Prognostic Factors and Outcome of Incompletely Resected Invasive Thymoma Following Radiation Therapy

By Ilja F. Ciernik, Urs Meier, and Urs M. Lütolf

Background: **Stage III and stage IV thymomas with significant macroscopic infiltration to the neighboring structures are rarely completely resectable. It therefore remains unclear to what extent tumors must be surgically debulked to improve prognosis.**

Patients and Methods: **We reviewed the cases of 31 patients with incompletely resected invasive thymoma and residual macroscopic disease who were referred to postoperative irradiation. Survival and local tumor control were analyzed. All patients were treated between 1958 and 1990 with megavoltage irradiation at doses ranging from 42 to 66 Gy. The shortest follow-up time for living patients was more than 5 years.**

Results: **The overall median 5-year survival rate was 45%. Eighteen stage III patients had a 5-year survival rate of 61% and a 10-year survival rate of 57%. Thirteen patients had stage IV disease and 5- and 10-year survival rates of 23% and 8%, respectively. Univariate and multivariate analyses confirmed a worse prognosis for stage IV disease. Epithelial or spindle-cell thymoma was associated with stage IV disease. Twenty-two percent of patients with stage III disease had epithelial or spindle-cell thymoma, versus 69% of patients with stage IV disease ($P = .02$ for univariate and $P = .05$ for multivariate analysis). Initial tumor diameter greater than 10 cm correlated with poor prognosis in the univariate analysis ($P = .05$). However, more importantly, debulking of tumor did not significantly improve outcome when compared with patients who received biopsy only. The median survival rate of patients with stage IVa disease did not differ from that of those with stage IVb disease. Mediastinal control was achieved in 23 patients (74%). Stage IV disease did not correlate with an increase in local treatment failure after irradiation, although epithelial or spindle-cell thymoma predisposed for local treatment failure (46% v 11%; $P = .04$ in univariate and $P = .055$ in multivariate analysis).**

Conclusion: **Tumor debulking leaving macroscopic residual thymoma, as opposed to biopsy alone, does not improve prognosis when followed by radiation. Radiation therapy for local tumor control is most effective in nonepithelial-predominant thymomas.**

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THYMOMAS are defined as tumors that originate from epithelial structures of the thymus. They must be differentiated from the rarer thymic carcinomas, as well as from non-Hodgkin's lymphomas, germ cell and neurogenic tumors, and other neoplasms.[1,2] Half of the neoplasms of the anterior mediastinum are benign, and histology is consistent with thymoma in as many as 10% of cases. Similarly, 5% to 10% of the malignant tumors of the anterior mediastinum are represented by thymomas.[2] Thymomas are treated by complete resection, especially in the absence of significant infiltration of the surrounding tissue, and such treatment yields a low recurrence rate, ie, less than 5%.[3,4] On the other hand, locally advanced thymomas tend to recur frequently, even if completely resected. Recurrence rates from 20% to 80% have been reported.[4-8] It is common practice to administer postoperative adjuvant radiotherapy for invasive thymomas, although further studies are needed to confirm the benefit of routine adjuvant radiation.[3,4]

For large invasive thymomas, with invasion of major vessels or cardiac structures, complete resection is more difficult to achieve, and tumor reduction plus postoperative radiotherapy has been shown to be an effective treatment.[4,9,10] For these patients, the importance of aggressive surgical resection and tumor debulking is unclear, although frequently assumed. Recent studies have involved radical surgery with vascular resection and artificial grafts, or the use of chemotherapy.[11-16] Other strategies involve neoadjuvant radiotherapy or chemotherapy.[17] Only a minority of studies present data concentrating on incompletely resected thymomas, and little information is available about the treatment options that do not involve chemotherapy for patients with stage IV thymomas. Thus, the optimal treatment of patients with advanced thymoma remains controversial.

In this study, we review our experience of irradiated incompletely resected thymomas with respect to survival and local control.

PATIENTS AND METHODS

Between 1958 and 1990, 31 patients were referred to the Division of Radiation-Oncology of the University Hospital of Zürich, Switzerland. In all patients, surgical intervention left macroscopically residual thymoma resulting from invasion to neighboring structures.

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Table 1. Histologic Diagnosis of 31 Patients With Incompletely Resected and Irradiated Malignant Thymomas

Diagnosis	No. of Patients
Epithelial thymoma	9
Spindle-cell thymoma	4
Lymphocytic thymoma	7
Mixed-cell thymoma	6
Atypical thymoma	4
Reticular thymoma	1

Twelve women and 19 men were included in this review. The mean age was 43.8 years (range, 23 to 74).

