Which stages of thymoma benefit from adjuvant chemotherapy post-thymectomy?

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Summary

A best evidence topic in cardiac surgery was written according to a structured protocol. The question addressed was ‘Which stages of thymoma benefit from adjuvant chemotherapy post-thymectomy?’ Altogether more than 150 papers were found using the reported search, of which only eight represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated; these studies have mainly reported the survival and recurrence rates of post-thymectomy patients who received adjuvant radiotherapy or chemoradiotherapy, and adjuvant radiotherapy alone was only used in a small group of patients in these studies. We did not find any randomized controlled trials comparing adjuvant chemotherapy with chemo/radiotherapy and, due to a very small incidence of this tumour, it is unlikely to see any trials in future. Studies were mainly retrospective or institutional reports and showed that, despite the high sensitivity of this tumour to chemotherapy agents and the use of chemotherapy as one of the main treatment modalities in the advanced stages of thymoma, current data are not supporting postoperative chemotherapy as a sole adjuvant treatment in advanced stages of thymoma. We conclude that, in patients with thymoma, surgical resection with or without radiation therapy is the gold standard treatment for early-stage disease (I and II). Adjuvant radiotherapy/chemoradiotherapy should be considered for Masaoka stage III (A and B) or above, and it is also advised to add adjuvant therapy for all patients with cortical fenestration, even in stages I and II. But there is no evidence that chemotherapy alone improves the survival in patients with completely resected stage III and IV thymomas and thymic carcinoma. In patients with extra-radiation field disease, however, the use of chemotherapy can potentially improve survival but no follow-up data on this group of patients are available.

Keywords: Review • Thymoma • Adjuvant chemotherapy

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the ICVTS [1].

THREE-PART QUESTION

In [patients with thymoma] does treatment with [adjuvant chemotherapy] result in [increased survival]?

CLINICAL SCENARIO

During a joint thoracic oncology meeting the histology results of a patient with stage IIIA Masaoka thymoma are presented. You have recently performed a thymectomy on the patient and histology confirms negative resection margins. One of the oncologists advises that the patient should be commenced on adjuvant chemotherapy to improve survival. You resolve to check the literature yourself.

SEARCH STRATEGY

We searched Medline from 1950 to May 2011 using OVID interface [exp adjuvant chemotherapy/OR chemotherapy.mp] AND [exp thymoma/OR thymectomy.mp OR exp thymectomy/OR thymoma.mp].

SEARCH OUTCOME

One hundred and fifty-eight papers were found using the reported search. From these, eight papers were identified that provided the best evidence to answer the question. These are presented in Table 1.
The main adjuvant therapy after resection of thymoma was found to be adjuvant radiotherapy and not chemotherapy; however, in some series adjuvant chemoradiotherapy and adjuvant chemotherapy alone were also performed. Overall, data on the role of adjuvant chemotherapy in thymoma are scarce, but all the papers strongly advised a multimodality approach to this disease. In a survey, conducted in 52 centres on the management of thymic tumours among members of the European Society of Thoracic Surgeons (ESTS), only three had used chemotherapy alone [2]. Venuta et al. [3], in 2003, reported the results of their multimodality treatment in 45 patients with stage III thymic tumours who underwent induction chemotherapy and postoperative

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**RESULTS**

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**Table 1: Best evidence papers**

