Surgical Treatment and Prognosis of Primitive Neuroectodermal Tumors of the Thorax

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Introduction: Primitive neuroectodermal tumors (PNETs) are rare, rapidly progressive, small- round cell tumors with a poor prognosis despite multimodal therapy, including surgery and chemoradiotherapy. The treatment of choice was unknown since no clinical series with surgical therapy had been reported. We evaluated the impact of multimodal treatment in patients with PNETs located in the thoracic region.

Methods: Between 1998 and 2006, 25 patients with PNETs in the thoracic region were treated in 3 tertiary-care hospitals. The patients consisted of 15 males and 10 females with a mean age of 27.2 years (range, 6–60). The tumor was in the chest wall in 20 (involving the costovertebral junction in 9), the lung in four, and the heart in one patient. Twelve patients received neoadjuvant chemotherapy (54.5%), and 22 of 25 patients underwent surgery.

Results: In patients who received neoadjuvant treatment, the mean regression rate was 65.4% (range, 30–100%). Eighteen (82%) patients underwent chest wall resection, while 7 (32%) had vertebral resections, and the remaining 4 (16%) had pulmonary resections. A complete resection was possible in 18 of 22 patients (82%). Patients with incomplete and complete resections had 25% and 56% 5-year survival rates, respectively ($p = 0.13$). The progression-free 3-year survival rate was 36% and the median survival time was 13 months. The complete resection rate was significantly higher in patients receiving neoadjuvant therapy ($p = 0.027$). The 5-year survival rate of the patients with or without neoadjuvant therapy was 77% and 37%, respectively ($p = 0.22$) although it prolonged the disease-free survival ($p = 0.01$). The 5-year survival rate of patients without costovertebral junction involvement was 66%, whereas patients with PNETs involving the costovertebral junction had a 21% 3-year survival. The difference was statistically significant ($p = 0.01$). The 5-year progression-free survival rate of patients without costovertebral junction involvement was 58%, whereas patients with PNETs involving the costovertebral junction had a 14% 1-year progression-free survival ($p = 0.004$).

Conclusions: PNET is an aggressive malignancy that often requires multimodal therapy. Induction chemotherapy leads to a greater complete resection rate and better disease-free survival, while involvement of the costovertebral junction indicates a poorer survival.

Key Words: PNET, Chest, Multimodal therapy and lung.

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Primitive neuroectodermal tumors (PNETs), from malignant small round cell tumors that also include Ewing sarcoma (ES), rhabdomyosarcoma, neuroblastoma, and lymphoma,[1,2] were first described by Askin et al.[3] These tumors have a very high rate of local recurrence and a propensity to metastasis[4] and despite combined chemoradiotherapy plus surgery, the prognosis is generally poor.[5] Complete resection with adequate margins is the goal, but too few series of patients and survival have been reported to evaluate the role of surgical therapy in this entity.

We report the outcome and survival of patients with PNETs who had neoadjuvant chemoradiotherapy or surgery alone to determine the role of neoadjuvant therapy.

PATIENTS AND METHODS

Between 1998 and 2006, 25 patients with PNETs located in the thoracic region were treated in three institutions. Twenty-two of the 25 patients underwent surgery. The patients comprised 15 males and 10 females with a mean age of 27.2 years (range, 6–60). Three patients (12%) underwent chemotherapy only without surgical intervention: one patient had complete regression with induction chemotherapy (Figure 1), one patient refused the planned surgery, and intracardiac involvement precluded surgical resection in one patient. The remaining 22 patients (88%) underwent surgical resections that included thoracotomy, chest wall resection, and pulmonary resection when needed (Table 1). Patients were analyzed retrospectively; since this is a retrospective study, approval of the institutional review boards was not required.

