Editorial

Morphological assessment of thymic carcinoma through imaging: is computed tomography useful in selecting patients for surgery and in predicting incomplete resection?

Adriano Massimiliano Priola, Sandro Massimo Priola

Department of Diagnostic Imaging, San Luigi Gonzaga University Hospital, Orbassano, Torino 10043, Italy

Correspondence to: Adriano Massimiliano Priola. Department of Diagnostic Imaging, San Luigi Gonzaga University Hospital, Regione Gonzole 10, Orbassano, Torino 10043, Italy. Email: adriano.priola@inwind.it.

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Thymic epithelial tumours are the most common primary neoplasm of the anterior mediastinum, accounting for up to one half of all mediastinal masses. Most of them are thymomas, whereas thymic carcinomas (TCs) are rare and represent less than 20% of all thymic epithelial tumours (1-3). Mean age at diagnosis of TC is 50–60 years and paraneoplastic syndromes, such as myasthenia gravis, are reported in less than 5% of patients with TC (1,4). Unlike thymoma, TC has no histological resemblance to the thymus and is characterized by a high cell density, a high degree of histologic anaplasia, obvious cell atypia, and increased proliferative activity (5). The most frequent histological type of TC is thymic squamous cell carcinoma, followed by a lymphoepithelioma-like carcinoma, sarcomatoid carcinoma, and thymic adenocarcinoma (6). TC has usually an aggressive behaviour and a worse prognosis compared to advanced thymoma (stage III and IV according to Masaoka-Koga staging system), and typically presents with a local invasion and/or metastatic spread in 50–65% of the cases at diagnosis (7-9). In detail, at presentation, only 20% of patients with TC have early disease after surgical resection (Masaoka stage I, 10% of cases; stage II, 10% of patients), 45% of patients have a macroscopic invasion of neighbouring structures, 15% of patients have pericardial and/or pleural implants, and 20% of patients have distant lymphogenous or hematogenous metastases (3). Although there are no internationally accepted guidelines about the optimal treatment strategies for TC, and therapy is not yet standardized, complete surgical tumour resection, which is known as the most consistent and significant prognostic factor for a disease-free survival and overall survival rate, as well as of the surrounding fat of the anterior mediastinum, is the mainstay of treatment in primarily resectable TC (2,3,10). Conversely, in patients with supposed advanced TC (stage III or IVa) on the basis of preoperative imaging studies, the treatment strategies are selected on the basis of the tumour histotype, involved structures in local invasion and extent of pleural dissemination (2). However, multimodal treatment regimens, which include systemic medical therapy (induction chemotherapy and adjuvant chemotherapy), surgical therapy, and postoperative radiotherapy, are generally used in primarily unresectable or locally advanced TC as part of a curative-intent sequential strategy (2,3,10). The use of the induction of treatments for the downstaging of the tumour mainly depends on the suspected tumour invasion at radiological imaging in neighbouring structures such as great vessels, pericardium and thoracic wall. By using induction chemotherapy, partial remission is achieved in 40–70% of the primarily unresectable thymic epithelial tumours with a rate of complete resection (R0) of up to 77% of cases and a rate of microscopic residual disease (R1 resection) of 14% of cases (11). Nevertheless, the role and timing of neoadjuvant treatments is still debated and no standardized therapy

protocols have been developed yet. However, in order to achieve long-term survival rates, a radical surgical resection of the TC with no microscopic residual disease should be achieved whenever possible for stage III and stage IVa of the disease (2,3,12,13).

