Treatment outcomes in 23 thoracic primitive neuroectodermal tumours: a retrospective study

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Abstract

OBJECTIVES: Thoracic primitive neuroectodermal tumour is an aggressive malignancy with poor survival despite multimodality treatment regimens. Early diagnosis of the tumour by histological, immunohistochemical, ultrastructural and cytogenetic techniques and early total surgical resection of the tumour with intensive chemoradiation may improve outcomes.

METHODS: Over 30 years, 23 patients (median age 29.5) with primitive neuroectodermal tumours (15 chest wall, 4 lung, 3 costovertebral sulcus and 1 anterior mediastinum) were diagnosed by transthoracic needle biopsy (43%) or excisional biopsy (57%). Treatment of a localized disease (Stage I and II) in 19 patients included surgery (wide excision of chest lesions in 11, 4 lung resections, excision of 3 costovertebral sulcus and 1 anterior mediastinal tumours, and resection of adjacent tissues involved by tumour en bloc) with adjuvant chemoradiation. Four metastatic chest wall tumours (Stage III) had chemotherapy and radiation alone.

RESULTS: Tumour recurred in 5 (2 chest wall, 2 costovertebral sulcus and 1 lung) requiring further chemotherapy, radiation and completion pneumonectomy for a lung recurrence. The incidence of recurrent tumour in 7 years for Stage I was 21 vs 40% ($P = 0.4$) for Stage II lesions and 16% after the neoadjuvant chemotherapy vs 30% ($P = 0.04$) after adjuvant chemoradiation. Four with recurrence, except one with a chest recurrence, succumbed to second relapse (78–96 months). All four Stage III chest tumours succumbed to advanced disease (30 months). The Kaplan–Meier disease-free survival of the overall group (23 patients) was $82 \pm 2\%$ at 5 years and $64 \pm 3\%$ at 10 years. The 10-year disease-free survival of 19 patients with localized tumours was 76%, but was high at 90% for chest wall tumours and low 33% for costovertebral sulcus tumours ($P \leq 0.01$). The 10-year disease-free survival was 86% for Stage I vs 60% ($P = 0.02$) for Stage II tumours; and 83% for neoadjuvant vs 76% ($P = 0.06$) for adjuvant chemoradiation and radiation.

CONCLUSIONS: The primitive neuroectodermal tumours are aggressive neoplasms with poor prognosis. Early diagnosis and total surgical excision of localized tumours with neoadjuvant or adjuvant chemotherapy and radiation improved disease-free survival.

Keywords: Askin tumour • Chest wall • Lung • Mediastinum • Chemotherapy • Radiation therapy

INTRODUCTION

Primitive neuroectodermal tumour (PNET), classified previously as Askin tumour or Ewing’s sarcoma, is a malignant neoplasm of the thoraco pulmonary region, grouped in the family of small round blue-cell tumours. PNET is now recognized as a distinct entity by the recent application of cytogenetic, immunohistochemical and ultrastructural studies for diagnosis [1, 2]. Though the multimodality treatment of chemotherapy and radiation including total surgical excision was well established for this highly aggressive malignant lesion, the reported survivals were poor [1, 3]. The purpose of this study was to analyse the outcomes of the multimodality treatment regimen in this group of PNETs of the thoracic region with a hope that the inferences drawn would influence the future management of this aggressive malignancy. The retrospective analysis of 23 consecutive cases of thoracopulmonary PNETs treated in a single institution over the period of 30 years formed the basis of this study.

MATERIALS AND METHODS

From 1980 to 2010, 23 cases of PNET treated at Newark Beth Israel Medical Center (NWBIMC) were retrospectively reviewed. This review is approved by the institutional review board and the ethics committee of the NWBIMC. There were 14 males and 9 females, and the age of the patients ranged from 19 to 64 years with a mean age of 29.5 years. The tumours were located on the anterolateral chest wall in 15, lung parenchyma in 4, anterior mediastinum in 1 and costovertebral sulcus or posterior mediastinum in 3. All patients presented with only mild symptoms of a short duration of 2–3 months. The patients’ clinical characteristics are given in Table 1. In one of the patients with a lung nodule, the lesion was contiguous with a nodular (5 × 3 cm) infiltration of the left chest wall. A 64-year old female presented with shortness of breath and an anterior mediastinal lesion with associated left pleural effusion and left upper lobe atelectasis with tracheal deviation to the right (Fig. 1).
Table 1: Characteristics of thoracic PNETs in 23 patients