The preoperative workup included routine biochemical tests, an electrocardiogram, basic pulmonary function tests, a chest radiograph, and thorax computerized tomography; two

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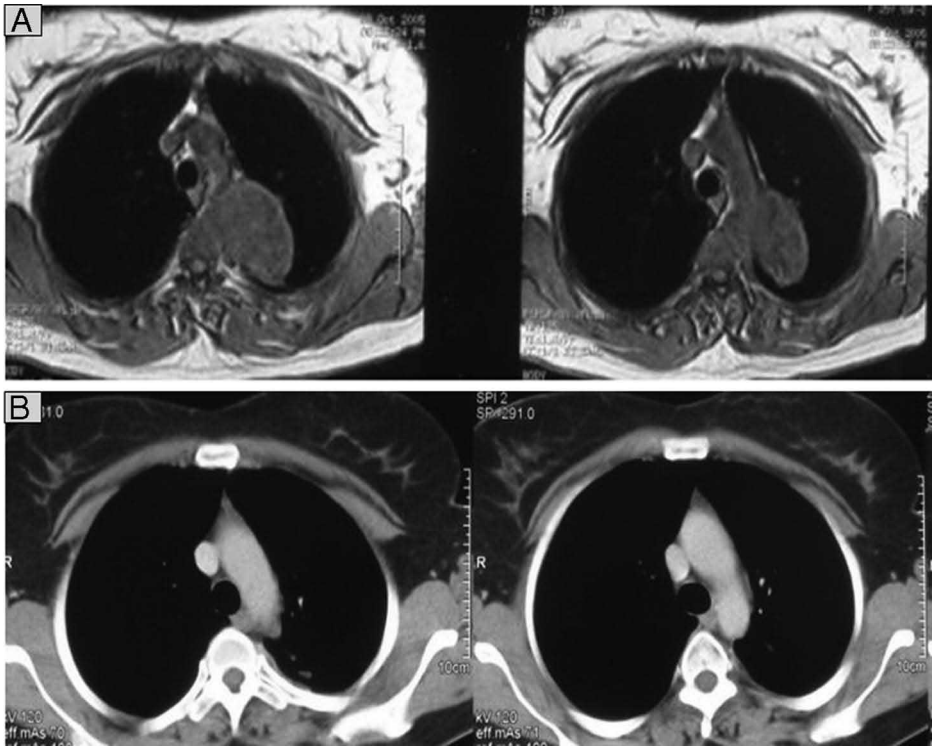

FIGURE 1. *A,* Chest magnetic resonance image of a patient showing a thoracic mass that was confirmed to be a PNET (primitive neuroectodermal tumor). *B,* Chest computerized tomography image of the same patient taken after neoadjuvant chemotherapy showing total regression.

had magnetic resonance imaging of the chest. A fiberoptic bronchoscopy was performed in most patients. The histopathologic diagnosis was made via a percutaneous needle aspiration or Tru-cut biopsy in 9 patients and an incisional biopsy in 6 patients. In 10 patients, the definitive tissue diagnosis was obtained at the thoracotomy despite all of the preoperative diagnostic procedures.

The characteristics of the patients are shown in Table 1. The primary site was the thoracic wall in 20 patients (80%), among whom the tumor involved the costovertebral junction in 9 (36%). The primary site was the lung in 4 (16%), and the heart in 1 (4%). The mean diameter of the tumors was 10.2 cm (range, 1–20). None of the patients had extrathoracic metastases.

In general, most of the patients who were known to have PNETs before surgery were referred for neoadjuvant therapy. Since the study was a retrospective multicenter study, a small number of patients who were thought to have a high likelihood of undergoing a complete resection underwent surgical intervention directly. Twelve patients (60%) completed the neoadjuvant therapy. The planned courses of chemotherapy consisted of vincristine 1.4 mg/m^2 of body-surface area (maximum dose 2 mg), actinomycin D 1.5 mg/m^2 per dose(substituted for doxorubicin when the total doxorubicin dose of 375 mg/m^2 was reached), and cyclophosphamide 1200–1800 mg/m^2, followed by mesna, given to prevent hemorrhagic cystitis caused by cyclophosphamide. The therapy included four to eight courses and was administered every third week. The response rate was evaluated after the fourth course. If the tumor did not respond to chemotherapy, the patients received radiotherapy and were operated on after the sixth course. The alternate therapy included iphosphamide 1800 mg/m^2, mesna 1800 mg/m^2, and etoposide 100 mg/m^2.

A chest wall resection was performed in patients with thoracic wall involvement. The resection was extended to remove all of the involved chest wall structures (i.e., muscles and fibrous tissue) when needed. The nondiseased ribs above and below the site were also resected. Macroscopically, a 3-cm tumor-free margin lateral to the tumor was obtained which, however, was impossible in patients with tumors invading the costovertebral junction. In these patients, the goal was simply a negative surgical margin. To reconstruct the chest wall, a synthetic mesh was used if the amount of chest wall resected was large, or the site was anterior or lateral.