Staging

Retrospective staging of the disease was based on the review of patients' charts and was performed according to the method reported by Masaoka et al.[18] Stage III tumors displayed macroscopic invasion of the neighboring structure, either the pericardium, great vessels, or lung. Stage IV tumors were characterized by pleural or pericardial dissemination (Stage IVa), lymphogenous or hematogenous metastasis, or both dissemination and metastasis (IVb). Before surgery, 13 patients had stage IV disease, seven stage IVa, and six stage IVb.

Histology

After 1975, the classification of an epithelial tumor of the thymus was based on the description by Rosai and Levine.[1] Patients with thymic carcinoma were excluded from this study. The histologic diagnoses are listed in Table 1.

Associated Disease and Symptoms

Three men and one woman suffered from myasthenia gravis. All but two patients (94%) were symptomatic at diagnosis. Chief complaints are listed in Table 2. Sixteen patients had more than one symptom leading to diagnosis.[19]

Tumor Diameter

At diagnosis, eight patients had tumors with a diameter less than 10 cm, and 10 patients had a tumor with a diameter greater than 10 cm. Tumor diameter was based on the anteroposterior chest x-ray and surgical report. Tumors with a diameter that could not clearly be classified as less than or greater than 10 cm were not scored.

Surgical Resection

All patients underwent thoracotomy in the attempt to remove or debulk a mediastinal mass. None of the patients received any invasive diagnostic procedures before thoracotomy. The amount of resection was evaluated according to the description of the surgeon in the operation notes, which were available in each case. There was either minor resection yielding sufficient tissue for histologic examination (16 patients), clearly leaving a tumor with a diameter of at least 5 cm, or an attempt for subtotal resection, leaving small amounts of tumor that mostly invaded major vessels or the pericardial structure, and of an estimated volume of less than $2 \times 2 \times 1$ cm (15 patients).

Radiation Therapy

All but one patient (who received 42 Gy) received at least 50 Gy (range, 42 to 76) irradiation to the anterior mediastinum. Twenty-three patients received $\geq$ 60 Gy, and eight received less than 60 Gy. The patients were irradiated once daily, five times per week, with a single dose of 2 Gy in respect to the midplane. The radiotherapy units used were a linear accelerator of 6 or 18 MeV, and a Betatron or a Telecobalt unit. Although radiation was applied by different machines, the calculation of the dose was consistent throughout the time of the reported treatments. Equally weighted fields with the calculation to midplane have been used. The only parameter that changed between machines used was dose homogeneity (relative change, 5% to 10%) due to differences in source isocenter distances and differences in energy. Radiation fields usually included two large opposing fields of 15×15 cm to 20×25 cm to a dose of 36 Gy; radiation was then continued with three fields of usually 8×8 cm to the area of residual tumor. The field encompassed the residual tumor with a margin of approximately 2 cm, unless excess pulmonary tissue was exposed, in which case a margin of only 1.0 to 1.5 cm was accepted. Dose was calculated at the central axis to the midplane. Ten patients received irradiation of the supraclavicular area with doses of 20 to 50 Gy (mean, 35). Seven of these patients had stage III and three stage IVb disease.

Follow-Up Time

The median follow-up time was 17.8 years. The shortest follow-up time for living patients was 65 months.

Statistical Analysis

Prognostic factors for survival were analyzed using the log-rank test based on the Kaplan-Meier survival method. Cox's proportional hazards model was used for multivariate survival analysis. The χ^2 test and Fischer's exact test (two-tailed) were used for comparison between two groups in the analysis of local tumor control, and multiple logistic regression was used for multivariate analysis. Statistical significance was accepted at P values less than .05.[20]

RESULTS

Overall survival data are presented in Fig 1. The 5-year survival rate was 45%, and the 10-year survival rate was 28%. Clearly, patients with stage IV thymoma had a worse prognosis than patients with stage III thymoma (Fig 2). Patients with stage III tumors had a 5-year survival rate of 61%, compared with 23% for patients with stage IV tumors. The 10-year survival rate for stage III patients was 57%, compared with only 8% for stage IV