<table>
<thead>
<tr>
<th>n</th>
<th>Tumour location and stage</th>
<th>Clinical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Chest wall and Stage I</td>
<td>Asymptomatic, firm masses (3–4 cm) involved soft tissues and underlying one to two ribs</td>
</tr>
<tr>
<td>4</td>
<td>Chest wall and Stage I</td>
<td>Asymptomatic, firm masses (4.1–7 cm) involved soft tissues and underlying two to three ribs</td>
</tr>
<tr>
<td>4</td>
<td>Chest wall and Stage III</td>
<td>Asymptomatic, firm masses, involved soft tissues and one to two ribs, with hilar lymph node metastases</td>
</tr>
<tr>
<td>1</td>
<td>Lung hilum and Stage I</td>
<td>Cough, fever, pleuritic chest pain and nodular right hilar lung mass</td>
</tr>
<tr>
<td>3</td>
<td>Lung parenchyma and Stage I (2), Stage II (1)</td>
<td>Chest pain, solid masses (4–5 cm) with areas of calcification and invasion to posterior rib margins. Infection to the vertebral bodies in two</td>
</tr>
<tr>
<td>3</td>
<td>Costovertebral sulcus* and Stage II</td>
<td>Chest pain, shortness of breath, solid masses (6 cm) with areas of calcification, left pleural effusion, atelectasis of left upper lobe. Tracheal deviation to right</td>
</tr>
<tr>
<td>1</td>
<td>Anterior mediastinum and Stage II</td>
<td>Chest pain, shortness of breath, solid masses (6 cm) with areas of calcification, left pleural effusion, atelectasis of left upper lobe. Tracheal deviation to right</td>
</tr>
</tbody>
</table>

n: number of patients. PNET: primitive neuroectodermal tumour. *Posterior mediastinum.

The clinical staging of the overall group tumours represented 11 Stage I and 4 Stage III chest tumours, 3 Stage I lung parenchymal tumours, 1 Stage II lung parenchymal tumour, 3 Stage II costovertebral sulcus (or posterior mediastinum) tumours and 1 Stage II anterior mediastinal tumour.

The clinical staging of the tumours was performed based on the extent of tumour disease as described.

**Chest wall tumours**: Stage I is a localized lesion encompassing the soft tissue, muscle and ribs with or without invasion to underlying pleura. Stage II is a lesion invading the lung parenchyma by direct extension, Stage III is a lesion associated with regional or hilar lymph nodal metastases and Stage IV is a lesion associated with distant metastases.

**Lung tumours**: Stage I is a localized lesion confined within the lung parenchyma. Stage II is a lesion invading the neighbouring structures such as chest wall, pericardium or visceria by direct extension, Stage III is a lesion associated with hilar or mediastinal lymph node metastases, Stage IV is a lesion associated with distant metastases.

**Mediastinal tumours**: Stage I is a localized lesion confined to the mediastinal space without direct invasion into the neighbouring structures such as ribs, vertebral bodies, lung parenchyma or other visceria. Stage II is a lesion invading the neighbouring structures by direct extension, Stage III is a lesion associated with regional lymph nodal metastases and Stage IV is a lesion associated with distant metastases.