Postoperatively, all tumors were confirmed pathologically to be PNETs. On pathologic examination of the biopsy material, sheets of primitive round cells and Homer—Wright rosettes were the principal microscopic features. Immunohistochemically, the tumor cells were intensely positive for neuron-specific enolase and the MIC-2 gene product (CD-99) and were consistently negative for leukocyte common antigen (CD-45), cytokeratin, smooth muscle actin, and beta human chorionic gonadotropin. A balanced reciprocal translocation, t(11;22) (q24;q12), was seen on chromosome analysis of the tumor cells in the sample of patients with cardiac PNETs.

Adjuvant chemotherapy was administered in 16 patients. Postoperative adjuvant therapy could not be administered in 6 of the 22 surgical patients (27.2%) because of poor performance status. The mean follow-up was 32 ± 28 months (range, 3–108).

TABLE 1. Clinical and Pathological Characteristics of 25 Patients

Patient No.	Sex	Age	Localization	Size (cm)	Neoadjuvant Therapy	Response Rate (radiologic) %	Operation	Margins	Adjuvant Therapy (or consolidation)	Local Recurrence Time (mo)	First Distant Metastasis Time (mo)	Treatment for Recurrence or Metastasis	Disease Free Period (mo)	Survival Time (mo)	Alive/Dead
1	M	6	TW	7	CT	80	TWR	NEG	RT	—	—	—	20	20	A
2	M	19	TW	4	—	NA	TWR	POS	CRT	—		—	100	100	A
3	F	18	TW	8	CT	80	TWR	NEG	CT	—	—	—	64	64	A
4	M	22	TW	6	CRT	95	TWR	NEG	CT	18	6	CRT	6	28	D
5	M	25	TW	7	—	NA	TWR	NEG	—	—	—	—	14	34	A
6	F	14	TW	8	CT	ND	TWR	NEG	CT	—	—	—	32	32	A
7	M	39	TW	14	—	NA	TWR	NEG	CT	3	—	TWR + CRT	3	44	D
8	M	38	TW	1	—	NA	TWR	NEG	CT	11	—	TWR + CRT	11	108	A
9	M	26	TW	20	CT	40	TWR	NEG	CRT	—	30	—	30	36	A
10	M	32	TW	7	CRT	30	TWR	NEG	—	33	—	TWR	33	33	A
11	M	21	TW	12	CRT	40	TWR	NEG	—	—	—	—	19	19	A
12	M	18	TW + CVJ	7	CT	85	TWR + LWR	NEG	CT	—	—	—	12	12	A
13	M	16	TW + CVJ	19	—	NA	TWR + Vertebra resection	NEG	—	6	—	CT	6	83	A
14	M	17	TW + CVJ	9	—	NA	TWR + Laminectomy	POS	CT	0	20	Cranial metastasectomy	0	36	D
15	F	11	TW + CVJ	7	CRT	60	TWR + Tumor excision (en bloc)	NEG	—	2	—	TW + LWR + CRT	2	4	D
16	F	47	TW + CVJ	10	—	NA	TWR + Laminectomy	NEG	CT	2	—	CT	2	6	D
17	F	31	TW + CVJ	20	—	NA	TWR + Tumor excision (en bloc)	POS	CRT	0	6	—	0	7	D
18	F	60	TW + CVJ	10	—	NA	TWR + Tumor excision (en bloc)	POS	—	0	—	—	0	3	D
19	F	38	TW + CVJ	25	—	NA	NO	NO	CRT	NA	3	—	NA	6	D
20	F	25	TW + CVJ	8	CRT	100	NO	NO	CRT	NA	—	—	NA	28	A
21	F	22	Lung	13	CT	35	Lobectomy	NEG	CRT	18	—	CRT	18	32	A
22	M	22	Lung	5	—	NA	Lobectomy	NEG	CRT	—	13	RT	13	18	D
23	F	28	Lung	11	—	NA	Lobectomy	NEG	CRT	3	—	CRT	3	15	A
24	M	47	Lung	5	CT	40	Lobectomy + TWR	NEG	CT	—	—	—	34	34	A
25	M	31	Heart	11	—	NA	NO	NO	CRT	NA		—	NA	17	D

M, male; F, female; TW, thoracic wall; TW + CVJ, thoracic wall with costovertebral junction involvement; CT, chemotherapy; CRT, chemoradiotherapy; RT, radiation therapy; TWR, tumor resection with thoracic wall; LWR, lung wedge resection; NEG, negative; POS, positive; D, died; A, alive; NA, not applicable; ND, not determined; NO, not operated on.

