Management of Abdominal Ewing’s Sarcoma: A Single Institute Experience

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Abstract
Ewing’s sarcoma (ES)/primitive neuroectodermal tumors (PNETs) are a rare group of tumors commonly arising from bones, uncommonly from soft tissues, and rarely from abdomen. The aim of the study was to analyze the outcome (recurrence-free survival [RFS]), patient characteristics, role of FDG-PET (fluorodeoxyglucose positron emission tomography) computerized scan, chemotherapy and radiation, and prognostic factors. We retrospectively studied patients diagnosed with abdominal ES/PNET and treated surgically between June 2005 and November 2019. Ten patients were included in the study, with a median age of 36.5 years (19–46 years). The median follow-up was 25 months (3–178 months). The site of origin was the retroperitoneum, small bowel, and abdominal wall in six, two, and two patients, respectively. 70% of patients were treated with induction chemotherapy. R0 resection was achieved in 90% of patients. With chemotherapy, there was significant reduction in tumor size ($p = 0.034$) with non-significant reduction in SUV max ($p = 0.31$). The 1- and 2-year RFS were 88.90% and 76.20%, respectively. Pathological peritoneal metastasis and ability to achieve R0 resection were prognostic factors affecting RFS. These patients must be offered multimodality treatment. Induction chemotherapy significantly reduces the tumor size. Pathological peritoneal metastasis and ability to achieving R0 resection significantly affect survival.

Keywords Ewing’s sarcoma · R0 resection · Induction chemotherapy · FDG-PET scan

Background
Ewing’s sarcoma (ES)/primitive neuroectodermal tumors (PNETs) are a well-known mesenchymal tumor belonging to a group of small round cell tumors (SRCTs) with simple sarcoma-specific genetic alterations between genes of TET/FET family and Erythroblast Transformation Specific (ETS) family with translocation of EWSR1 gene on chromosome 22q12 t(11;22)(q24;q12) occurring in 90% of cases [1]. ES/PNET expresses CD99 on its membrane that differentiates it from other SRCTs [2]. ES is commonly seen as a primary bone tumor, although it often arises from soft tissues (extra-osseous ES [EES]) [3]. ES/PNETs belong to the same spectrum of neoplasms known as Ewing sarcoma family of tumors (EFT) which also includes malignant small cell tumor of the chest wall (Askin tumor) and atypical ESS [4–6]. ES represents the least differentiated and PNET represents the most differentiated tumors [7]. Abdominal ES/PNETs are rare with few case reports in literature [8–20]. Abdominal ES/PNETs are often confused with other SRCTs such as embryonal rhabdomyosarcomas, neuroblastomas, and lymphomas. This makes it even more important for accurate diagnosis to provide evidence-based multimodality management for optimal outcomes.

The primary objective was to study the management of abdominal ES along with a review of literature.
Methods

Data Source and Patient Population

The demographic, clinical, radiological, treatment, histopathological, and survival data of patients were obtained retrospectively from hospital’s electronic medical records. The inclusion criteria were:

1. Biopsy proven abdominal ES/PNET disease
2. Age ≥ 14 years
3. Eastern Cooperative Oncology Group (ECOG) performance status 0–1
4. Surgical treatment in the institute

The exclusion criteria were:

1. Poor performance status (ECOG ≥ 2)
2. Presence of metastatic disease

Ten patients identified and registered between June 2005 and November 2019 were included in the study. The diagnosis was established by histopathological examination, and immunohistochemical analysis. Molecular study was not routinely performed for diagnosis in the institution. Disease was staged using 18-Fluorodeoxyglucose Positron Emission Tomography with Contrast Enhanced Computed Tomography (FDG-PETCECT) scan (except for two patients for whom CECT scan was done) and bone marrow biopsy was obtained in patients treated till 2010 (four patients). As a part of Institutional policy, PETCECT scan was selectively used from 2005 to 2010. After 2010, PETCECT scan was incorporated as a staging tool and subsequently bone marrow biopsies were omitted. Clinical tumor (cT) size (defined by its largest dimension) and maximum standardized uptake value (SUV max) were recorded and compared before and after chemotherapy. All patients were discussed in multidisciplinary joint clinics (MDJCs) involving surgical oncologist, medical oncologist, radiation oncologist, pathologist, nuclear medicine consultant, and radiologist. The chemotherapy regimen followed was EFT 2001 protocol [21, 22]. Post-chemotherapy, surgery was performed after clinical and radiological assessment through MDJC. Post-surgical resection, patients were continued on maintenance chemotherapy as per protocol. Complications were graded and recorded as per Clavien-Dindo classification of surgical complications [23]. Adjuvant radiation was given to patients based on histopathological findings, tumor volume, margin status, and response to chemotherapy. All patients were followed-up at three-monthly intervals for the first three years, six-monthly intervals for the next two years, and annually thereafter. In view of COVID-19 pandemic, all follow-ups after February 2020 were done via telephonic calls.

Statistical Analysis

The date of registration at the hospital was considered as date of diagnosis for statistical purposes. RFS was defined as interval between dates of diagnosis and appearance of first recurrence. RFS was calculated using the Kaplan–Meier method and compared using the log rank test. A univariate Cox regression hazard model analysis was used to analyze any prognostic factors of outcome and the hazard ratio (HR), relevant 95% confidence intervals (CIs) were calculated. P < 0.05 was considered to indicate a statistically significant difference. Wilcoxon signed rank test was used to test whether there was any significant change between pre-chemotherapy FDG-PETCECT scan (cT) size and SUV max due to chemotherapy. Spearman rho coefficient test was used to derive correlation between pathological tumor size (pT) with post-chemotherapy cT size and post-chemotherapy SUV max. The database of all patients in the review was compiled and analyzed using SPSS v.21 software (IBM Corp.).

Results

Baseline Patient Characteristics and Staging

Ten patients were analyzed in this study and the baseline patient characteristics, staging investigations, baseline cT size, and SUV max and post-chemotherapy cT size and SUV max are shown in Table 1. There were six males and four females with a median age of diagnosis of 36.5 years (range 19 to 46 years). The site of origin was retroperitoneum (six patients), small bowel (two patients), and abdominal wall (two patients).

Surgical Aspects

All patients (except one — patient E) underwent R0 resection of which five patients required multivisceral resections [Table 2 (A)]. The median blood loss was 450 ml (range: 100–1900 ml) and only three patients (A, D, and E) had Clavien-Dindo grade-1 complications. Table 2 (A) shows the histological features of these patients. The median pathological tumor size (pT) was 13.50 cm (range 2.20 cm to 20 cm). Five patients had disease involving the resected organs (B, E, F, G, and I). Two patients (E and I) had peritoneal metastasis, patient I underwent R0 resection while patient E underwent R2 resection (95% tumor was grossly debulked, residual multiple small deposits were present on parietal peritoneum and sigmoid colon mesentery).
| Patient | Age at diagnosis (years) | Sex | ASA | Date of registration | Date of surgery | Site of origin          | Bone marrow biopsy | Induction chemotherapy | Post-chemistry PET scan | SUVmax |
|---------|--------------------------|-----|-----|----------------------|-----------------|-------------------------|-------------------|------------------------|-------------------------|--------|
| A       | 35                       | Female | II* | 27.06.2005           | 01.09.2005      | Retroperitoneum         | Not done          | No                     | No                      |        |
| B       | 45                       | Male  | I   | 24.06.2006           | 23.11.2016      | Small bowel (ileum)     | Yes               | 1.40                   | 16.49                   | No      |
| C       | 44                       | Male  | I   | 08.09.2009           | 31.05.2010      | Retroperitoneum         | Not involved      | Yes                    | 7.90                    | 11.17   |
| D       | 25                       | Male  | I   | 29.03.2010           | 24.04.2010      | Abdominal wall          | Yes               | 7.90                   | 11.17                   | Yes     |
| E       | 23                       | Female | I   | 23.08.2010           | 14.03.2011      | Retroperitoneum         | Not involved      | Yes                    | 1.40                    | 5.60    |
| F       | 19                       | Male  | I   | 22.06.2012           | 02.11.2012      | Retroperitoneum         | Yes               | 20.00                  | 17.40                   | Yes     |
| G       | 46                       | Male  | I   | 03.11.2016           | 12.04.2019      | Pelvic retroperitoneum  | Yes               | 12.00                  | 14.74                   | Yes     |
| H       | 43                       | Female | II#| 19.04.2018           | 28.09.2018      | Abdominal wall          | Not involved      | Yes                    | 20.00                  | 17.40   |
| I       | 26                       | Male  | I   | 15.12.2018           | 23.05.2019      | Small bowel (jejunum)   | Yes               | 12.00                  | 14.74                   | Yes     |
| J       | 38                       | Female | I   | 22.11.2019           | 30.04.2020      | Retroperitoneum         | Yes               | 16.00                  | 10.34                   | Yes     |