**Diagnostic evaluation**

The diagnostic evaluation included complete blood count, serum chemistry, chest roentgenogram, computerized tomography, fibre optic bronchoscopy, pleural fluid cytometry, percutaneous tru-cut needle and/or excisional biopsy. The positron emission tomographic (PET) imaging with 18-fluoro-2-deoxyglucose was supplemented with computed tomography (CT) scan if hilar or mediastinal lymph node metastases were suspected. The pleural fluid cytometry examinations were non-diagnostic. The tru-cut needle biopsies of tumours were performed in all 23 cases. The diagnosis of PNET was confirmed preoperatively in 4 chest wall lesions with metastatic hilar nodes, 4 isolated chest lesions (4–7 cm size) and 2 parenchymal lung lesions. The needle biopsies were inconclusive in seven chest wall lesions (tumours of <4 cm size), two parenchyma lung lesions and all four mediastinal masses. The needle biopsies of both an endobronchial tumour and associated lung nodule were not diagnostic. Though the initial diagnosis was of Ewing’s sarcoma in 3 of 7 excised chest lesions, the diagnosis of PNET was later confirmed. Overall the preoperative diagnosis of PNET was made on needle biopsy only in 10 of 23 (43%) patients. The pathological examination included histology by light microscopy supplemented with immunohistochemical staining in all 23 patients. The ultrastructural and cytogenetic studies were performed in 17 patients to confirm the diagnosis.

**Morphology of primitive neuroectodermal tumours**

The tumours were solid and well circumscribed with a pale grey to greyish brown tan. Areas of necrosis and haemorrhage were seen in most of the tumours. The neoplasm was composed of sheets and cords of small round cells with scanty or indistinct cytoplasm, and round-to-oval nuclei, with coarse chromatin. Mitotic activity was moderate (Fig. 2). Rosettes were observed with cells surrounding a central core of fibrillary material (Homer-Wright rosettes) in the majority of the tumours. Necrosis of the tumour was extensive, and vein and lymphatic invasions were often observed. A periodic acid–Schiff stain was negative in the majority of the tumours, but only focally positive in some tumours. The immunohistochemical staining showed a strong and diffuse positivity for two or more markers such as: vimentin, CD99, neuron specific enolase (NSE), neurofilaments, S-100, Leu 7 and secretogranin. Positive staining with CD99 and
mediate plasmic glycogen, scattered microtubules and bundles of intermediate filaments and scattered microtubules suggestive of PNET.

Figure 2: Histopathology (magnification, ×100) of the tumour showing cords and sheets of small round cells with uniform appearance, scanty or indistinct cytoplasm, and round-to-oval nuclei. Mitotic activity was moderate. Homer-Wright rosettes (not shown in this figure) are often seen.

Figure 3: Electron microscopy of a tumour tissue obtained on needle biopsy showed cells with elongated interdigitating cytoplasmic processes, a few dense-core neurosecretory granules, moderate intracytoplasmic glycogen, bundles of intermediate filaments and scattered microtubules suggestive of PNET.

NSE with a negative stain for periodic acid-Schiff differentiated these tumours from other small round-cell tumours. The immunohistochemical staining was also negative for two or more markers such as: cytokeratin, chromogranin, synaptophysin, confirming the diagnosis of PNET and excluded other tumours such as lymphomas, carcinoma and sarcoma [4, 5]. The cytogenetic techniques demonstrated a characteristic reciprocal translocation t(11; 22)(q24; q12) with the detection of EWS/FLI-1 fusion gene transcripts, the findings that are specific for PNETs and Ewing sarcoma [6]. The t(11; 22)(q24; q12) results in expression of a chimeric RNA product, EWS-FLI1. This RNA product is expressed in over 85% of tumours belonging to the Ewing’s family, and is increasingly used as a definitive characteristic of these tumours. In this study, we evaluated reverse transcriptase-polymerase chain (RT-PCR) for EWS-FLI1 fusion transcripts in 17 small round cell tumours. The electron microscopy of tumours showed the presence of cells with elongated interdigitating cytoplasmic processes, a few dense-core neurosecretory granules, moderate intracytoplasmic glycogen, scattered microtubules and bundles of intermediate filaments (Fig. 3) that were highly suggestive of PNET [7].