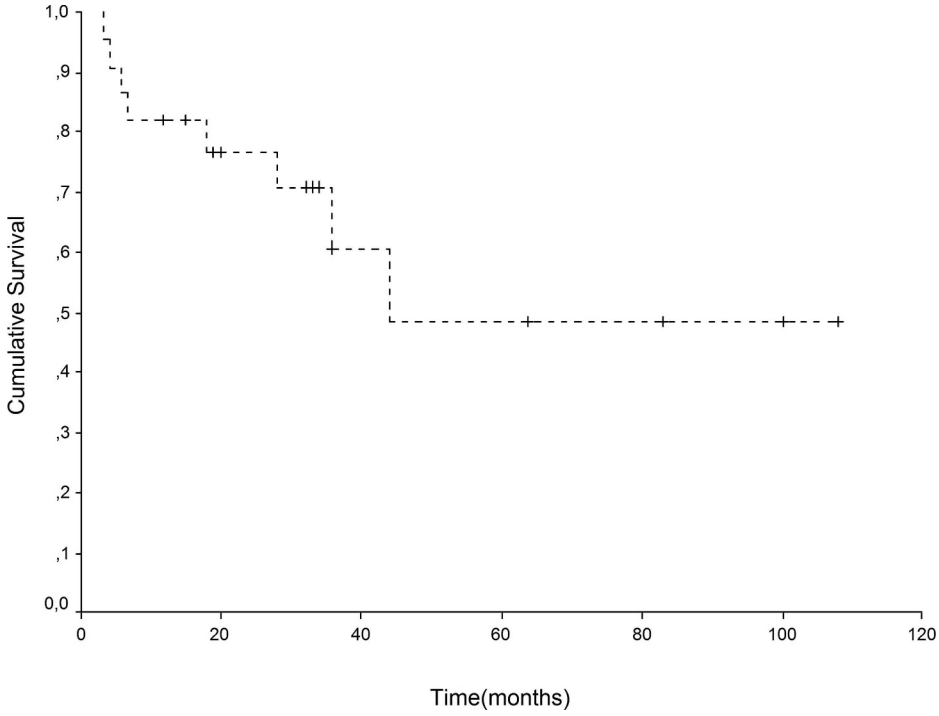

FIGURE 2. Overall survival curve of the patients who underwent surgical resection only.

Statistical Analysis

To compare frequencies, the χ^2 and Fisher exact tests were used. The survival analysis was performed only in the patients who had undergone surgical resection. Patient survival was expressed applying the Kaplan-Meier method using the thoracotomy time as time zero and time of death, if it occurred, as the end point. Differences in survival were determined using the log-rank test. The factors affecting survival were determined and the results were considered significant when $p < 0.05$.

RESULTS

All tumors in the patients given induction chemotherapy or radiotherapy responded. A complete radiologic regression (i.e., no lesion seen on computerized tomography) occurred in 2 patients (8%), whereas, the mean regression rate was 65.4% (range, 30–100; Table 1).

A lobectomy was performed in 4 patients (16%; with an additional chest wall resection in one patient), and a chest wall resection was performed in the other 18 (84%) patients. Of these patients, the tumor involved the costovertebral junction in seven, and a laminectomy ($n = 2$; 8%) or a vertebral body resection ($n = 1$; 4%) was performed in 3 of them. A complete resection was achieved in 18 of the 22 surgical patients (82%). Of the remaining four patients, the tumor originated from the costovertebral junction in three and the chest wall not close to the costovertebral junction in one. No early (first 30 days) or late (first 60 days) mortality occurred postoperatively.

Local recurrence or distant metastasis developed in 14 of the 22 surgical patients (64%). Treatment modalities which had been performed to these patients could be seen in Table 1.