<table>
<thead>
<tr>
<th>Author, date and country, study type (level of evidence)</th>
<th>Patient group</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venuta et al. 2003 Ann Thorac Surg, Italy [3] Report of results (level IV)</td>
<td>45 patients with stage III; with or without induction chemotherapy and underwent adjuvant chemoradiotherapy</td>
<td>Chemoradiotherapy improved the survival</td>
<td>10-year actuarial survival 80%78 and 20% recurrence</td>
<td>Multimodality treatment with adjuvant chemoradiotherapy offers encouraging results for stage III thymic tumours</td>
</tr>
<tr>
<td>Lucchi et al. 2005 Ann Thorac Surg, Italy [4] Report of results (level IV)</td>
<td>56 patients with stages III and IVA; induction/neoadjuvant chemotherapy and adjuvant chemoradiotherapy</td>
<td>Multimodality treatment of stage III and IVA results in a good long-term outcome</td>
<td>10-year survival was 48 and 45.7% for stage III and IVA thymomas</td>
<td>Multimodality treatment including neoadjuvant chemotherapy and adjuvant chemoradiotherapy improves resectability and survival</td>
</tr>
<tr>
<td>Strobel et al., 2004 J Clin Oncol, Germany [5] Report of results (level IV)</td>
<td>228 post-thymectomy followed for 21 years: 42 received adjuvant radiotherapy 33 received adjuvant chemotherapy</td>
<td>Adjuvant chemotherapy in stage II did not influence the outcome</td>
<td>Stage II with adjuvant chemotherapy, three recurrences and no deaths</td>
<td>Adjuvant chemo/radiotherapy was beneficial in stages III and IV. Masaoka stages I and II with R0 tumour resection may not require adjuvant therapy</td>
</tr>
<tr>
<td>Singhal et al., 2003 Ann Thorac Surg, USA [6] Report of results (level IV)</td>
<td>167 thymectomy. Stage III adjuvant radiotherapy. Stages I and II with and without adjuvant radiotherapy</td>
<td>No difference in stage II with and without adjuvant treatment</td>
<td>Stage II, 20 with and 20 without adjuvant treatment. The 5-year survival was 91%</td>
<td>Complete and margin-negative surgical resection alone is sufficient treatment for both stage I and II thymomas</td>
</tr>
<tr>
<td>Mangi et al., 2002 Ann Thorac Surg, USA [7] Report of results (level IV)</td>
<td>155 thymectomy, 49 had stage II</td>
<td>No difference in survival with or without radiotherapy with stage II thymoma</td>
<td>10-year disease-specific survival in stage II was 100% with and without radiotherapy</td>
<td>Most stage II patients do not require adjuvant radiation therapy</td>
</tr>
<tr>
<td>Ciccone et al., 2005 Semin Thorac Cardiovasc Surg, Italy [8] Cohort and time series (level III)</td>
<td>83 (group I) single approach, 128 (group II) multimodality treatment. Twenty reoperation for recurrence</td>
<td>All recurrent tumours were thymomas with cortical differentiation</td>
<td>Group I had 11 (13.2%) and group II had nine (7%) recurrences</td>
<td>Stage I and II thymomas can recur locally and/or produce lung metastasis. To decrease the recurrence rate, adjuvant therapy should also be administered to stage I and II thymomas with cortical differentiation</td>
</tr>
<tr>
<td>Kim et al., 2007 Onkol Rep, Korea [9] Report of results (level IV)</td>
<td>100 thymectomy. 42 stage III and IV; 20 adjuvant radiotherapy and 22 adjuvant chemo/radiotherapy</td>
<td>Recurrence 28% No difference in the survival between adjuvant radiotherapy only and adjuvant chemo/radiotherapy</td>
<td>Prognostic factors of survival: age, WHO type, stage, local invasion</td>
<td>Pleural involvement at diagnosis was the important prognostic factor and innovative therapeutic approaches warrant further investigations</td>
</tr>
<tr>
<td>Kondo et al., 2003 Ann Thorac Surg, Japan [10] Cohort and time series (level III)</td>
<td>1320 patients from 115 institutions with different stages of thymomas</td>
<td>Stage I surgery, stage II and III surgery and additional chemo/radiotherapy. Stage IV radiation or chemotherapy</td>
<td>5-year survival rates of total resection 93%, subtotal resection 64%, inoperable 36%</td>
<td>Total resection is the most important. Adjuvant therapy is not valuable for totally resected thymomas</td>
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</table>
chemoradiotherapy; the 10-year actuarial survival in their patients was almost 80% with a recurrence rate of only 20%. These results were found to be more encouraging compared with their previous reports of only 47% 10-year survival without standardised induction or adjuvant treatment.