*Hypothyroid, #Diabetes
cT, clinical tumor size
### Table 2 Surgical, histopathological, chemotherapy, radiotherapy and recurrence details

(A) Surgical and histopathological features

| Patient | Site                | Tumor location                                                                 | Type of surgery                        | Surgical details                                           | Resection | Blood loss (ml) | pCD grade | pT Size (cm) | pN | pM | Necrosis (%) | Organ involved on microscopy |
|---------|---------------------|---------------------------------------------------------------------------------|----------------------------------------|-----------------------------------------------------------|-----------|----------------|------------|--------------|----|----|-------------|-----------------------------|
| A       | Retroperitoneum     | Left retroperitoneal mass along the left paravertebral region from the level of splenic hilum to the lower pole of right kidney, abutting left psoas muscle and pushing the left kidney superolaterally; extending across the midline and in close contact with the descending aorta which is pushed anteromedially | Multivisceral en-bloc Resection        | Tumor mass excision + Left Nephrectomy + Left Adrenalectomy + Left Psoas excision | R0        | 1501–2000      | 1          | 13.00        | No | No | -           | -                           |
| B       | Small bowel (ileum) | Mass involving 20 cm ileal loop. Nodule found distal to it in ileum about 30 cm from IC junction | Multivisceral en-bloc Resection        | Tumor mass excision + Small bowel resection              | R0        | <500           | 0          | 14.00        | No | No | -           | Small bowel                |
| C       | Retroperitoneum     | Mass in right retroperitoneum with obliterated planes with gall bladder        | Multivisceral en-bloc Resection        | Tumor mass excision + Gall Bladder + Bile duct           | R0        | <500           | 0          | 3.00         | No | No | -           | -                           |
| D       | Abdominal wall      | Mass in lower abdominal parietal wall                                            | Resection                              | Tumor wide Excision                                      | R0        | <500           | 1          | 15.00        | No | No | -           | -                           |
### Table 2 (continued)

(A) Surgical and histopathological features

|   | Surgical and Histopathological Features |
|---|----------------------------------------|
| E | Retroperitoneum | Multiple large conglomerate masses in abdomen, pelvis, right iliac fossa infiltrating cecum, transverse colon and parietal wall. Peritoneal deposits in pelvis extending into hepatorenal pouch and posterior to liver. | Cytoreductive Surgery | Tumor mass excision + peritoneal nodules excision + Right hemicolectomy + Right adnexectomy | R2 | 1501–2000 | 1 | 20.00 | No | Yes | 15 | Colon, peritoneum, adnexa |
| F | Retroperitoneum | Left retroperitoneal mass infiltrating descending colon and displacing the bowel loops | Multivisceral en-bloc resection | Tumor mass excision + Left Colectomy | R0 | <500 | 0 | 15.00 | No | No | 30 | Colon |
| G | Pelvic retroperitoneum | Left pelvic retroperitoneum involving left kidney, ileal segment, sigmoid colon, upper rectum | Multivisceral en-bloc resection | Colon, Kidney, Small Bowel | R0 | 501–1000 | 0 | 16.00 | No | No | - | Small bowel |
| H | Abdominal Wall | Mass in anterolateral abdominal wall of right lumbar region extending up to right iliac region and overlying skin infiltrating the muscles | Resection | Tumor wide Excision + Mesh repair | R0 | <500 | 0 | 8.00 | No | No | 87 | - |
Table 2 (continued)