Eighteen of 22 patients (82%) who underwent surgical resection were reported as having complete resections. The rate of complete resection was 100% and 64% in patients who received induction chemotherapy followed by surgery and surgery alone respectively. Induction chemotherapy had a higher rate of complete resection ($p = 0.027$).

The overall 5-year survival rate in the surgically resected PNETs patients was 48% and the median survival time was 44 months (Figure 2). Patients who had incomplete or complete resection had 25% and 56% 5-year survival rates, respectively ($p = 0.13$). The mean survival time in patients with incomplete resection was 7 months. The progression-free 3-year survival rate in the surgically resected PNETs patients was 36% and the median survival time was 13 months (Figure 3).

The estimated median survival time and 5-year survival rate for patients with chest-wall tumors was 44 months and 48%, respectively. The 5-year survival rate of patients without costovertebral junction involvement was 66%, whereas patients with PNETs involving the costovertebral junction had a 21% 3-year survival (median survival time was 7 months, Figure 4). The difference was statistically significant ($p = 0.01$). Patients with costovertebral junction involvement had nearly the same survival than the pulmonary PNET patients (3-year survival 36%; $p = 0.23$, Figure 4). The 5-year progression-free survival rate of patients without costovertebral junction involvement was 58%, whereas patients with PNETs involving the costovertebral junction had a 14% 1-year progression-free survival ($p = 0.004$). Patients with costovertebral junction involvement had a worse disease-free survival than the pulmonary PNET patients (2-year survival 25%; $p = 0.3$).

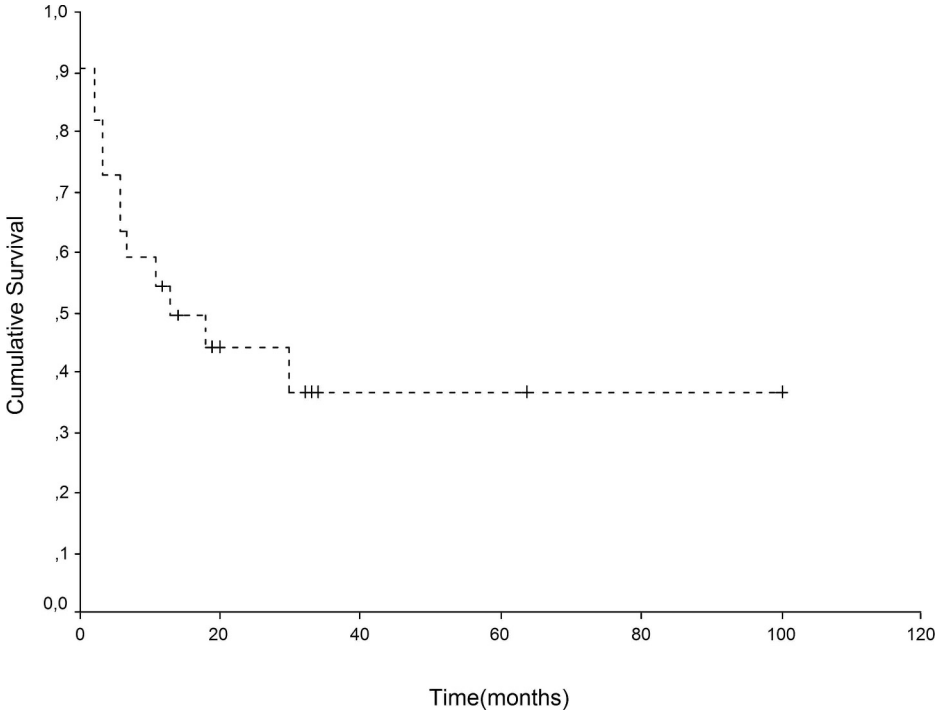

FIGURE 3. Disease -free survival curve of the patients who underwent surgical resection only.

