Review

A Review of the Place and Role of Radiotherapy in Thymoma

Dorothy C. Lombe,[1] Branislav Jeremic[2,3]

Abstract

Thymomas, tumors that arise from the epithelial cells of the thymus gland, are the most common tumors of the anterior mediastinum despite their overall rarity. They are not classified together with malignancies although it is recognized that they can be invasive and persistent even after attempted treatment. Because of their rarity, optimal treatment protocols remain a challenging topic. Although surgery is recognized as the cornerstone of management, the role and benefit of use of postoperative radiotherapy (PORT), remains questionable. Unequivocal evidence, although exclusively from retrospective studies, indicates that stage I thymoma is adequately treated with complete resection alone. As for stage II there is still a need to better determine the indications of PORT. For stage III and IV, existing data point to the fact that PORT plays a significant role in the management of thymoma. In patients for whom radiotherapy (RT) is indicated, 50 Gy appears to be adequate for microscopic disease and higher doses should be used for macroscopic tumor. With advances in RT delivery techniques, which allow for higher doses to be delivered to larger areas affected by tumor while sparing normal tissue, it is prudent to identify a place for this modality in the optimal management of thymoma patients.

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Introduction

Thymomas, tumors that arise from the epithelial cells of the thymus gland, are the most common tumors of the anterior mediastinum despite their overall rarity. They are not classified together with malignancies although it is recognized that they can be invasive and persistent even after attempted treatment. They grow in close proximity to critical structures like the heart, great vessels, and lungs, hence making it potentially very difficult to treat without causing great morbidity to a long-surviving patient.

The incidence of thymoma in the United States based on Surveillance, Epidemiology, and End Results (SEER) databases has been reported to be 0.13-0.15 per 100,000.[1,2] Thymomas present as a spectrum of signs and symptoms, from incidental findings on chest radiographs to severe chest pain and superior vena cava syndrome. Myasthenia gravis has been strongly associated with thymoma, with up to a third of patients presenting with it.[1] Thymoma occurs equally in men as in women. The most common age group of patients are those in their 7th decade and least common in children and young adults.[1]

The Masaoka Staging (Table 1) is widely accepted as a standard of clinical staging of thymomas.[1,3] It was first proposed in 1981 by Masaoka et al and revised in 2009. Because of evolution of surgical techniques from simple thymectomies to extended thymectomies, existence of lymph node metastases became more evident, which led to development of tumor, node, metastases (TNM) staging of thymoma in 1991.[3,4] The heterogeneity between the Masaoka and World Health Organization (WHO) TNM staging lies in the placement of N2 disease in stage IVB and stage III, respectively.[3,4] The WHO also developed a histological classification in 1999 (Table 2) and it is noted to be an indicator of good prognosis in thymoma.[5]

Radiotherapy (RT) has long been established as an important component of the armamentarium against this disease, although its outstanding benefit versus toxicity in the postoperative setting remains debatable. The practice of RT has continuously evolved with development of 3-D conformal therapy, 4-dimensional (4D) treatment planning and delivery, intensity-modulated radiation therapy (IMRT) and adaptive RT, and proton use.[6]

The National Comprehensive Cancer Network guidelines recommend surgery as the cornerstone in resectable tumors.[7] To obtain clear resection margins that can be deemed monotherapy-adequate,

[1]Division of Radiation Oncology, Stellenbosch University, Tygerberg Hospital, Cape Town, South Africa
[2]Institute of Lung Diseases, Sremska Kamenica, Serbia
[3]BioIRC Center for Biomedical Engineering, Kragujevac, Serbia

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Address for correspondence: Dorothy C. Lombe, MD, Department of Radiation Oncology, Gene Louw Building, Tygerberg Hospital, Francie Van Zijl Drive, 7500 Cape Town, South Africa
E-mail contact: dotchillo@yahoo.com

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Table 1 Modified Masaoka Staging System of Thymomas[1]

Stage	Description
I	Macroscopically and microscopically completely encapsulated
II	(A) Microscopic transcapsular invasion
	(B) Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium
III	Macroscopic invasion into neighboring organs (ie, pericardium, great vessels, lung)
	(A) Without invasion of great vessels
	(B) With invasion of great vessels
IV	(A) Pleural or pericardial dissemination
	(B) Lymphogenous or hematogenous metastasis

one might require resection of adjacent critical structures. However, some investigators recommend that postoperative RT (PORT) can be considered for various indications[8-12] and others do not find the use of PORT beneficial.[13-18] Where there is R1 or R2 resection PORT is sometimes recommended and with the latter, chemotherapy administration might even be considered. The dose of RT has been stipulated by some as 45 to 50 Gy for clear or close margins, 54 Gy for microscopically positive resection, and 60 Gy for gross residual disease.[8]

