ORIGINAL ARTICLE

The Impact of Postoperative Radiotherapy for Thymoma and Thymic Carcinoma

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ABSTRACT

Introduction: The optimal role for postoperative radiotherapy (PORT) for thymoma and thymic carcinoma remains controversial. We used the National Cancer Data Base to investigate the impact of PORT on overall survival (OS).

Methods: Patients who underwent an operation for thymoma or thymic carcinoma were categorized into Masaoka-Koga stage groups I to IIA, IIB, III, and IV. Patients who did not undergo an operation or those who received preoperative radiation were excluded. Kaplan-Meier estimates of OS and univariate and multivariate Cox proportional hazards regression analyses were performed. Propensity score–matched analyses were performed to further control for baseline confounders.

Results: From 2004 to 2012, 4056 patients were eligible for inclusion, 2001 of whom (49%) received PORT. On multivariate analysis of OS in the thymoma cohort adjusted for age, WHO histologic subtype, Masaoka-Koga stage group, surgical margins, and chemotherapy administration, PORT was associated with superior OS (hazard ratio [HR] = 0.72, $p = 0.001$). Propensity score–matched analyses confirmed the survival advantage associated with PORT. Subset analysis indicated longer OS in association with PORT for patients with stage IIB thymoma (HR = 0.61, $p = 0.035$), stage III (HR = 0.69, $p = 0.020$), and positive margins (HR = 0.53, $p < 0.001$). The impact of PORT for stage I to IIA disease did not reach significance (HR = 0.76, $p = 0.156$).

Conclusions: In this large database analysis of PORT for thymic tumors, PORT was associated with longer OS, with the greatest relative benefits observed for stage IIB to III disease and positive margins. In the absence of randomized studies assessing the value of PORT, these data may inform clinical practice.

Keywords: Thymoma; Thymic carcinoma; Adjuvant radiation; Postoperative radiotherapy; National Cancer Data Base

Introduction

The thymic epithelial tumors, thymoma and thymic carcinoma, represent the most frequent tumors of the anterior mediastinum, although they remain relatively rare overall.[1] Surgery stands as the primary therapeutic modality in the curative setting, as extent of resection has consistently been shown to be independently prognostic of improved survival.[2,3] The intimate association of these tumors with critical mediastinal structures can make complete resection difficult, particularly for advanced-stage disease.[4,5] As a result, there has been a longstanding interest in utilizing

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postoperative radiotherapy (PORT) to improve outcomes. However, the precise indications for PORT and its magnitude of benefit have been difficult to ascertain.[6–8] The low annual incidence of thymic tumors renders the execution of randomized trials challenging, leaving only limited, conflicting data regarding the utility of PORT.

Large registry data sets, such as the Surveillance Epidemiology and End Results (SEER) database, have proved useful for investigating clinical questions in thymic tumors and other rare diseases for which there are inadequate data to address relevant questions. Given a lack of prospective evidence, several investigators have previously utilized the SEER database and other national data sets to investigate the role of PORT for thymic epithelial tumors.[9–17] Although these studies have been fairly heterogeneous in their design, consistent themes have emerged. PORT appears beneficial for patients with advanced disease (Masaoka-Koga stage III–IV)[9,10] but of minimal utility for completely encapsulated tumors (Masaoka-Koga stage I),[13–15] and it remains controversial for Masaoka-Koga stage II disease.[15,16] Improved outcomes with the addition of PORT have been more readily demonstrated for patients with aggressive thymic carcinoma, as opposed to for those with thymoma histologic subtypes.[18–21] Many retrospective, large-database studies have been unable to control for important confounders, including surgical margin status, histologic subtype, and use of chemotherapy; these studies have called for future studies to incorporate the aforesaid variables to provide more robust analyses.

The National Cancer Data Base (NCDB), which was queried for this study, includes additional information on these important variables. As a large hospital-based registry representing more than two-thirds of all cancer cases in the United States, the NCDB draws from a substantial number of institutions nationwide, thereby increasing the number of cases available for analysis. In this largest reported series on PORT for thymic tumors, we utilize the NCDB, with its unprecedented body of critical patient- and disease-specific factors, to describe outcomes and prognostic factors that identify patients who may benefit from adjuvant radiotherapy.

Methods

Data Source and Patient Selection

The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. It is a hospital-based registry that represents 70% of all cancer cases in the United States, drawing data from more than 1500 commission-accredited cancer programs. The data used in the study are derived from a deidentified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used, or for the conclusions drawn from these data by the investigators.[22] Before the present analysis was begun, appropriate exemption was obtained from our institutional review board.

The analysis was restricted to adult patients (age $\geq$18 years) in whom thymoma or thymic carcinoma, defined as International Classification of Disease for Oncology, Third Edition (ICD-O-3), histologic codes for thymoma (8580–8585) and thymic carcinoma (8002, 8010, 8012, 8013, 8020, 8021, 8070-8072, 8074, 8140, 8240, 8243, 8246, 8586, 8588, and 8589) with corresponding topographic codes C37.9 (thymus) and C38.1 (anterior mediastinum), had been diagnosed.[23] All patients included in the analysis were recorded as having undergone an operation and had their disease diagnosed from 2004 to 2012. All included cases had known treatment-related variables with respect to surgery, chemotherapy, and radiotherapy delivery, with unknowns excluded from this analysis. Treatment data coded in the NCDB are limited to the first course of treatment, defined as all methods of treatment recorded in the treatment plan and administered to the patient before disease progression or recurrence. Cases for which radiation was coded as being delivered before surgery or intraoperatively were excluded. Cases in which death occurred within 1 month of diagnosis were omitted from analysis.

Patient Demographics and Treatment Variables

Potentially relevant patient and treatment characteristics were selected a priori. Retrievable data included age, race, sex, insurance status, median income, treatment facility type, distance to facility, Charlson-Deyo comorbidity score, year of diagnosis, surgical margin status, WHO histologic subtype, use of radiation, use of chemotherapy, and derived Masaoka-Koga stage group. To facilitate clinical applicability of this report, cases within the database were categorized according to the Masaoka-Koga staging system for thymic epithelial tumors: stage I to IIA (invasive tumor confined to gland of origin or localized, NOS), stage IIB (adjacent connective tissue), stage III (adjacent organs/structures in mediastinum), and stage IV (further contiguous extension, lymph nodes, or metastasis). As neither the SEER database nor the NCDB codes for microscopic transcapsular invasion, stage I disease could not be distinguished from stage IIA disease.