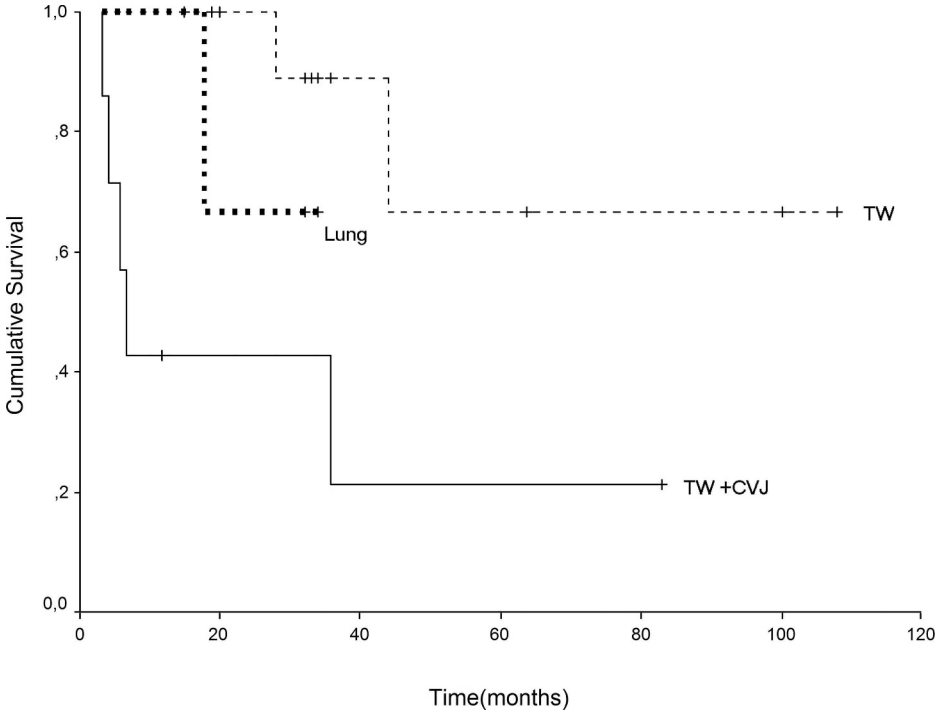

FIGURE 4. Survival curves based on tumor location. TW, Thoracic wall; TW + CVJ, Thoracic wall with costovertebral junction involvement.

The 5-year survival rate of the patients with or without neoadjuvant therapy was 77% and 37%, respectively (p = 0.22; Figure 5). The rate of locoregional recurrence and metastasis was lower in the patients receiving neoadjuvant chemoradiotherapy and surgery. However, the difference was not significant (p = 0.08). Neoadjuvant therapy seemed to prolong the disease-free survival (p = 0.01; Figure 6). When analyzing the patients with complete resections, the 1-year disease-free survival rate was 28% in patients who did not receive neoadjuvant therapy, whereas the 5-year disease-free survival was 57% in patients who did receive neoadjuvant therapy (p = 0.006).

Adjuvant therapy conferred no survival benefit (p = 0.4). When we analyzed the patients who underwent com-

