited supraglottic and/or subglottic extension, making them amenable to conservation surgery, and without gross radiologic AC involvement, for which GRACI criteria would unfortunately not seem to be pertinent. However, Kirchner in his study of whole organ sections found that AC tumors with impaired VF mobility had a higher tendency to invade the thyroid cartilage than AC tumors with normal VF mobility [18].

We found that CT underestimated the rate of thyroid cartilage invasion when VF mobility was impaired. Again, this is probably related to the lack of predictive value of sclerosis as a radiologic diagnostic criteria for microscopic cartilage invasion. VF mobility is a subjective parameter, but all of the cases in this study were evaluated by experienced otolaryngologists and head and neck surgeons. Decreased VF mobility can be caused by tumor bulk, but also by paraglottic space invasion, which may lead to cartilage invasion. Cartilage involvement may be one cause of decreased local control for T2 laryngeal tumors treated with radiation therapy, as compared to T1 tumors [19, 20]. This may also explain a decreased rate of local control for some types of T2 tumors treated with transoral laser surgery [21, 22].

Our retrospective study has several shortcomings. We did not perform a centralized review of the images or a centralized review of the pathology slides. Our aim was to use “real life” data, as in the study by Daisne et al. [6], as compared to a clinical research situation the results of which are often difficult to duplicate in real life. We did have an advantage, however, that in both centers, each CT was reviewed by the specialized radiologist at the time of the tumor board, when the treatment options were discussed. Our study spanned 16 years of changes in CT technology and image quality, which may have had an effect on our results, as well.

The long span of the study may also have introduced heterogeneity in the pathological analyses, and small foci

of cartilage invasion may have been missed, consequently underestimating the incidence of thyroid cartilage invasion.

How can we do better? Magnetic resonance imaging (MRI) has a higher reported positive predictive value than CT scan, with rates from 93 to 96 % [6, 22, 24, 25]. Thus, when the hyaline cartilage and/or the fatty marrow layer in the thyroid cartilage enhances on T1-weighted sequences with gadolinium, cartilage invasion is very likely. However, the specificity of MRI may be as low as 55 %, due to non-specific changes in signal intensity on MRI, which may be related to a localized inflammatory reaction adjacent to the tumor leading to many false-positive diagnoses [3, 4, 6]. MRI also carries the problem of motion artifacts due to breathing and patient compliance due to the duration of the sequence acquisitions. Becker et al. [3] have stated that “the diagnosis of neoplastic invasion of the thyroid cartilage should, therefore, be made with caution on MR imaging”. Katsounakis et al. [26] found a good correlation between CT and MRI for staging, however, in lower stage tumors T1, T2. New technologies with stronger field magnets, higher signal to noise ratios and shorter acquisition times may improve the specificity of MRI in the future [6], but until then MRI may be considered as too sensitive and not specific enough for the diagnosis of thyroid cartilage invasion, especially for early or mid stage lesions exhibiting only inner cortex invasion. Studies of early to mid stage tumors combining CT and MRI data are warranted.

In the study by Daisne et al. [6], 18-FDG-PET was shown to have a high specificity for gross tumor volume evaluation as judged by the pathological tumor specimen after total laryngectomy. In this study, CT and MRI tended to overestimate the size and extension of the laryngeal lesions as compared to PET or pathology. However, none of the three imaging modalities were able to show superficial mucosal extensions that were found on pathology. 18-FDG-PET is currently limited by the large size of the voxels, reducing its spatial resolution. Kurooka et al. [13] have recently shown that an intense heterogenous accumulation of the radioactive tracer (Tc-99c-hydroxymethylene diphosphonate) in the thyroid cartilage on bone scintigraphy was highly predictive of thyroid cartilage invasion. Nishiyama et al. [27] used a simultaneous dual isotopic SPECT technique to evaluate cartilage status in 19 patients, with a sensitivity of 80 % and a specificity of 93 %. Radionuclide imaging may prove to be a means of improving preoperative staging of laryngeal cancer in the future, but sufficient data is currently lacking.

Conclusions

Microscopic inner cortex thyroid cartilage invasion with radiologic sclerosis is difficult to accurately diagnose. CT scan was not effective in predicting thyroid cartilage

invasion in these early- to mid-stage lesions treated with conservation surgery, overestimating cartilage invasion for AC lesions and underestimating invasion for lesions with decreased VF mobility. These tumor characteristics should be taken into account for treatment planning, for endoscopic laser resection, open surgery with thyroid cartilage resection or for non-surgical therapy.

Conflict of interest None.