Taking into account these frequently conflicting findings, we have carried out a literature search of articles published in the English language to identify relevant studies describing important aspects in the management of thymoma and have focused on the place and role of PORT in this disease. We used the search engines PubMed, Scopus, and Google scholar. In particular, we attempted to use available data on the need for PORT in the multidisciplinary management of thymoma with regard to improvement of outcomes for the treatment of patients. We selected and tabulated a few studies that addressed the questions that could help us identify the best treatment approach to thymomas holistically (Table 3).[8-34] We studied articles with a variety of characteristics vis a vis those that compared different stages, different histology, completeness of resection, and indeed, those with complete resection in patients who received PORT. Because of the disease rarity, all studies were retrospective in nature. Some studies with thymic carcinomas as part of the cohort, were excluded because of the negative effect they have on outcomes, because of their particularly aggressive nature. Those that were included had taken into account the effect of the outcomes of thymic carcinomas on the cohorts. Ultimately, the indications for PORT in the context of thymoma have to take into account various factors such as histological subtype, Masaoka stage, and extent of surgery. RT delivery and the dose of RT prescribed also have to be optimal to achieve favorable outcomes.

Table 2 World Health Organization Histologic Classification[5]

Type	Description
A	A tumor composed of a population of neoplastic thymic epithelial cells having a spindle or oval shape, lacking nuclear atypia, and accompanied by few or no nonneoplastic lymphocytes
AB	A tumor in which foci having the features of type A thymoma are admixed with foci rich in lymphocytes
B1	A tumor that resembles the normal functional thymus in that it combines large expanses having an appearance practically indistinguishable from normal thymic cortex with areas resembling thymic medulla
B2	A tumor in which the neoplastic epithelial component appears as scattered plump cells with vesicular nuclei and distinct nucleoli among a heavy population of lymphocytes. Perivascular arrangement of tumor cells resulting in a palisade effect might be seen
B3	A type of thymoma predominantly composed of epithelial cells having a round or polygonal shape and exhibiting no or mild atypia. They are admixed with a mild component of lymphocytes, resulting in a sheet-like growth of the neoplastic epithelial cells
C	A thymic tumor (thymic carcinoma) exhibiting clear-cut cytological atypia and a set of cytoarchitectural features no longer specific to the thymus, but rather analogous to those seen in carcinomas of other organs. Type C thymomas lack immature lymphocytes; whatever lymphocytes might be present are mature and usually admixed with plasma cells

Histology

Thymomas are histologically heterogeneous and care must be taken to identify histologic subgroups of patients who benefit from a particular intervention. Song et al[33] and Gao et al[35] investigated 42 WHO subtype B2 and 172 WHO subtype B3 patients, respectively. B2 subtype thymomas are moderately aggressive and B3 are more aggressive and can be grouped with thymic carcinomas in the literature.[36] For B2 tumors, PORT did not influence disease-free survival (DFS) or overall survival (OS) in multivariate analysis and patients with B3 tumors with stage III or IV benefitted from PORT.[33,35] Gao et al divided patients with WHO type B3 into those who attained successful treatment (R0 or complete response after PORT) and those that did not (R1+l; partial response or stable disease).[35] From these 2 groups they measured freedom from recurrence (FFR) and time to progression (TTP), respectively, and found that the resection margin status and Masaoka stage had a significant effect on the FFR and TTP. For stage III and IV, multivariate analysis showed Masaoka stage and PORT were prognostic factors for OS in keeping with results from Song et al.[33]

In the study of Oh et al,[29] which was a review of 110 patients with Masaoka stage I and II disease, they found no difference with or without PORT. A better DFS for patients with histological subtypes WHO A-B1 than B2-C in stage I was observed. Patients eligible for PORT were based on the surgeon's judgement on high risk factors such as invasiveness or adhesiveness. This introduced bias because of a subgroup of patients in the PORT group who had baseline high risk factors.

Chen et al[13] reported on stage II patients. WHO pathologic subtype and tumor size were statistically significant predictors for survival in univariate analysis of their data. They demonstrated no survival advantage between the PORT group and the surgery-only group, and attributed this to the fact that the PORT group had more patients with WHO subtype B3, which is more aggressive ($P = .03$). The PORT group in the Chen et al study[13] also appeared to have had more patients with invasion of pericardium and pleura than just microscopic invasion of the capsule ($P = .012$).

Vassiliou et al[26] found that in their study most patients with stage III and IV disease had histological subtype B3 or C and it is among these that most the disease recurrences occurred after PORT. Kim et al[25] also found a statistically significant correlation between Masaoka stage and WHO histologic types. Twenty-six of 28 (93%)