Hence, radiological imaging plays a key role in the treatment planning. Indeed, the decision-making for induction therapy or for surgical resection as first-line therapy mainly depends on the ability of the morphological imaging [computed tomography (CT), magnetic resonance (MR)] in detecting a local invasion into the perithymic fat tissue or neighbouring organs and for demonstrating pleural or pericardial implants (2,3,14). About thymic epithelial tumours, despite the positive impact of a thoracic MR in the clinical decision process-making by thoracic surgeons, and despite the evidence of its usefulness in preoperative tumour staging supported by the current radiology literature, thoracic MR remains underutilized in clinical practice (15-20). Currently, contrast-enhanced CT is still considered the cross-sectional imaging technique of choice in staging of thymic epithelial tumours, including TC, for detecting a local invasion, pleural seeding and metastatic disease (2-4,21). In this setting, results reported by Hayes and colleagues in their recently published article add valuable information to optimize the clinical decision-making process in patients with TC at their diagnosis (22). Indeed, on a relatively large number of patients with TC who had a resection of their tumour in this retrospective study, the authors address an important question in the management of TC, namely the usefulness and capability of the CT scan in predicting an incomplete tumour resection, either with microscopic (R1) or macroscopic residual disease (R2) after surgical resection, by analysing a set of preoperative morphological characteristics of the tumour which have been also correlated with Masaoka-Koga staging system of thymic epithelial tumours.

In their study, the authors reviewed 41 patients with a histologically confirmed TC across a period of 21 years, who underwent a surgical removal of the tumour. Most of tumours were classified as Masaoka-Koga stage IV (22/41, 54% of patients; 12 stage IVa, 10 stage IVb), followed by stage III (12/41, 29%), stage IIb (4/41, 10%), and stage I (3/41, 7%). Thirty-one patients (76%) received neoadjuvant platinum-based chemotherapy but none had neoadjuvant radiation therapy. Adjuvant treatments were administered in 71% of patients (29/41) and consisted mostly of exclusive radiation therapy (19/29), in order to reduce the risk of recurrence over time, followed by a combined treatment and chemotherapy alone. Overall, one half of the patients (21/41, 51%) had a complete surgical resection with no residual disease (R0), whereas the remaining 20 patients had an incomplete resection with a microscopic (10/41, R1) or macroscopic (10/41, R2) residual disease. Of note, 3 out of 10 patients who did not receive neoadjuvant chemotherapy had an incomplete R1 resection. Among a lot of morphological CT aspects investigated by using CT, the authors found that the degree of tumour contact with adjacent vessels and the larger maximum tumour size were significantly associated with an incomplete R1 or R2 resection (P value of 0.038 and 0.014, respectively). On a pre-operative CT, the cut-off value for discriminating a R1/R2 resection versus R0 resection was a tumour contacting with an adjacent mediastinal structure higher than 25% and maximum tumour size larger than 7.5 cm. The area under the receiver operating characteristic curve was close to 0.800 by using tumour size as unique discrimination criterion and was not significantly improved by adding the degree of tumour contact (P value of 0.205). Other CT features analysed by authors were more frequent, in incomplete R1/R2 resection, albeit no significant differences with R0 resection status were found. This finding was probably due to the small cohort enrolled in the study, as supposed by the authors. Lastly, tumour size, infiltration of mediastinal fat, and the loss of fat plane between tumour and great vessels were significant predictive pre-operative CT parameters of Masaoka-Koga stage in discriminating early (stage I, II) from advanced (stage III, IV) disease.

Strengths of the present study include its relatively large sample size, considering the rarity of the disease, and the identification of some tumour characteristics on pre-operative CT scan which are significant predictors of an incomplete resection. Indeed, most of previously published studies on CT and/or MR, focused generally on the thymic epithelial tumours (both thymomas and TCs) or included solely thymomas which were grouped in early disease (Masaoka-Koga stage I and II) and advanced disease (stage III and IV) (4,14,17-20). The correct prediction of early or advanced disease before surgery at diagnostic imaging is essential to plan appropriately treatment strategies, because the latter receives neo-adjuvant chemotherapy and, thus, there is an increasing interest in the identification of tumour characteristics on preoperative imaging which allow this discrimination (2-4,7,10). CT findings most frequently reported to be associated with local invasiveness of thymic epithelial tumours in previous studies were tumour size

(largest diameter on axial planes >5 cm, depending on studies), lobulated or irregular contours, calcifications, infiltration of surrounding fat, lung infiltration, great vessel invasion or encirclement (3,23,24). Anyhow, Hayes and colleagues first reported CT characteristics of TCs alone which could be helpful to predict risk of resection in order to optimize the treatment strategies before surgery.