Similarly, in 2005, Lucchi et al. [4] published their series of 56 patients with Masaoka stages III and IV thymomas, who underwent multimodality treatment with induction, neoadjuvant therapy, surgery and adjuvant therapy; only one patient in their series had adjuvant chemotherapy, whereas seven underwent chemoradiotherapy postoperatively. They concluded that a multimodality treatment with induction chemotherapy, surgery and adjuvant chemoradiotherapy improves the outcome; however, a standard treatment for the advanced stages of thymoma requires large, multicentric, randomized trials.

A retrospective analysis by Strobel et al. [5] on a larger series of 228 patients with thymoma and thymic squamous cell carcinoma, who were followed for 20 years, showed that adjuvant chemotherapy had no influence on the outcome of patients with WHO type A, AB and B1 thymomas and of patients with completely resected type B2 or B3 tumours in Masaoka stage II. They performed adjuvant radiotherapy only in stage III thymoma cases, which showed good results compared with those with no postoperative treatment.

Although adjuvant chemoradiotherapy is still used in some centres for Masaoka stage II, no evidence has showed any increased survival rates after adjuvant therapy in completely resected and margin-negative, Masaoka stages I and II thymomas [6, 7]. In these series radiotherapy was the main treatment modality post thymectomy and proved to have no additional benefits over surgery alone. These reports confirmed that complete resection of the early-stage thymoma does not require any additional treatment.

A report by Ciccone et al. [8] showed that relapses occur in thymomas with cortical fenestration (World Health Organisation Type B) even in stage I and II thymomas and they concluded that, to decrease the recurrence rate of thymomas, adjuvant chemotherapy should be administered also for stage I and II thymomas with cortical fenestration. Their adjuvant therapy included radiotherapy for stage III and IV thymomas; however, they administered chemotheraphy as an adjuvant or primary treatment to patients with recurrent thymomas.

A retrospective single institutional report by Kim et al. on 100 patients who underwent thymectomy showed no difference in the 5-year survival in stage II and IV thymomas between patients who underwent adjuvant chemo/radiotherapy compared with those with adjuvant radiotherapy only [9].

The largest series on this topic was published in 2003 by Kondo et al. [10] reporting data on 1320 patients with thymoma from 115 centres. Their report revealed that patients with stage I thymoma and thymic carcinoma were treated with surgery only and those with stage II and III thymomas underwent surgery and adjuvant chemo/radiotherapy, and finally in stage IV treatment mainly included radiation or chemotherapy. They showed 5-year survival rates of 93, 64 and 36% with total resection, subtotal resection and inoperable thymoma and thymic carcinoids, respectively. However, in thymic carcinomas lower survival rates were observed. They also showed that prophylactic mediastinal radiotherapy could not prevent local recurrences effectively in patients with totally resected stage II and III thymomas, and adjuvant therapy including radiation or chemotherapy did not improve the prognosis in patients with totally resected stage III and IV tumours. However, this review was based on the reports of several institutions with different chemotherapy and radiotherapy regimens and, therefore, the true effect of chemotherapy for invasive thymomas and thymic carcinomas could not be ascertained.

**CLINICAL BOTTOM LINE**

In patients with thymoma, surgical resection with or without radiation therapy is the gold standard treatment for early-stage disease (I and II), and complete resection is the most important factor that positively influences their survival. It is difficult to determine the overall pattern of recurrence in thymoma and there is no clear evidence available on the optimal type and regimen of postoperative treatment. Current data suggest that adjuvant radiotherapy/chemoradiotherapy should be considered for Masaoka stage III (A and B) or above. It is also advised to add adjuvant therapy to all patients with cortical fenestration even with stages I and II. But there is no evidence that chemotherapy alone improves the survival in patients with completely resected stage III and IV thymomas and thymic carcinoma.

However, despite controversies regarding the use of adjuvant chemotherapy, it has been tried to prevent extra-radiation field recurrence, but no follow-up data are available [9]. Overall, despite the high sensitivity of thymomas to chemotherapy and its use for induction, neoadjuvant and palliative therapy as well as in patients who are not surgical candidates [11], its use as a sole adjuvant treatment with the current evidence was not found to improve survival.

**Conflict of interest:** none declared.

**REFERENCES**