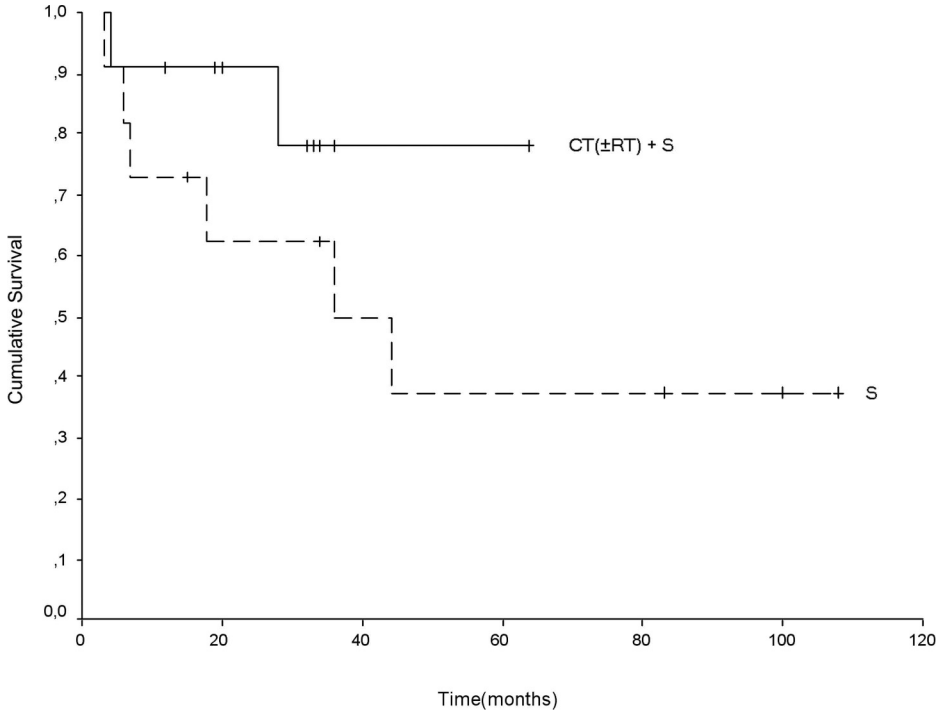

FIGURE 5. Patient survival according to the method of control: chemotherapy (±radiotherapy) and surgery (CT(±RT)+S) versus surgery (S) alone.

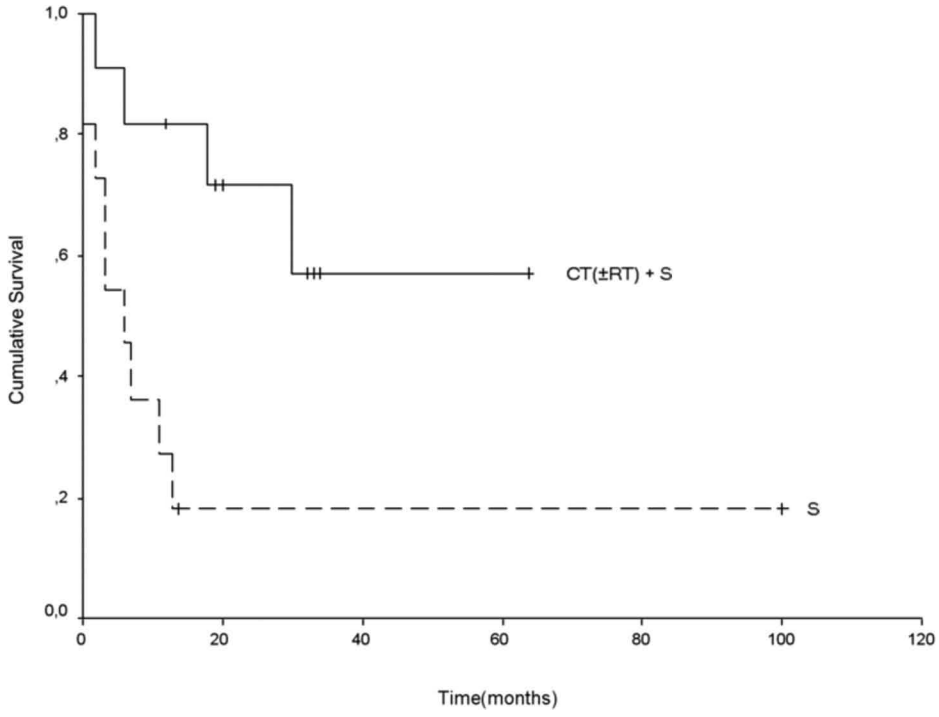

FIGURE 6. Disease-free survival of patients according to the method of control: chemotherapy (±radiotherapy) and surgery (CT(±RT)+S) versus surgery (S) alone.

plete resection (R0), adjuvant therapy showed no beneficial effect ($p = 0.7$). Age, sex, and site of tumor were of no importance in terms of survival.

DISCUSSION

PNETs are small round cell malign neoplasms of neuroectodermal origin. Malignant small round cell tumors also include rhabdomyosarcomas, neuroblastomas, and lymphomas.[1,2] The combination of a shared chromosomal translocation (t[11;22] [q24;q12]), cellular physiology, and clinical response has led to categorizing PNETs in the Ewing sarcoma family of tumors. These tumors often involve the thoracic wall, and primary pulmonary and cardiac involvement is quite rare.[1] PNETs can be differ-

entiated by characterizing the neural ultrastructure (e.g., neurosecretory granules, neurofilaments, and neurotubules) on electron microscopy or the mmunohistochemical expression of at least four neural markers, including CD-99, NB-84, NSE, S-100, desmin, myogenin-MyoD1, CK, and LCA.[1,2,6,7] Approximately 90–95% of ES/PNET are characterized by rearrangements of the EWS gene on 22q12 and ETS-related oncogenes, most commonly FLI1 on 11q24.[1]