Table 2. Chief Complaints Leading to the Diagnosis of an Invasive Thymoma

Complaint	No. of Patients
Coughing	9
Thoracic pain	9
Dyspnea	7
Chronic fatigue	5
Myasthenia gravis	4
Fever	4
Superior vena cava syndrome	3
Common cold	2
No symptoms/positive chest x-ray	2

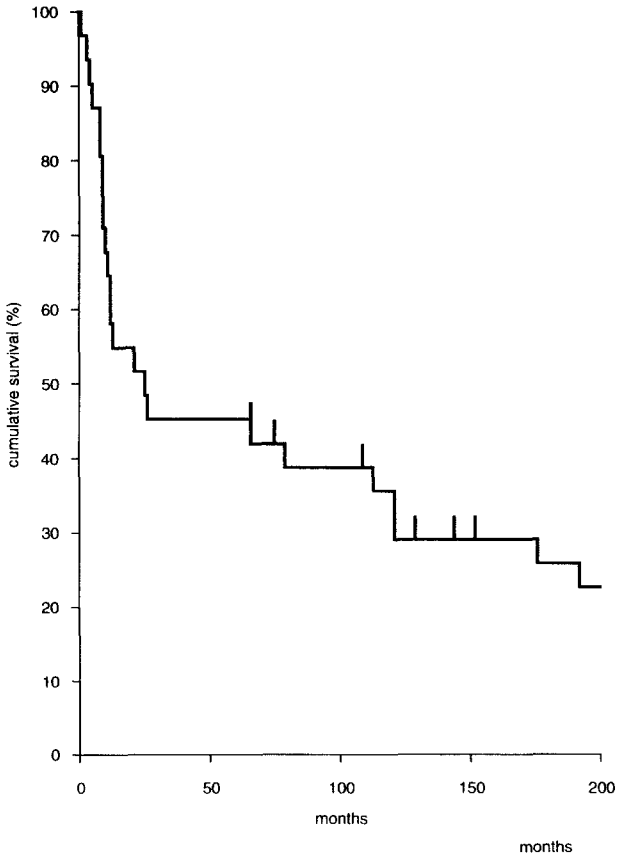

Fig 1. Survival of 31 patients with stage III or IV thymoma after incomplete surgery and radiation therapy to the mediastinum.

patients ($P = .0005$ by log-rank test; $P = .05$ by multivariate analysis).

Patients with stage IVa and IVb disease had the same prognosis. Subset analysis of patients with stage III disease involving infiltration of the lung compared with those without such infiltration did not show any difference in outcome. Two of six patients with stage IVb disease whose metastases were resectable had disease-free survival durations of 65 and 120 months.

Fifteen patients had a recurrence (48%). Twelve patients had failure of intrathoracic tumor control; among these, eight suffered from local mediastinal treatment failure (26%). Tumor progression led to death within 27 months in 13 of 15 patients (87%). One patient had an apparent pleural recurrence 10 years after mediastinal irradiation, and another developed liver metastasis 9 years after treatment. Seven of 15 patients (47%) had extrathoracic tumor progression: to the liver (n = 4), kidney (n = 4), adrenals (n = 2), retroperitoneal lymph nodes (n = 1), and bone (n = 1). Extrathoracic metastases were the cause of death in three patients (20%) with progressive thymomas: renal insufficiency in two patients, and hepatic insufficiency in one patient. Mediastinal control was achieved in 23 of 31 patients (74%). Local recurrence or local tumor progression was not influenced by the amount of surgery (tumor debulking *v* biopsy) or by the stage of the thymoma. On the other hand, epithelial predominant-type histology (including spindle-cell thymomas) appeared to predispose for local recurrence compared with thymomas of other histologic types. Six of 13 (46%) epithelial thymomas showed mediastinal tumor progression, compared with two of 18 (11%) thymomas with other histologies ($P = .055$ by multivariate analysis; Table 3).

Epithelial-predominant thymoma (including spindle-cell thymoma) correlated with stage IV disease; nine of 13 patients (69%) with this type of thymoma presented with stage IV disease, whereas only four of 18 patients (22%) with nonepithelial thymomas presented with stage IV disease ($P = .05$ by multivariate analysis).

Surgical resection in the patients reviewed in this study did not include any option of artificial vascular grafting and angioplasty to achieve complete resection. Surgery was therefore minor (biopsy only) in 16 patients and subtotal (tumor debulking) in 15 patients. Both groups yielded similar results in respect to survival and local tumor control.