**Treatment**

All (19 patients) with localized lesions (Stage I and II) of the chest wall, mediastinum and pulmonary parenchyma were treated by the multimodality treatment strategy of surgery, postoperative adjuvant radiotherapy, and chemotherapy. Six patients with a preoperative diagnosis of PNET on needle biopsy (4 chest tumours, 2 lung tumours) received preoperative chemotherapy (neoadjuvant chemotherapy) followed by surgery and postoperative (adjuvant) radiotherapy. The surgery of the chest wall lesions involved the excision of the mass with wide margins (a minimum of 2 cm margin was mandated) encompassing surrounding muscle, soft tissues and up to two to three ribs, with a normal rib above and below included in the resection. If four or more ribs were removed in resection, the resulting defect in the chest wall was closed with prosthetic Marlex mesh and either pectoralis major, serratus anterior or latissimus dorsi muscle flaps (3 patients). Three costovertebral sulcus tumours were excised totally including involved segments of the ribs and with a wedge of vertebral body (in 2 patients). The resection also encompassed segments of a normal rib above and below to get an adequate margin. Total resection of the anterior mediastinal mass was performed including the thymus, involved pericardium and contiguous left upper lobectomy with hilar lymph node dissection.

Patients with lung tumours required three lobar resections with hilar node dissections and a right pneumonectomy with resection of hilar and mediastinal nodes. None of the patients showed evidence of metastases in the lymph nodes on histological examination. In one of the lobar resections, the left lower lung lobe was excised en bloc with chest wall from fifth to ninth rib (10 × 12 cm of the chest wall) due to chest wall involvement. The chest wall was reconstructed using transposition latissimus dorsi muscle flap over Marlex mesh gauze sheeting. In another, the lobar resection (of left lower lobe) encompassed resection of a large endobronchial tumour (4 × 3 cm). This patient had refused to receive adjuvant chemotherapy and radiation therapy. After a 3-year disease-free interval, a recurrence of a lung tumour required completion left pneumonectomy, and partial resection of the left atrial wall. Postoperatively, the patient received intensive radiotherapy and chemotherapy.

Overall 12 anterolateral chest wall resections with reconstruction of the chest wall in four, two pneumonectomies, four lobar lung resections and resection of the four mediastinal tumours were done. Stage III chest wall tumours (4) were treated only by chemotherapy and radiotherapy.

The chemotherapy regimen consisted of cycles of doxorubicin, vincristine cyclophosphamide and dactinomycin, alternated with cycles of doxorubicin, vincristine, isophosphamide or etoposide given every 3–4 weeks for a completion of a total of 12 cycles. The neoadjuvant chemotherapy regimen consisted of three courses of vincristine, doxorubicin and cyclophosphamide alternated with a course of vincristine, dactinomycin and ifosfamide and was given >12–14-week period. The commonly used dosage of drugs were: vincristine 1.5 mg/m² push, maximum dose 2 mg; doxorubicin 40 mg/m² >4 h × 2 days; cyclophosphamide 1200 mg/m² >30 min; dactinomycin 1.25 mg/m² push, maximum dose, 2 mg; ifosfamide 1800 mg/m² >1 h × 5 days; etoposide 100 mg/m² >1 h × 5 days.
Adjuvant radiation therapy of 45–60 Gy (average dose 47) was given in fractionated doses. The management summary in 23 patients is given in Table 2.

Statistical analysis

The discrete variables such as chemotherapy regimen used, tumour location and clinical stage of the tumour were analysed by unpaired (two-tailed) t-tests to study the outcomes. A P value of ≤0.05 was considered statistically significant.

RESULTS

There were no operative deaths (operative mortality of 0%) in 19 patients (Stage I and II) treated by surgical excision and there were no deaths at initial hospitalization or chemotherapy-related mortality in a group of 23 patients. There were no significant intraoperative complications in 19 patients subsequent to surgical resection of the tumour. In 1 patient admitted with a recurrent tumour of the left hilum 3 years after an initial operation, a brief intraoperative bleeding occurred from the left atrial cuff suture line subsequent to excision of the recurrent tumour of the left hilum with left atrial wall extension. This was repaired by reinforcing the suture line without cardiopulmonary bypass. Postoperative morbidity occurred in 4 of 19 patients (21%). Staphylococcal wound infection occurred in 1 patient after resection of a chest wall tumour and was treated conservatively with debridement and antibiotics. The transient intercostal neuralgia noticed in 1 patient subsequent to resection of a costovertebral sulcus tumour with wedge resection of a vertebral body was managed by a regional nerve block. Upper lobe atelectasis and/or pneumonia occurred in 1 patient after excision of a parenchymal lung tumour with lower lobectomy and a chest wall resection. It was managed by supportive therapy and antibiotics. One patient, subsequent to neoadjuvant therapy and post-right pneumonectomy, required a ventilator support >72 h.

