Extended Abstract

Advances in thoracic surgery for thymic tumors: extended abstract

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Most thymic tumors are thymomas and they are found either incidentally or with diagnostic workup for myasthenia gravis (MG). There are 4 typical radiological findings: (I) the small mediastinal tumor with a more or less central position well surrounded by thymic tissue, (II) the large but well-confined tumor with visible or anticipated tissue layers between the tumor and pericardium, lung, and sternum as well as the larger vessels, (III) the thymic tumor with an irregular shape, without tissue layers as margin to the other mediastinal organs, and supposedly showing tumor, node, metastasis (TNM) stage III features during mediastinal dissection or at least being in close contact with the phrenic nerve, and (IV) a tumor with primary questionable resectability and requiring a biopsy for differential diagnosis before the therapeutic decision.

Open surgery *vs.* minimally invasive surgery (MIS)

A meta-analysis of published reports between 1995 and 2014 analyzed MIS versus open surgery for thymoma and found MIS thymectomy to be safe and to achieve similar oncological results compared to open thymectomy for selected patients with thymic malignancy (1).

The actual report from the European Society of Thoracic Surgeons (ESTS) database compared retrospective data between 1990–2010 with prospective data between 2007–2017. The increased percentage of MIS thymectomies from 6 to 33% contained robotic surgery (2% to 13%) (2).

Increasing numbers of robotic, as well as thoracoscopic non-robotic thymectomies (6% to 14% and 8% to 15%, respectively), were registered in the US between 2010–2014. With propensity-matching analysis, there were no differences in the 5-year overall survival (OS) rate between robotic-assisted thymectomy and thoracoscopic non-robotic thymectomy (3). Another national database analysis confirmed equal 5-year survival of open and MIS thymectomy (4). Most of the actual literature summarized data of patients operated on until nearly 5 years back, therefore, according to the general acceptance of MIS, the namely robotic-assisted technique for thoracic surgery, a further tremendous increase in MIS for thymic epithelial tumor (TET) can be expected by looking at actual records.

A meta-analysis investigating the influence of the surgical technique for thymectomy on complete stable remission (CSR) in MG has shown solid evidence for MIS thymectomy. Extended minimally invasive techniques were found to have CSR rates comparable to extended transsternal techniques in patients with thymoma, and are thus suitable in the hands of skilled surgeons (5).

Tumor size has a potential impact on the prognosis of patients with thymoma

In terms of tumor size, a single-center study of 154 patients found that thymoma size >4 cm was an independent predictive predictor for progression, which was also shown in TNM stage I thymoma (6). No difference in mid-term oncological results with robotic thymectomy for large thymoma (n=39, mean 6.2 cm) compared to small thymoma (n=42, mean 2.9 cm) was found with a cut-off at 4 cm of size (Charité-Universitätsmedizin Berlin, unpublished data).

Repeatedly the feasibility of robotic thymectomy for larger thymoma as compared to sternotomy has been shown (7,8). A technical recommendation for the larger thymomas

is the use of a 4-trocar-robotic approach including the subxiphoid entrance.

The Korean Association for Research of the Thymus accomplished another four-center research on limited thymectomy for early-stage thymoma. Limited thymectomy was not inferior to complete thymectomy in 295/762 patients with early-stage thymoma in terms of recurrence (9). Large thymoma and limited thymectomy appear to be related to an increased risk of MG after surgery. Patients with thymoma should have their acetylcholine receptor antibody (AchR-Ab) levels evaluated before and after surgery (10).

Surgery-related aspects with TETs

The extent of surgical resection and the choice of whether to perform lymph node dissection also have an impact on the clinical prognosis of patients with TETs. Among 13/131 patients with lymph node involvement, only patients with thymic carcinoma (25%) or B2/B3 thymoma had been affected. Though long-term outcomes in thymic tumors were not improved, lymph node dissection improved the prediction of prognosis by more accurate staging (11).

In the Japanese Nationwide database, surgical results of patients with Masaoka-Koga stage III thymoma were shown to be satisfactory unless chest wall invasion was present (12).