Many of the larger studies on PNETs have suggested that these tumors are highly aggressive neoplasms that rapidly give rise to metastatic disease and death.[1,8] The effect of surgery in the treatment of this disease is controversial. As seen in our series, despite complete resection and adjuvant chemotherapy, the patients usually developed locoregional and distant metastases.[2,4,8,9] In our study, only four patients were disease-free after multimodal treatment. In contrast, 3 of the 11 patients with chest wall involvement had recurrences (27.3%) despite all efforts to achieve a wide surgical resection margin, as described by others.[10,11] Grier et al.[11] reported that 142 of 371 patients with a PNET or Ewing sarcoma relapsed.

PNETs usually respond to chemotherapy,[4,8–12] and patients undergoing definitive surgery after initial chemotherapy have more successful complete resections of the tumor.[10] In our series, neoadjuvant chemotherapy resulted in significantly more complete resections. This finding has never been reported for a series of isolated thoracic PNETs. In our study, the patients with incomplete resections had very limited survival and the patients who survived for a long time were those who had wide tumor-free margins. Shamberger et al.[10] concurred with this finding. Chemotherapy leads to tumor shrinkage, which in turn allows operability with wide tumor-free margins. In the Mayo Clinic experience, as analyzed by King et al.[6] the 5-year recurrence-free rate was 56% for patients resected with a 4-cm margin compared with 29% for those resected with a 2-cm margin. We did not analyze the length of the disease-free margins, although we tried to maintain at least 3 cm laterally, or one nondiseased rib vertically, as the surgical margin when possible. Note that complete resection of tumors involving the costovertebral junction is technically demanding, despite neoadjuvant therapy, due to the neighbouring vertebral body. In our series, the tumors invaded the costovertebral junction in 9 patients (36%). Of these, seven patients had surgical resections: two patients underwent laminectomy, one required vertebral resection, and four had complete resections. The resections were incomplete (R1) in three patients. Nevertheless, three of the four patients with complete resections (75%) developed locoregional recurrence. In these patients, resection with wide resection margins was impossible because of the site. In our survival analysis, costovertebral junction involvement was a significant prognostic factor. Some adjuvant radiotherapy modifications, such as brachytherapy or the CyberKnife, could be beneficial in these patients. These modalities have been shown to be effective in the treatment of PNETs, different tumors of the spine, lung cancer or tumors in other parts of the body.[13–15]

In addition, whether "adjuvant" surgical resection following chemotherapy confers better survival is not certain.[10,12] This uncertainty exists partly because almost all case reports are for thoracic PNETs. In our series, neoadjuvant therapy followed by the widest possible resection resulted in less recurrence and longer survival. This conclusion has been supported by some other studies.[8,11]

In addition, we found that, neoadjuvant treatment resulted in a significantly better recurrence-free survival. For these reasons, we recommend that all patients with thoracic PNETs receive neoadjuvant treatment before planned surgery. In our series, the mean regression rate was 65.4% (range, 30–100). Given this response rate, we speculate that a higher dose, shorter duration of chemotherapy, and more chemotherapy courses could result in a higher response rate and longer survival in these patients.

Primary lung PNETs without pleural or chest involvement is extremely rare. We had four such patients. In patients with pulmonary PNETs, achieving complete resection is difficult because of probable inoculation metastases and visceral pleural invasion. The mean 2-year event-free survival rate was 25% in these patients.

This study has certain limitations. First, despite all our efforts and the multicenter nature of the study, the number of patients was small, precluding subgroup analysis. Second, we were not able to document the details of adjuvant radiotherapy. In addition, varying neoadjuvant approaches complicated the outcome assessment. For this reason, we also could not evaluate the value of additional neoadjuvant radiotherapy in our patients.

In conclusion, patients undergoing definitive surgery after initial chemotherapy had a higher success frequency of complete thoracic PNET resections and better disease-free survival. Patients who underwent the widest possible resection survived longer, and had fewer metastases and locoregional recurrence. Incomplete resection was found to be futile. Patients with a tumor invading a vertebra (i.e., the costovertebral junction) had a discouraging prognosis despite extended resection. However, even with multimodal therapy, patients with thoracic PNETs had an unsatisfactory survival and high recurrence rates. Further studies are warranted to define the ideal management.

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