Dr Keshavjee. I have one other question. When you talk about R0 versus R1 and R2 resection and the difficulty in showing a difference between R1 and R2 resection, from your knowledge of the database, do we have enough information to say, whether you did an R0 resection by doing advanced surgery, like an SVC resection or something like that, that you have a better result than having R1 disease left behind in terms of what we do for our patients, because sometimes when you look at aggregate data, you might give surgeons an excuse to just say, “Well, yes, I’ll just sort of debulk this tumor and radiate it,” and is that okay or is that inferior surgery?

Dr Ahmad. Well, I think based on the data that we have, what I can say safely is that every effort should be made to achieve an R0 resection and there is really no substitute for an R0 resection.

Dr Keshavjee. That is current dogma, but your data that you showed did not reflect that, right? That is what I think is the danger in looking at data like this, that it did not reflect the dogma that you believe is correct. I believe it, too, but I am just saying that that might be an erroneous interpretation of the data.

Dr Ahmad. Yes, I agree.

Dr Keshavjee. Thank you.

Dr Thomas K. Waddell (Toronto, Ontario, Canada). I will follow up on the point that you just raised because I must say that I did not quite understand what you meant by that. The R1 survival was the same as R2, so my interpretation was

that it means that unless you get all of it out, there is no point in doing any surgery. Is that the point you were trying to discuss? I think we do not know what happens to anybody who has no surgery.

Dr Ahmad. Exactly. I think that is what I should clarify some more. You do not have nonsurgically treated patients in the database, so it is hard to compare. If you leave tumor behind or not do surgery at all, how are they going to do in comparison with medical therapy alone? However, historically, if you look at medically treated patients only, their survivals are anywhere between 20% and 30%, as opposed to R1-resected patients in this series where we had survivals up to 40%.

Dr Anthony J. Acinapura (Brooklyn, New York). Your data suggested that adjuvant therapy is an important factor in overall survival. Some of the more recent publications are suggesting neoadjuvant chemoradiation therapy is equally important and has also been able to allow for more R0 resections. Do you have any data on that?

Dr Ahmad. We were actually unable to show whether adjuvant or neoadjuvant treatment had any benefit. In fact, any chemotherapy or any treatment ended up improving survival. So at this point, based on these data, it is hard for me to conclude that adjuvant therapy itself had any association with overall survival. All we can say is that chemotherapy and radiation helped improve overall survival.

EDITORIAL COMMENTARY

Rarest of a rare disease: Challenges in advancing our knowledge of thymic carcinoma

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See related article on pages 95-101.

Thymic epithelial tumors, with a reported incidence of 3.2 per 1,000,000¹ and thus affecting less than 200,000 people in the United States, are classified as a rare disease by the National Institutes of Health (<http://rarediseases.info.nih.gov>). The inclusion of rare diseases in the Orphan

Drug Act of 1983 has led to the alternative name “orphan diseases.” Thymic carcinoma is a subset of thymic epithelial tumors, having approximately one tenth the incidence of all thymic epithelial malignancies.¹ Thus, the difficulties of acquiring and increasing our knowledge of this orphan disease are confounded by the exceptional rarity of this rarest of a rare disease and the retrospective acquisition of most of the information concerning thymic carcinoma. An understanding of some of these difficulties may enhance the readers’ understanding and permit a more focused interpretation of the current article prompting this commentary.²

DATA SET AND ANALYSIS

The planned inclusion of thymic malignancies in the 8th edition of the *AJCC Cancer Staging Manual* was the impetus to acquire data concerning thymic epithelial tumors, which in turn was the stimulus for formation of the

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International Thymic Malignancy Interest Group.³ In an attempt to increase the size of the database, International Thymic Malignancy Interest Group data were amalgamated with those of the European Society for Thoracic Surgery. Subset analysis of the thymic epithelial tumor database resulted in a “limited data” subset of 1042 patients with thymic carcinoma treated in 67 of 73 centers.² This represents the largest thymic carcinoma experience yet to be reported; however, the pool from which these patients were derived is unknown, eliminating any epidemiologic assessment. There is no doubt of the considerable granularity of data and substantial missing data in this retrospectively constructed data set, such that age was reported in 85% of patients, pathologic Masaoka stage in 80% of patients, World Health Organization histology in 68% of patients, and clinical Masaoka stage in 39% of patients. This variable data collection necessitated the following qualification: “The number of cases analyzable for each variable and test are reported.”² The exact method of dealing with missing data is not stated.

As with all retrospective data, if a variable is not recorded, it cannot be retrieved and analyzed. An example of such a potentially important unrecorded variable is the presence of regional lymph node metastases (pN+). Surprisingly, this was reported in only 20 patients. Providing insight into the shortcoming of the data set and analysis, the authors disappointingly state that “the role of lymph node involvement could not be studied due to the small number of patients with positive nodes and also due to the fact that there is no consistent practice of lymphadenectomy or lymph node sampling.”²

The depth and extent of the challenges encountered in this project may be further appreciated by a careful focus on the analysis of outcomes. Of the 2 measures of outcomes—death and recurrence—death status is irrefutable, but it was known in only 80% of patients. Recurrence, the other outcome, is a soft end point. Because no protocol for detection of recurrence was used, this part of the analysis is subject to question. This outcome measure is further confounded by the potential difficulty of clinical detection of recurrence in radiated and surgical fields. The interpretation of the impact of this clinical problem is obscured by the problem of missing data. In the 92% of patients for whom status of radiation therapy use was known, it was used in 78%, and in 72% of all 1042 study patients regardless of whether their treatment status was known.

The authors reported that radiation therapy was used in 72%; thus, missing variables were managed in the analysis as if radiation therapy had not been administered. Awareness of these examples, other data peculiarities, and analysis challenges should be noted in the interpretation of the results.

RESULTS

Despite a large number of events (deaths and recurrence), only 2 predictors of overall survival (R0 resection and use of any radiation therapy) and 2 predictors of recurrence (use of any radiation therapy and male gender) were identified. This is in marked distinction to the recently reported analysis of the European Society for Thoracic Surgery segment of the data.⁴ In only 229 patients with richer data, results were more definitive and convincing. R1 or R2 resections ($P < .0001$), advanced stage (Masaoka–Koga III–IV) ($P = .02$), and failure to use postoperative adjuvant radiation therapy ($P = .03$) were associated with poorer survival.

RARE DISEASE

This experience is a first attempt at assembling an international thymic carcinoma database. Many shortcomings can be addressed in prospective data collection. The results are not surprising and do not need statistics to confirm that use of effective local therapies is associated with improved survival. The recurrence associations should be viewed with skepticism.

In the future, advancing our knowledge of thymic carcinoma will require borrowing from our understanding of similar but more prevalent cancers from other sites and carefully assembling and analyzing the scarce available data. This effort will be magnified by participation and collaboration with rare disease efforts, such as that administered by the National Institutes of Health (<http://rarediseases.info.nih.gov/gard/5201/thymic-epithelial-tumor/resources/>).

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