The length of hospital stay of the 19 patients ranged from 6 to 32 days with a mean hospital stay of 11 ± 2 days; the mean hospital stay for chest wall tumours was 8 ± 1 days, 9 ± 2 days for mediastinal tumours and 11 ± 1 days for parenchymal lung tumours.

Follow-up

The overall follow-up of 23 patients ranged from 24 months to 15 years (mean 108 months) from the initial treatment. Patients had routine physical examination, chest roentgenograms, chest computerized tomography, complete blood counts and serum chemistry on the follow-up.

The tumour recurred in 5 (26%) of 19 patients within 7 years subsequent to multimodality treatment including surgical resection. Recurrence was experienced in 2 (18%) chest lesions, 2 (66%) costovertebral sulcus tumours and 1 (25%) lung lesion. All these 5 patients with recurrence were treated with further radiation and chemotherapy and surgical re-excision in 1 (in a recurrent lung tumour) in an attempt to achieve remission.

We have analysed the effects of variables such as the tumour location, the clinical stage of the tumour and neoadjuvant chemotherapy vs postoperative adjuvant chemoradiation on treatment outcomes such as tumour recurrence and survival. In a group of 6 patients (4 Stage I chest lesions, 2 Stage I lung lesions) who received neoadjuvant chemotherapy prior to surgical resection, the tumour recurred in 1 chest lesion, with a recurrence rate of 16%. This patient with recurrence succumbed 7 years after initial treatment with a mortality rate of 16%. Among 13 patients (7 chest lesions, 3 costovertebral sulcus, 2 lung lesions and 1 anterior mediastinal lesion) who had initial surgical resection followed by postoperative adjuvant chemotherapy and

### Table 2: Management summary of 23 thoracic PNETs

<table>
<thead>
<tr>
<th>n</th>
<th>Tumour location and Stage</th>
<th>Biopsy*</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Metastatic chest lesions and Stage III</td>
<td>Needle</td>
<td>Chemotherapy and radiation</td>
</tr>
<tr>
<td>4</td>
<td>Chest wall tumour and Stage I (&lt;4 cm)</td>
<td>Needle</td>
<td>Neoadjuvant chemotherapy, wide excision, radiotherapy</td>
</tr>
<tr>
<td>7</td>
<td>Chest wall tumour and Stage I (&lt;4 cm)</td>
<td>Excision</td>
<td>Wide excision, adjuvant chemoradiation</td>
</tr>
<tr>
<td>3</td>
<td>Costovertebral sulcus and Stage II</td>
<td>Excision</td>
<td>Wide excision encompassing costal arches above and below, wedge excision of vertebral bodies in two, adjuvant chemoradiation</td>
</tr>
<tr>
<td>1</td>
<td>Anterior mediastinum with invasion to LUL and Stage II</td>
<td>Excision</td>
<td>Wide excision encompassing thymus, pericardium, upper lobectomy and hilar node dissection, adjuvant chemoradiation</td>
</tr>
<tr>
<td>1</td>
<td>LLL and Stage I</td>
<td>Needle</td>
<td>Neoadjuvant chemotherapy, lobectomy and hilar node dissection, adjuvant radiotherapy</td>
</tr>
<tr>
<td>1</td>
<td>Right lung hilum and Stage I</td>
<td>Needle</td>
<td>Neoadjuvant chemoradiotherapy, right pneumonectomy, hilar node dissection</td>
</tr>
<tr>
<td>1</td>
<td>LLL with chest wall invasion and Stage II</td>
<td>Excision</td>
<td>Lobectomy with en bloc excision of chest lesion, hilar node dissection, chest wall reconstruction, adjuvant chemoradiotherapy</td>
</tr>
<tr>
<td>1</td>
<td>LLL with endobronchial tumour and Stage I</td>
<td>Excision</td>
<td>Lobectomy and hilar node dissection no adjuvant chemoradiotherapy</td>
</tr>
<tr>
<td></td>
<td>Recurrent lung tumour with left atrial wall invasion in 3 years</td>
<td></td>
<td>Pneumonectomy, left atrial wall excision hilar and mediastinal node dissection adjuvant chemoradiotherapy</td>
</tr>
</tbody>
</table>