(A) Surgical and histopathological features

| Patient | Mass involving jejunal loop around 40 cm from DJ flexure. Limited peritoneal deposits in B/L anterolateral parietal peritoneum | Resection | Tumor mass excision + Small bowel resection + peritoneal nodule excision | R0 | <500 | 0 | 10.50 | No | Yes | Small bowel, peritoneum |
|---------|------------------------------------------------------------------------------------------------------------------|----------|------------------------------------------------------------------------|----|------|---|------|----|-----|--------------------------|
| I       | Small bowel (jejenum)                                                                                               | Resection| Tumor excision <500 0 10.50 No Yes - Small bowel, peritoneum          |    |      |   |      |    |     |                          |
| J       | Retroperitoneum Mass in interaortocaval region (infrahiilar) adherent to IVC. Another mass in left paraaortic region (infrahiilar), close to origin of IMA | Resection| Tumor excision <500 0 10.50 No Yes - Small bowel, peritoneum          |    |      |   |      |    |     |                          |

(B) Chemotherapy, radiotherapy, recurrences

| Patient | Induction chemotherapy | Maintenance chemotherapy | Adjuvant radiotherapy | Recurrence | Recurrence date | Recurrence operated |
|---------|------------------------|--------------------------|----------------------|------------|-----------------|---------------------|
| A       | No                     | Yes                      | Yes                  | No         |                 |                     |
| B       | No                     | Yes                      | No                   | No         |                 |                     |
| C       | Yes                    | Yes                      | No                   | No         |                 |                     |
| D       | No                     | Yes                      | Yes                  | No         |                 |                     |
| E       | Yes                    | Yes                      | No                   | Yes        | 04.10.2011      | No. palliative chemotherapy |
| F       | Yes                    | Yes                      | Yes                  | No         |                 |                     |
| G       | Yes                    | Yes                      | No                   | No         |                 |                     |
| H       | Yes                    | Yes                      | Yes                  | No         |                 |                     |
| I       | Yes                    | Yes                      | No                   | Yes        | 24.10.2019      | Yes (R0) (04.02.2020) |
| J       | Yes                    | Yes                      | No                   | No         |                 |                     |

*CD Grade, Clavien-Dindo Grade; IMA, Inferior Mesenteric Artery
Table 2 (B) provides the details of induction, maintenance chemotherapy, and adjuvant radiotherapy received by these patients. Patient B underwent emergency surgery in view of intra-luminal bleeding. The patient presented with anemia (hemoglobin 5.1 gm/dL) and 12 × 10 cm mass. Two patients (E and I) had recurrences [Table 2 (B)], patient I was re-challenged with chemotherapy and underwent cytoreduction to achieve R0 resection whereas patient E was deemed unresectable and continued palliative chemotherapy.

FDG-PETCT Scan

Eight patients underwent baseline FDG-PETCT scan, and post-chemotherapy FDG-PETCT scan of one patient was not available, hence, seven patients’ data were available for analysis (Table 1). Chemotherapy did not cause any statistical significant difference between pre-chemotherapy and post-chemotherapy median SUV max (p = 0.31); however, there was significant reduction in cT size with chemotherapy (p = 0.034). On univariate analysis, post-chemotherapy SUV max and cT size were not prognostic or predictive of recurrence. There was a weak positive correlation between pT size and cT size (rho = 0.252; p = 0.585) and between pT size and post-chemotherapy SUV max (rho = 0.500; p = 0.253).