A comprehensive analysis of thymoma-related paraneoplastic syndromes includes 507 patients from 407 publications across 59 years and 123 unique paraneoplastic disorders. Surgical resection is related to increased OS and helps achieve remission of the paraneoplastic syndrome in the majority of patients (13).

The conservation of the phrenic nerve is a crucial consideration for surgery in advanced stage thymomas, particularly in patients with severe comorbidities such as MG. The nerve-sparing method was possible in 37/140 patients with Masaoka-Koga stage III and IVa thymoma during median sternotomy surgery and allowed for suitable local control with postoperative radiotherapy (PORT) (14). Robotic-assisted operation technique can also perform adequately phrenic nerve-sparing thymectomy in selected cases of advanced thymoma (Charité database video, Video S1).

Development in non-surgical treatment options for TETs accompanying surgery should also be considered

Surgical therapy for thymic tumors with pleural involvement should select the patients and should be performed in a multimodality setting. The procedural choice depends upon the extent of tumor distribution. In 152 patients from 12 institutions over 37 years the ESTS working group found surgery-supported multimodality setting efficient for local control with excellent results regarding OS, disease-free survival (DFS), cancer-specific survival (CSS), and freedom from recurrence (FFR) (15). In certain patients, surgical cytoreduction with hyperthermic intrathoracic chemotherapy (HITOC) was possible, and the survival rates were promising (16).

Future decision making for comprehensive therapy of TETs might also include immune check-point inhibitor therapy, but their potential risk of severe autoimmune adverse events would have to be better controlled (17).

Targeted therapy for thymic malignancies is encouraging but limited by the small number of druggable genetic abnormalities that have been identified to date. Multi-targeted kinase inhibitor Lenvatinib's activity and safety research show that it might be used as a conventional therapy option for patients with advanced or metastatic thymic cancer who have already been treated (18).

In 14 patients with Masaoka stage II invasive thymoma with lesions of the thymoma capsule, intraoperative radiotherapy was proven to be safe when given locally to the tumor bed at a dosage of 10 Gy. There was no obvious increase in operation- or radiation-related complications, nor was there any effect on critical organs like the heart or lungs. Long-term effectiveness should be expected (19).

Forty-one thymomas and 49 thymic carcinomas with complete excision in stage pT3N0M0 were evaluated in a multi-institutional investigation. Adjuvant treatment for thymic cancer with superior vena cava (SVC) or innominate vein invasion was linked with increased survival, whereas lung invasion was related to poor survival (20).

The latest advances to support surgery by PORT consist of the summary of 3 publications: PORT improved the recurrence-free survival (RFS) and OS in Masaoka/Koga stage III but did not show a survival benefit in stage II in 668 thymoma patients (527 stage II and 141 Stage III) treated between 1/2000 and 12/2013 in 4 Korean hospitals (21). Patients with completely resected Masaoka-Koga stage II/ III thymoma may benefit from PORT, according to a meta-analysis of 4,746 patients from five Japanese studies (22). A phase III, open, randomized research comparing PORT to surveillance in stage IIb/III Masaoka-Koga thymoma following complete surgical resection has just begun, with 314 patients from 15 specialized French institutions expecting to have outcomes in 2028 (23).

In summary, refinements of minimally-invasive and extended operation techniques are embedded in new and improved therapeutic tools of the comprehensive treatment strategy of thymic malignancies.

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Footnote

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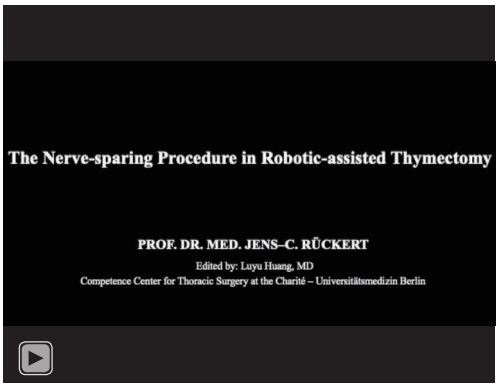
Supplementary



Video S1 Nerve-sparing operation technique for robotic-assisted thymectomy in a 60-year-old female patient with myasthenia gravis accompanied by an 8 cm WHO-B3 thymoma.

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