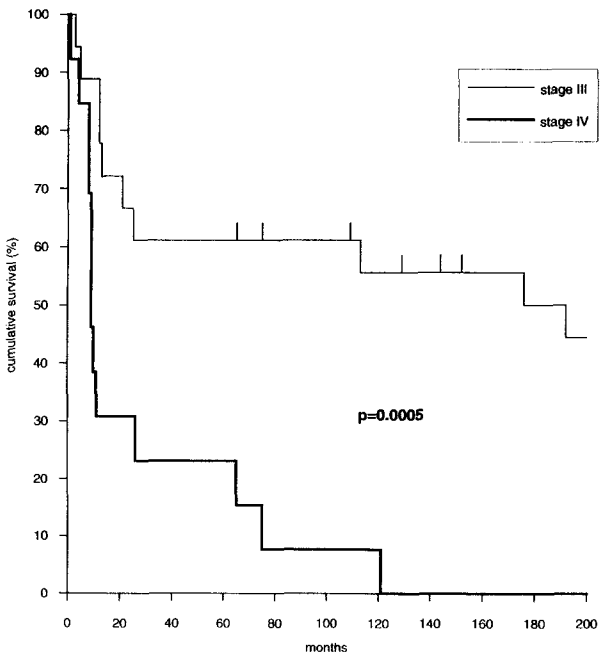

Fig 2. Survival of patients with stage III *v* stage IV disease.

Table 3. Correlation of Histology With Progression of Thymoma

Histologic Type	Tumor Progression	P*	Local Recurrence	P*
Epithelial v lymphocytic	66.7% (6/9) v 42.9% (3/7)	.3	44.4% (4/9) v 14.3% (1/7)	.2
Epithelial v mixed	66.7% (6/9) v 33.3% (2/6)	.2	44.4% (4/9) v 0% (0/6)	.06
Epithelial v all other histologic types	66.7% (6/9) v 40.9% (9/22)	.2	44.4% (4/9) v 18.2% (4/22)	.1
Spindle-cell v lymphocytic	75.0% (3/4) v 42.9% (3/7)	.3	50.0% (2/4) v 14.3% (1/7)	.2
Spindle-cell v mixed	75.0% (3/4) v 33.3% (2/6)	.2	50.0% (2/4) v 0% (0/6)	.05
Spindle-cell v epithelial	75.0% (3/4) v 66.7% (6/9)	.8	50.0% (2/4) v 44.4% (4/9)	.9
Spindle-cell and epithelial v all other histological types	69.2% (9/13) v 33.3% (6/18)	.048	46.2% (6/13) v 11.1% (2/18)	.043†/0.055‡

*χ^2 analysis.
†Confirmed by Fisher's exact 2-tailed test.
‡Multiple regression analysis.

Radiotherapy with ≥ 60 Gy was applied in 23 cases. Complications were observed in three patients (13%). One of these patients had constrictive pericarditis and pulmonary fibrosis and died 9 months after radiotherapy; another died 66 months after thoracic irradiation with constrictive pericarditis, and the third patient died 10 years after irradiation with chronic radiation-induced myelitis. All three received 60 Gy to the anterior mediastinum. Although numbers are to small for statistical analysis, no such complications have been observed in patients treated with less than 60 Gy.

Irradiation of supraclavicular lymph nodes was performed in 10 patients, seven with stage III disease. No correlation with local control or survival could be established. Sources of radiation used were documented for 31 patients. We did not observe any association of either Betatron, Telecobalt, or 6-MeV Linac machines with an increased risk of local failure.

On diagnosis, a tumor diameter greater than 10 cm correlated with worse prognosis than smaller thymomas by univariate analysis. The median 5-year survival rate for patients with large thymomas was 30%, versus 52% for patients with smaller thymomas ($P = .05$).

Duration of symptoms before diagnosis, as well as associated myasthenia gravis, did not influence disease outcome.