References

- Sobin LH, Gospodarowicz M, Wittekind C (eds) (2010) UICC International Union Against Cancer. TNM classification of malignant tumors, 7th edn. Wiley-Blackwell, West Sussex
- Hartl DM, Landry G, Hans S, Marandas P, Brasnu D (2010) Organ preservation surgery for laryngeal squamous cell carcinoma: low incidence of thyroid cartilage invasion. *Laryngoscope* 120:1173–1176
- Becker M (2000) Neoplastic invasion of laryngeal cartilage: radiologic diagnosis and therapeutic indications. *Eur J Radiol* 33:216–229
- Becker M, Zbären P, Delavelle J et al (1997) Neoplastic invasion of the laryngeal cartilage: reassessment of criteria for diagnosis at CT. *Radiology* 203:521–532
- Li B, Bobinski M, Grandour-Edward R, Farwell DG, Chen AM (2011) Overstaging of cartilage invasion by multidetector CT scan for laryngeal cancer and its potential effect on the use of organ preservation with chemoradiation. *Br J Radiol* 84:64–69
- Daisne JF, Duprez T, Weynand B et al (2004) Tumor volume in pharyngolaryngeal squamous cell carcinoma: comparison at CT, MR imaging and FDG PET and validation with surgical specimens. *Radiology* 233:93–100
- Beitler JJ, Muller S, Grist WJ et al (2010) Prognostic accuracy of computed tomography findings for patients with laryngeal cancer undergoing laryngectomy. *J Clin Oncol* 28:2318–2322
- Thoeny HC, Delaere PR, Hermans R (2005) Correlation of local outcome after partial laryngectomy with cartilage abnormalities on CT. *Am J Neuroradiol* 26:674–678
- Castelijns JA, Becker M, Hermans R (1996) Impact of cartilage invasion on treatment and prognosis of laryngeal cancer. *Eur Radiol* 6:156–169
- Tart RP, Mukherji SK, Lee WR, Mancuso AA (1994) Value of laryngeal cartilage sclerosis as a predictor of outcome in patients with stage T3 glottic cancer treated with radiation therapy. *Radiology* 192:567–570
- Murakami R, Furusawa M, Baba Y et al (2000) Dynamic helical CT of T1 and T2 glottic carcinomas: predictive value for local control with radiotherapy. *Am J Neuroradiol* 21:1320–1326
- Blitz AM, Aygun N (2008) Radiologic evaluation of larynx cancer. *Otolaryngol Clin N Am* 41:697–713
- Kurooka H, Kawabe J, Tsumoto C et al (2009) Examination of pattern of RI accumulation in thyroid cartilage on bone scintigraphy. *Ann Nucl Med* 23:43–48
- Kazkayasi M, Onder T, Ozkaptan Y, Can C, Pabuscu Y (1995) Comparison of preoperative computed tomographic findings with postoperative histopathological findings in laryngeal cancers. *Eur Arch Otorhinolaryngol* 252:325–331
- Bradley PJ, Rinaldo A, Suarez C et al (2006) Primary treatment of the anterior vocal commissure squamous carcinoma. *Eur Arch Otorhinolaryngol* 263:879–888
- Fernandes R, Gopalan P, Spyridakou C, Joseph G, Kumar M (2006) Predictive indicators for thyroid cartilage involvement in carcinoma of the larynx seen on spiral computed tomography scans. *J Laryngol Otol* 120:857–860
- Barbosa MM, Araujo JF Jr, Boasquevisque E et al (2005) Anterior vocal commissure invasion in laryngeal carcinoma diagnosis. *Laryngoscope* 115:724–730
- Kirchner JA (1998) Atlas on the surgical anatomy of laryngeal cancer. Singular Publishing Group Inc., San Diego, pp 36–60
- Frata P, Cellai E, Magrini SM et al (2005) Radical radiotherapy for early glottic cancer: results in a series of 1087 patients from two Italian radiation oncology centers. II. The case of T2N0 disease. *Int J Radiat Oncol Biol Phys* 63:1387–1394
- Fein DA, Mendenhall WM, Parsons JT et al (1993) T1–T2 squamous cell carcinoma of the glottic larynx treated with radiotherapy: a multivariate analysis of variables potentially influencing local control. *Int J Radiat Oncol Biol Phys* 25:605–611
- Peretti G, Piassa C, Mensi MC, Magnoni L, Bolzoni A (2005) Endoscopic treatment of cT2 glottic carcinoma: prognostic impact of different pT subcategories. *Ann Otol Rhinol Laryngol* 114:579–586
- Peretti G, Piazza C, Bolzoni A et al (2004) Analysis of recurrences in 322 Tis, T1 or T2 glottic carcinomas treated by carbon dioxide laser. *Ann Otol Rhinol Laryngol* 113:853–858
- Connor S (2007) Laryngeal cancer: how does the radiologist help? *Cancer Imaging* 7:93–103
- Youssef DM, Gad K, Tufano RP (2006) Resectability issues with head and neck cancer. *Am J Neuroradiol* 27:2024–2036
- Duflou S, Chrestian M, Guelfucci B, Chapsaur P, Moulin G, Zanaret M (2002) Comparaison dans les cancers du larynx entre l'imagerie par résonance magnétique et les coupes histologiques après laryngectomie. *Ann Otolaryngol Chir Cervicofac* 119:131–137
- Katsounakis J, Remy H, Vuong T, Gélinas M, Tabah R (1995) Impact of magnetic resonance imaging and computed tomography on the staging of laryngeal cancer. *Eur Arch Otorhinolaryngol* 252:206–208
- Nishiyama Y, Yamamoto Y, Yokoe K et al (2004) Superimposed dual-isotope SPECT using ^{99m}Tc-hydroxymethylene diphosphonate and ²⁰¹Tl-chloride to assess cartilage invasion in laryngopharyngeal cancer. *Ann Nucl Med* 18:527–532