Outcomes and Prognostic Factors

The median follow-up was 25 months (range: 3–178 months). The 1- and 2-year RFS of the cohort was 88.90% (95% CI: 70.60 to 100%) and 76.20% (95% CI: 52.1 to 100%), respectively (Fig. 1). Overall survival (OS) could not be calculated, as there were no events in the series. The only prognostic factors associated with recurrence were presence of pathological peritoneal disease/metastasis (p = 0.0026) and ability to achieve R0 resection (p = 0.11) (Table 3). Two patients developed recurrences, patient E had recurrences as retroperitoneal and mesenteric disease with subcutaneous umbilical nodule, and patient I developed recurrence in the form of peritoneal deposits in diaphragmatic peritoneum, pelvis, and transverse mesocolon.

Discussion

There are subtle biological differences between ES/PNET arising from bones and EES that lead to varying presentation in terms of age, tumor characteristics, clinical features, treatment strategies and outcomes [24–26]. ES/PNETs most often present as primary skeletal tumor in the trunk or axial skeleton in adolescents and young adults. Due to the rarity of EES the available literature is scarce and limited to few case reports. However, in recent years, there has been an increase in case reports which might be because of the recognition of EES and abdominal ES/PNET as a separate entity and improved cytogenetic and molecular diagnostic methods. Hence, it becomes necessary to identify this rare group of patients early in the course of disease.

Patient characteristics in EES differ than in those with skeletal ES/PNET. In our study of 10 patients (six males, four females), the median age at diagnosis was 36.5 years. The median age across different case reports of abdominal ES/PNET have been in similar age-groups (15–35 years) [8, 10, 12–15, 20, 21]. National Cancer Database (NCDB) and Surveillance, Epidemiology, and End Results (SEER) database studies show that the median age of patients at diagnosis of EES is older than its skeletal counterparts and has female predilection. EES patients are more likely to be <5 or ≥ 35 years at diagnosis [25, 26]. The average tumor size did not differ between skeletal ES/PNET and EES [25].

ES/PNET tumors have increased rate of glycolysis and hence the cells retain avidity. Meta-analysis of 23 studies by Huang et al. showed sensitivity and specificity that were 86% and 80%, respectively, with higher sensitivity and specificity (93% and 90% respectively) for detecting recurrences [27]. Hawkins et al. [28] and Salem et al. [29] conducted retrospective studies and showed that FDG-PETCT scan correlates with histologic response, is prognostic and predictive of survival outcomes. In our study, there was significant difference between pre-chemotherapy and post-chemotherapy cT size (median cT size 11.40 cm vs 7.30 cm respectively, p = 0.034). However, the SUV max did not statistically differ in pre-chemotherapy and post-chemotherapy setting (10.34 vs 4.60 respectively, p = 0.31). This could either be because of less number of patients, or biological differences in behaviors between abdominal ES/PNETs with its skeletal counterparts. We also did not find a strong positive correlation between pT size and cT size or post-chemotherapy SUV max. However, chemotherapy did bring about significant reduction in cT size (p = 0.034).

The NCDB retrospective cohort study analyzed 2660 ES/PNET patients (2004–2014) containing 1682 (63.2%) skeletal ES/PNET and 978 (36.8%) ESS patients. They concluded that EES patients have well-differentiated tumors, more likely to be in stage I disease with no significant difference in metastatic disease at diagnosis, perioperative outcome and no significant difference in OS of the entire cohort (median OS: 47.5 months for skeletal ES/PNET and 48.2 months for EES) [25]. In the SEER database of 2202 patients, the OS for localized ESS was superior to skeletal ES/PNET in both 5- and 10-year OS: 69.7% vs 62.6% and 65.2% vs 55.3%, respectively. However, when localized and metastatic ES/PNETs were analyzed together or in metastatic disease alone, the OS is similar in ESS and skeletal ES/PNET. They also suggested that patients with ESS had worse OS in the first 24 months but better OS after 24 months as compared...
to skeletal ES/PNET patients, after controlling for other known prognostic factors suggesting that extra-skeletal site has greater impact on the long-term outcomes [26]. Studies with small number of patients also showed no significant differences in survival outcomes [30, 31].

In our study, the 1- and 2-year RFS were 88.90% and 76.20%, respectively. This survival figures are impressive since they represent patients who were operated upon and did not include metastatic/inoperable patients. With multimodality uniform treatment comprising of induction chemotherapy, surgery, maintenance chemotherapy, and adjuvant radiation (when indicated) superior outcomes can be expected.