However, authors are aware of the limits of their results which mainly lie in the small study cohort that have precluded to obtain statistical data based on the multivariate analysis with construction of an appropriate logistic regression model. Hence, they underline the need for a larger prospective or retrospective multi-centre study or studies. In addition, a potential major limitation of this study, which derived from its retrospective design, is the use of different CT scanners without standardization in CT protocols. As an example, the use of different slice thicknesses (from 3 to 7.5 mm, with 83% of examinations set at 5 mm), avoiding the use of thin sections less than 3 mm, could have affected the evaluation of morphological characteristics (such as infiltration of surrounding fat and neighbouring organs or vessels and evaluation of fat planes around the tumour margins) because of a different amount of partial volume effects between the tumour and mediastinal fat or adjacent structures which strongly depends on slice thickness. Indeed, partial volume effects are more obvious with the use of a higher slice thickness and could be mistaken for tumour infiltration with an erroneous assessment of CT features at tumour boundaries (4). In this background, the imperfect reliability of preoperative CT in predicting Masaoka-Koga staging system of thymomas is demonstrated in a recent retrospective analysis on a large cohort which reported 51% of the tumours in stage III were misclassified as stage I–II at CT and 37% of early tumours (stage I–II) were misclassified as advanced tumours (stage III) at CT (9).

In addition, although CT is considered the reference standard in the preoperative assessment of thymic epithelial tumours, MR is an alternative and effective morphological modality which can provide more specific characterization when compared to CT (4,15). As an example, MR is superior to CT in the evaluation of fat planes between tumour and neighbouring organs and structures because of its better contrast resolution (4,7,15,23,25). Nevertheless, MR of the thorax is not routinely employed in the evaluation of thymic epithelial tumours, it is rarely ordered as preoperative imaging technique by thoracic surgeons (who are often unaware of its value), and it is usually reserved for a further evaluation of equivocal CT findings of local invasion as a second-line technique (14-16). CT generally remains, in most centres, the imaging modality of choice although it has significant limitations that include differentiation of lymphoid or rebound thymic hyperplasia from tumours, discrimination between the early and the advanced disease of thymic epithelial tumours, detection of local invasion, and detection of tiny pleural implants in stage IVa tumours (4,14,23). In addition, the use of conventional morphological T1-weighted and T2-weighted MR images is more reliable, when compared to the CT in detecting haemorrhage, cystic areas, or necrotic changes, by demonstrating heterogeneous signal intensity, which are more frequent in TCs compared to thymomas (4,23).

Furthermore, at present, radiology is increasingly confronted with the demand of obtaining a more functional or dynamic imaging source, for information beyond a morphological assessment, especially in oncology, with the aim to improve diagnostic performance and patient outcome (2-4,7). For instance, neither contrast-enhanced CT nor standard MR is able to detect early mediastinal or pleural/pericardial local invasion. In this case, dynamic MR with cine sequences is more reliable to detect a tumour invasion by detecting the sliding motions between the tumour and cardiovascular structures (2). Regarding quantitative MR imaging, as an example, significant data sets are available about the ability of diffusion-weighted quantitative MR in predicting histological type of thymic epithelial tumours according to WHO classification, in predicting early from advanced thymic epithelial tumours based on Masaoka-Koga surgical staging system, and in predicting disease free survival by measuring the apparent diffusion coefficient that reflects the movement of water molecules within the tumour (7,14,17-20,25).

In conclusion, the study of Hayes and colleagues add valuable and useful information in the management of TC, with the goal of optimizing clinical decision making and patient outcomes. However, beyond morphological assessment of tumours obtained by using CT, radiologists, thoracic surgeons and oncologists should kept in mind the potential of diagnostic and functional imaging through the use of a preoperative MR of the thorax, with the aim to improve characterization and stratification of disease and to predict surgical outcome or response to treatment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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