n: number of patients. LLL: left lower lobe of the lung; LUL: left upper lobe of the lung. *Biopsy performed to make confirmatory diagnosis.
radiation, 4 experienced recurrence (2 costovertebral sulcus, 1 chest and 1 lung lesion), with a recurrence rate of 30%. Three patients (2 costovertebral sulcus and 1 lung lesion) with recurrence succumbed with a mortality rate of 23% in 8 years. The incidence of recurrent tumour disease after the neoadjuvant therapy regimen when compared with postoperative adjuvant chemoradiation was 16 vs 30% ($P = 0.4$).

Recurrent tumour was seen in 3 (2 chest wall and 1 lung) of 14 (11 chest wall and 3 lung) Stage I lesions with a recurrence rate of 21%. Two of these 3 patients with recurrence (1 lung lesion and 1 chest lesion) succumbed with a mortality rate of 14% in 8 years. Tumour recurrent in 2 (costovertebral sulcus) of 5 (3 costovertebral sulcus, 1 anterior mediastinal and 1 lung) Stage II tumours with a recurrence rate of 40%, and both patients with recurrence succumbed with a mortality of 40% in 8 years. The incidence of recurrent tumour disease for Stage I disease when compared with Stage II was 21 vs 40% ($P = 0.4$).

Overall 4 patients with recurrent tumour disease (2 costovertebral sulcus, 1 chest lesion and 1 lung lesion) and all 4 patients who presented initially with metastatic chest wall tumours (Stage III) succumbed to recurrent and progressive disease. The summary of the results are given in Table 3.

Overall 14 of the 23 patients with thoracic tumours are continuously disease-free 6–14 years (median 7 years) and none of these patients had local recurrence. The 10-year disease-free survival after neoadjuvant chemotherapy was 84% (5/6) when compared with 77% ($P = 0.06$) for patients (10/13) who received postoperative adjuvant chemoradiation. The 10-year disease-free survival for Stage I tumours was 86% when compared with 60% ($P = 0.02$) for Stage II tumours. The disease-free survival (Kaplan–Meier) of the overall group (23 patients) of thoracic tumours was 82 ± 2% at 5 years and 64 ± 3% at 10 years (Fig. 4). The disease-free survival of 19 patients with localized thoracic disease (Stage I and II) was 76 ± 3% at 10 years. The 10-year disease-free survival of localized chest tumours was 90% when compared with 33% ($P < 0.01$) for costovertebral sulcus tumours.

**DISCUSSION**

PNET of the thoracopulmonary region is a rare neoplasm that occurs predominantly in children and young adults and is thought to originate from the embryonal cells migrating from the neural crest. Classified previously as Ewing’s sarcoma or Askin’s tumour, PNET is an aggressive neoplasm composed of undifferentiated small round cells and commonly present as a chest wall lesion with extensions to pleura and lung parenchyma [1, 2]. Though PNETs are well described in the literature, most of them are case reports of tumours located in the chest wall, lung, kidney, urinary bladder, myocardium, pancreas, retroperitoneum and the female genital tract [8–10].

PNETs should be considered in the differential diagnosis of all chest wall tumours, parenchymal lung nodules and mediastinal tumefactions regardless of age. There were only very few reported cases of PNETs arising as primary tumours of the lung without pleural or chest wall involvement. In Askin’s original series of 20 cases, there were no instances of isolated non-pleural-based parenchymal disease [1]. Our series represent tumours of the chest wall in 65%, primary tumours of the lung

![Figure 4: Kaplan–Meier disease-free survival curve of the overall group of 23 patients with thoracic primitive neuroectodermal tumours. Notably, the survivals were 82 ± 2% at 5 years, 64 ± 3% at 10 years.](image-url)
parenchyma in 17%, posterior mediastinum in 13% and anterior mediastinum in 4% of the cases. Any tumour suspected to be a PNET should be biopsied either by a needle or by a complete and wide surgical excision of a lesion to provide tissue for histological, immunohistochemical, cytogenetic and ultrastructural studies. The accuracy of a needle biopsy, in this study, was only 43%, requiring further technical improvements. Though cytogenetic and ultrastructural studies were performed in most of our cases, the diagnosis of PNET can often be made if the small cell tumour is positive for at least one of the markers of neural differentiation: NSE, S-100, Leu 7 and secretogranin [11].

