Review Article

Induction chemoradiotherapy for unresectable thymic tumors

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Abstract: Curative treatment of locally advanced thymic neoplasms is challenging where optimal multi-modality therapy is not well defined. Thymic tumors that are deemed unresectable at presentation should always be re-considered for resection by a multi-disciplinary team after attempting an induction treatment strategy. Induction strategies have been evaluated in small single institution retrospective and some multi-institution prospective series with no superiority of chemoradiotherapy compared to chemotherapy alone. Despite less robust radiographic response rates compared to induction chemotherapy alone (often around 70%), combination chemotherapy + concurrent radiation therapy appears to increase the rate of complete resection (around 80%), but at the cost of increased perioperative morbidity and mortality. This review outlines the limited published literature addressing the role of induction chemoradiotherapy for "unresectable" thymic neoplasms and provides some insight into interpreting the data.

Keywords: Thymoma; radiation; chemotherapy; thymic carcinoma

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Introduction

The majority of thymomas are discovered at an early stage, Masaoka-Koga stage I or II or $T1_{a-b}2N0M0$ (proposed 8th edition staging of thymic tumors) (1), where surgical resection remains the mainstay of curative treatment. Approximately 1/3rd of patients will present with locally advanced thymoma, namely stage III disease, where a multimodality approach has become the care standard. Induction chemotherapy has been widely adopted for locally advanced disease despite the lack of randomized clinical data (2,3). Combination chemotherapy + radiation as an induction strategy has appeal since the biologic interaction may potentiate treatment effect and enhance complete resection. Preoperative radiation allows for more precise planning compared to the post-operative treatment volume delivered to the bed of the resected tumor. Proponents of induction chemoradiotherapy hypothesized that there would be less chance for pleural seeding during surgical resection and fewer local recurrences.

Evaluation of induction chemotherapy combined with radiation for locally advanced or "unresectable" thymic neoplasm is poorly studied. One of the earliest prospective multicenter trials that examined the efficacy of chemotherapy followed by radiation for limited stage unresectable thymoma was performed in a cooperative group trial and published in 1997 (4). This study analyzed 23 patients accrued from 1983–1995 with thymoma and thymic carcinoma [Masaoka stage III (n=22), stage IVA (n=1)] who received 2–4 cycles of chemotherapy (cisplatin, doxorubicin, cyclophosphamide) followed sequentially by 54 Gy of intensity-modulated radiation therapy (IMRT) to the primary tumor and regional lymph nodes. Chemotherapy response alone was 70% and the addition of radiation increased the complete or partial response rate in 5/23 patients. No patient underwent surgical resection. A local failure rate of 65% was observed and results showed that patients treated with 4 cycles of chemotherapy had improved survival compared to 2 cycles. The authors reported a 53% 5-year overall survival (*Table 1*).

Since induction chemotherapy given concurrently with radiation has been successfully used to improve complete resection in advanced thoracic cancers such as superior sulcus tumors (7) or locally advanced distal esophageal cancers (8), our institution employed a strategy of

Table 1 Relevant studies examining multimodality treatment with chemoradiotherapy for thymoma

Author	Year	n	Stage	Chemo	Radiation dose	Response rate	Complete resection	5-year OS
Loehrer *et al*. (4)	1983–1995	23	III, IV	Cisplatin, cyclophos, doxorubicin (2–4 cycles)	Sequential 54 Gy	70	–	53%
Wright *et al*. (5)	1997–2006	10	III, IVA	Cisplatin, etoposide (2 cycles)	Concurrent 40–45 Gy	40	80	69%
Korst *et al*. (6)	2007–2012	21	I, II, III	Cisplatin, etoposide (2 cycles)	Concurrent 45 Gy	47	77	71%

2 cycles of chemotherapy (cisplatin, etoposide) given in combination with 40–45 Gy IMRT to the primary tumor followed by surgical resection. Wright and colleagues reported on this retrospective series of 10 patients accumulated from 1997–2006 (5). Most patients (80%) harbored tumors >8 cm and the study included 7 patients with Masaoka stage III, and 3 patients with stage IVA disease (see *Table 1*). Only one patient had a thymic carcinoma. The radiographic response rate was only 40%; likely related to a reduced dose intensity of chemotherapy. All patients underwent surgery 4–8 weeks after induction where complete resection (R0) was achieved in 8 (80%) patients. No patient exhibited a complete pathologic response; however, 4 patients had near pathologic complete response. Of note, PET scan did not appear to correlate with radiographic response or pathologic response. The authors reported a 69% 5-year overall survival with a median follow-up of 41 months.

The published results from Wright *et al.*, spawned a prospective, multi-institutional phase II trial of induction treatment with 2 cycles of cisplatin/etoposide concurrently with 45 Gy IMRT (6). The study enrolled 21 patients from four institutions with specific inclusion criteria and included 14 patients with thymoma and 7 patients with thymic carcinoma (see *Table 1*). A radiographic response was noted in 47% of patients (best seen in thymic carcinoma). Complete resection was achieved in 77% of patients. Surprisingly again, no complete pathologic responses were encountered. In contrast, induction chemotherapy alone has been associated with a 10–15% complete response rate in reported series (9-12). It remains to be seen if an excellent pathologic response translates into a more favorable prognosis. Five patients had <10% viable tumor (4 of these were thymic carcinomas). Nine patients (41%) experienced a grade III/IV toxicity and there were 2 postoperative deaths. The authors reported 71% 5-year overall survival. Although there was a high rate of complete surgical resection, superiority of induction chemoradiotherapy over induction chemotherapy alone was not established with this trial.

Other than tumor stage, R0 resection remains the most consistent prognostic factor in published series. Although, combination induction chemoradiotherapy for thymic tumors appears to increase the rate of complete resection, there is clearly more associated treatment toxicity and the surgical field becomes more difficult to navigate by virtue of radiation fibrosis. Locally advanced thymomas that appear difficult to resect should be considered for induction chemotherapy to maximize the chance of a complete resection. If a surgeon is already committed where complete resection cannot be safely achieved, it makes sense to debulk as much tumor as possible balancing the risks to adjacent structures and postoperative complications with the benefit of reducing tumor bulk in an otherwise indolent tumor. Debulking has been associated with improved overall survival in a meta-analysis comparing incomplete resection to observation in "unresectable" thymoma (13). The surgeon should then leave clips behind to facilitate directed postoperative radiation therapy.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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