ES/PNET is considered a systemic disease with majority patients have subclinical metastatic disease at the time of diagnosis even in the absence of overt metastasis. Modern treatment protocols utilize initial chemotherapy (induction/neoadjuvant) followed by local treatment and further chemotherapy (maintenance/adjuvant). Induction chemotherapy is important to downstage the tumor to achieve R0 resection, improve local control and control metastatic disease [32–34]. EES patients respond to the same chemotherapy regimens as skeletal ES and should be treated similarly [35–38]. The chemotherapy protocols have evolved over years with the IESS-I-III studies leading to the current regimen which constitutes alternating cycles of ifosfamide and etoposide (I/E) to vincristine, Adriamycin, and cyclophosphamide (VAC) backbone (VAC/I/E) [39–41].

All of our patients received chemotherapy as per EFT 2001 protocol. Three patients did not receive induction chemotherapy (patient B underwent emergency surgery in view of bleeding while the reason for patients A and D were not available).

ES/PNET is a radiosensitive tumor. Radiation is more commonly used in skeletal ES/PNET as compared to EES [26]. There are no randomized control trials comparing surgery and radiation. Surgery is the preferred modality of choice for local control if the tumor can be resected with negative margins without excess morbidity and with a reasonable functional result. Surgery also avoids the risk of secondary radiation-induced sarcomas and provides for analysis of degree of necrosis. However, if a tumor is unresectable following induction chemotherapy, the patient should be referred for definitive radiation. Data from skeletal ES/

| Table 3 Prognostic factors |
|-----------------------------|
| Prognostic factors | P value |
| 1 | Sex | 0.86 |
| 3 | Subsite of origin | 0.65 |
| 4 | Multivisceral resection | 0.13 |
| 5 | Nephrectomy | 0.41 |
| 6 | Colectomy | 0.73 |
| 7 | Small bowel resection | 0.56 |
| 8 | Peritoneal disease | **0.0026** |
| 10 | R0 vs R2 resection | 0.11 |
| 11 | Induction chemotherapy | 0.56 |
| 12 | Adjuvant radiation | 0.24 |
| 15 | Pathological metastasis | **0.0026** |
| 16 | Post-chemotherapy PET cT size | 0.558 |
| 17 | Post-chemotherapy PET SUVmax | 0.149 |
| 18 | Pathological tumor size (pT) | 0.46 |

Values in bold are statistically significant
PNET tumors provide for the indications of adjuvant radiation in the following settings:

i. Bulky tumors in difficult sites
ii. Macro- or microscopic residual viable tumor after surgery
iii. Positive or inadequate surgical margins
iv. High risk chest wall tumors

In our series, 4/10 patients (40%) received adjuvant radiation, two patients had retroperitoneal origin, and two had abdominal wall origin.

In our study, presence of peritoneal metastasis was found to be statistically significant factor (p = 0.0026) and R0 resection (p = 0.11) was found to be non-significant factor but with trend towards significance (Table 3).

The limitations of our study are its small number of cases, the lack of events observed, and lack of long-term data. However, as we have limited our study to exclusively include abdominal ES/PNETs who underwent surgical resection, this number is still significant. The lack of events observed in our study shows that this subset of patients have good prognosis with multimodality approach, aggressive surgical resection, and salvage surgery whenever feasible.

**Conclusion**

Abdominal ES/PNET being a rare entity requires special attention with accurate histopathological diagnosis, IHCs and molecular studies (in special cases) and baseline imaging with FDG-PET/CECT. Tumor size on FDG-PET/CECT is predictive of tumor response to chemotherapy. All patients must be offered multimodality treatment including induction chemotherapy, surgery, and maintenance chemotherapy and adjuvant radiation when indicated. Every attempt to obtain R0 resection must be made and induction chemotherapy significantly reduces the tumor size. Presence of pathological peritoneal metastasis and inability to achieve R0 resection affect survival significantly.

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