DISCUSSION

Noninvasive or microscopically invasive thymomas presenting in stage I or II, as well as most stage III thymomas,[18] are completely resectable and recurrence remains uncommon after surgery alone. Reoperation of recurrent thymoma yields complete resection and favorable outcome in some cases and remains the first treatment option.[3,14,21,22] Advanced thymomas with infiltrating neighboring organs, pericardial or pleural dissemination, or lymphogenous or hematogenous metastasis are subject to more complex management, which remains controversial.[4,12,13,17,23,24] The role of surgery and radiotherapy alone in such advanced cases has been reviewed in only a few studies. Most of these include patients with completely resected thymomas.[4-6,11,18,19,25-31] Jackson and Ball[7] reported 28 incompletely resected and irradiated thymomas with an overall survival rate of 53% at 5 years, which is slightly higher than the 5-year survival rate of 45% in the current study. The 5-year survival rate of 61% for patients with stage III disease in the present series is on the high side of the expected range, which can be calculated according to the data in Table 4 to be between 50% and 60%. In most references in Table 4, survival rates have been based on series that include completely resected thymomas.

For stage IV disease, it is more difficult to give an appropriate 5-year survival rate, but a rate greater than 35% seems optimistic.[3,29,32] In the current literature, stage III has only rarely been found to have a better prognosis compared with stage IV thymomas, which is clearly the case in our study.[5,6,32] Urgesi et al[29] observed a significantly worse prognosis in patients with stage IVa compared with stage III disease.

An interesting finding in this study was that the prognosis of patients with stage IVa thymomas did not differ from the prognosis of patients with IVb thymomas. This might be explained by the fact that patients with resectable metastatic tumor to the supraclavicular nodes or to the pulmonary lobes received treatment with complete resection of metastasis. One patient, not included in the present series, received preoperative radiation to the mediastinum and supraclavicular lymph nodes, which harbored metastatic thymoma. Complete resection was performed later, and the patient is alive and disease-free for longer than 10 years. Therefore, neoadjuvant treatment

Table 4. 5-Year Survival Rates for Patients With Stage III and IV Thymomas

First Author	Survival Rate (%)		Comment
	Stage III	Stage IV	
Bergh[26]	41		43 patients, 39 patients with complete resection, 28 patients with postoperative RT; survival rate includes all invasive thymomas
Masoaka[18]	70	50	31 patients in stage III and 10 in stage IV; 96 patients, 47 patients with complete resection, 62 patients with postoperative RT
Verley[8]	50 (II-IV)		67 patients with invasive thymoma, 21 patients with complete resection; all invasive thymomas received RT; rate includes all invasive thymomas
Lewis[30]	50 (II-IV)		47 patients with partial resection or biopsy, 39 of these received RT. 227 patients with complete resection; rate includes all invasive thymomas
Nakahara[11]	100		35 patients after complete resection and postoperative RT
Krüger[44]	57		13 patients, 1 with complete resection, subtotal in 7 patients and biopsy in 4 patients, all with postoperative RT
Curran[4]	53		36 patients with stage III, 7 patients with complete resection; 28 of 60 patients with invasive thymoma received RT. Relapse-free survival rate indicated
Arakawa[19]	72 (II-IV)		30 patients with invasive thymoma, 15 patients with complete resection, all with postoperative RT
Pescarmona[32]	54	63	26 patients in stage III and 8 patients in stage IV; all operated, RT?, amount of resection?
Urgesi[29]	68	50	59 patients with stage III, 33 with complete resection, all with postoperative radiotherapy; 18 patients with stage IV, all with incomplete resection and RT
Jackson[7]	53 (III-IV)		28 patients with incompletely resected irradiated invasive thymomas
Maggi[3]	71	59	241 patients, 30 patients with incomplete resection; 53 patients in stage III, 21 patients in stage IVa, 28 patients with postoperative RT
Wilkins[44]	58		85 patients with stage I-III, 14 with stage III, 81 with complete resection. 12 patients with stage III received RT. No CXT for stage III
Wang[5]	67	37 (IVa), 24 (IVb)	41 patients in stage III, 8 patients in stage IVa, and 4 patients in stage IVb. 55.7% of 61 study patients received postoperative RT
Pollack[6]	50	29	10 patients in stage III (4 with postoperative RT, and 4 with postoperative RT and CXT), 29 patients in stage IVa (one with RT, 4 with CXT, and 2 with RT and CXT); complete resection in 21 of 36 patients
Shimizu[12]	47		57 patients with invasive tumors, 87.5% of patients with complete resection; RT?
Present series	61	23	32 patients, none completely resected, all irradiated

Abbreviations: RT, radiation therapy; CXT, chemotherapy.

with radiation or chemotherapy or more aggressive surgical methods, as well as combined modality treatment, might be more appropriate to achieve intrathoracic tumor control in stage IVa thymoma.