The recommended and established therapy for a localized thoracic PNET consists of a multimodality treatment regimen of neoadjuvant or adjuvant chemotherapy, and radiation, including wide surgical excision of a tumour. All primary thoracic tumours require wide excision of a lesion with normal tissue margins such as ribs, vertebrae, pleura or pericardium etc. A primary tumour located in the lung parenchyma or a chest tumour invading the lung parenchyma mandates anatomical lung resections with hilar and/or mediastinal lymph node dissection as performed in primary lung carcinoma, though the propensity for lymph nodal involvement and its significance in the prognosis of lung PNET are currently not known [12].

The significant improvement in survivals observed for Stage I lesion in this study, when compared with Stage II disease, could be attributed to achieving adequate tissue margins at resection, including the strategy of repeat excision of a recurrent tumour, if feasible, and intensive chemotherapy and radiation. The incidence of recurrent tumour disease was not significantly reduced in Stage I lesions when compared with Stage II lesions, suggesting that tumour characteristics other than the local tissue invasion may be the predictor of recurrent disease after complete surgical excision. The staging system we have proposed to predict the prognosis, in this study, is limited by lack of adequate number of tumours representative of different thoracic sites, hence the effect of staging on outcomes should be carefully extrapolated.

If the lesion is diagnosed preoperatively on a needle biopsy, neoadjuvant chemotherapy is recommended prior to surgical resection with anticipated improvements in outcome. Neoadjuvant chemotherapy reduces the tumour size and improves the resection rates as well as the survivals as reported in several studies [11, 13]. Though the neoadjuvant chemotherapy, in this study, when compared with postoperative adjuvant chemoradiation has not significantly reduced the incidence of recurrent tumour disease, it has improved 10-year disease-free survival (84 vs 77%) with a statistical power barely missing significance, a result that could be attributed to a limited number of patients treated by a neoadjuvant therapy regimen. The adjuvant chemotherapy and radiation ablates residual microscopic disease after surgical excision of a tumour and was also shown to improve the overall survivals and disease-progression-free survivals [11, 13]. The surgical resection of a chest wall tumour before radiation also allows accurate marking of the area of involvement to permit limited radiation of the thorax [12, 14].

The chemotherapy and radiation also achieved temporary remission in metastatic and recurrent disease and improved 10-year disease-free survivals in 20% of our patients with recurrence. These results substantiate the claim for the use of intensive chemoradiation in recurrent disease and metastatic disease. The commonly recommend chemotherapy regimen includes several cycles of agents such as vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide [15, 16].

Several previous studies have reported poor long-term survivals in PNETs despite multimodality treatment regimens [11, 13, 14, 17, 18]. The improved outcomes observed for localized disease in this group were probably due to the predominance of chest wall and Stage I tumours comprising 65 and 74% of the tumours, and the use of neoadjuvant chemotherapy in some, which were all associated with improved 10-year disease-free survival. In addition, the early diagnosis of the tumours by the ample use of current laboratory techniques and aggressive management strategy of re-excision of a localized recurrent tumour disease with intensive chemotherapy and radiation could have contributed to the improved outcomes. The inadequate surgical margins achieved during resection for costovertebral sulcus tumours could have resulted in poor results for this lesion, but neoadjuvant therapy probably would have improved the outcomes, if the diagnosis of PNET was confirmed preoperatively on a needle biopsy.

Though this study is limited by its retrospective analysis in a diverse group of thoracic PNET tumours, in which some of the adjuvant treatment protocols were not standardized, the improvements in the diagnosis by needle biopsy leading to a diagnosis of the tumour at an early stage would enable the institution of neoadjuvant chemotherapy and total and wide surgical excision of lesions as a part of the multimodality treatment strategy with anticipated improvement in outcomes.

Conflict of interest: none declared.

REFERENCES