Complete resection, if surgically possible, has been associated with better local control and longer survival.[3,4] On the other hand, tumor debulking did not improve survival in this study. This is consistent with other works and supports the view that only macroscopically complete tumor reduction influences prognosis.[4,5,7,22,29,33,34] On the other hand, some investigators observed an influence of tumor reduction on survival.[3,6,18] It remains to be shown whether debulking allows the radiation oncologist to decrease the size of the field and thus help to reduce the risk of radiation-induced long-term side effects. Others have suggested the use of vascular grafting and angioplasty to achieve complete resection. Shimizu et al[12] reported 10 of 20 patients (50%) being cured, while four (20%) died during the early postoperative period. In respect to survival and acute complications, it remains to be shown whether large surgical approaches will be of benefit in the long term, and whether salvage treatment remains possible.

Tumor diameter might be linked to resectability and thus influence prognosis. Lewis et al[30] reported a worse prognosis for thymomas with a diameter greater than 15 cm. In this study, univariate analysis suggested an association with worsening prognosis for patients with a thymoma with a diameter greater than 10 cm at diagnosis. This finding is in contrast to the observation of Wang et al,[5] who reported similar survival rates for patients with thymomas with a diameter of greater than or less than 10 cm.

Associated syndromes, such as myasthenia gravis and anemia, were not registered frequently enough for statistical analysis. Only 13% of our patients presented with myasthenia gravis, which is a lower prevalence than expected. Although Pollack et al[6] reported 5.6% of patients with thymoma suffering from myasthenia gravis, prevalence rates of 30% to 59% are more common.[3,7,10,18,29,32] Some investigators have suggested an adverse effect of associated syndromes[4,30,35]; however, more recently, my-

asthenia gravis has been suggested not to worsen prognosis significantly.[5,8,18,29,32]

Histologic classification as reported by Rosai and Levine[1] has not been shown to correlate with the malignant potential of thymomas in several studies, and its impact on prognosis is generally believed to be of little importance.[4,5,18,24,26,29,35] Others suggested epithelial-type thymomas to predispose for more malignant thymomas.[8,30] Shimizu et al[12] reported a significantly worse prognosis for epithelial thymomas if surgery was incomplete; however, in case of complete resection, histologic type did not influence survival. Monden et al[10] observed a recurrence rate of 29% in epithelial thymomas compared with 14% in lymphocytic thymomas. Wang et al[5] noted a shorter survival time for spindle-cell tumors compared with other tumors. Our results support the view that epithelial and spindle-cell thymomas are more aggressive than lymphocytic or mixed-cell thymomas. Others have noted a more favorable outcome for spindle-cell thymomas or a worse prognosis for mixed thymomas.[3,6,18,27] As recent histologic typing[35] is more frequently performed according to the classification reported by Marino and Müeller-Hermelink,[36] several investigators have linked cortical thymomas to invasiveness.[31,37-39] It is our belief that this new classification allows the identification of potentially aggressive encapsulated tumors, and it might influence decision making for adjuvant postoperative radiotherapy in completely resected thymomas. Histologic differentiation among epithelial, spindle-cell, mixed, and lymphocytic thymomas should be maintained, as it provides relevant prognostic information in advanced, incompletely resected thymomas.

Radiation therapy resulted in local control in 74% of patients in the present series, despite macroscopic residual disease in all patients. Marks et al[40] reported local control in six patients after incomplete resection. Urgesi et al[29] reported local control in 90% of patients.[29] In the series reported by Curran et al,[4] 16 of 20 patients (80%) with incomplete resection experienced local control after radiotherapy. Jackson and Ball[7] reported that 18% of patients died of local failure. Wagner et al[41] showed local control in six of 10 cases (60%), and local control rates of 60% after biopsy or partial resection have been reported by Kersh et al[42] as well.

Total radiation doses of 40 to 50 Gy have been suggested to be optimal, but local treatment failure after higher doses is well known.[4,7,9,41] We did not observe any improved local tumor control with doses $\geq$ 60 Gy; on the contrary, three patients with radiation sequelae were treated with 60 Gy. Although this finding is not statistically significant, it suggests that irradiation with doses $\geq$ 60 Gy should be avoided, as there is no evidence for better mediastinal control, but there is an increased risk of radiation-induced injury.[42,43]

Radiotherapy remains a strong tool in the treatment of residual thymomas after surgery, and prospective investigations are needed to determine optimal multimodality treatment in infiltrating thymomas.

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