Retroperitoneal Sarcomas- A Challenging Problem

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Abstract Retroperitoneal sarcomas are relatively rare tumours and usually present in a locally advanced stage. Liposarcoma is the most common histopathology. If operable, surgery is the treatment of choice. The role of adjuvant chemotherapy or radiotherapy is not yet defined. Advanced cases are treated by chemotherapy. The prognosis is poor in patients with positive resection margins, high-grade tumours and recurrent tumours.

Keywords Retroperitoneal sarcoma · Soft tissue sarcoma · Sarcoma

Introduction

Retroperitoneal sarcomas (RPS) are relatively rare tumors of mesenchymal origin and constitute around 10–15 % of all soft tissue sarcomas [1, 2]. Radical surgery is the most effective treatment available till date. The results of surgery are quite inferior to that of extremity sarcomas because of the large size at presentation and difficulty in resecting the tumour because of its anatomical location. Neoadjuvant and adjuvant treatment with chemotherapy or radiotherapy have also not shown any consistent benefit. In tumours that have been adequately excised, the final outcome depends on the tumour grade.

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Clinical Presentation

Although RPS may present at any age, the peak incidence is the sixth decade of life [3] and the incidence is almost equal in men and women with a slight male predominance [4]. The most common presentation is an asymptomatic abdominal mass [2]. They are usually asymptomatic, but may present with pain, early satiety, symptoms of bowel obstruction, neurologic symptoms of pain radiating to lower limb or ipsilateral lower limb oedema [1, 2, 5]. They may also be diagnosed incidentally. A proper history of the duration and the symptoms related to the mass has to be elicited. A physical examination gives an idea regarding the size and extent of the tumour. On examination, a large abdominal mass is often present. Differential diagnosis includes lymphoma, germ cell tumour, ovarian tumours in females, renal mass, gastrointestinal stromal tumours and adrenal tumours [5–7]. Examination should include the testis in men and all lymph node basins (to rule out lymphoma).

Investigations

The investigation of choice in patients suspected of having a RPS is a contrast enhanced computed tomography (CT) of the abdomen and pelvis [8–11]. A CT scan reveals the size and extent of the tumour and its relation to the surrounding vessels, organs and skeletal structures (Fig. 1). Metastatic deposits can also be seen on CT scan. The CT scan findings are essential for planning surgical resection of the tumour.

It is also essential to know the status of the kidneys, as resection of one kidney is quite frequent during surgery for RPS [12]. The status of the other kidney should also be evaluated using CT scan, intravenous pyelogram or renal scintigraphy if one kidney is to be resected.

Fig. 1 CT scan showing large retroperitoneal sarcoma

Imaging cannot reliably predict the histological type of sarcoma. Liposarcoma may occasionally be diagnosed on CT scan by the presence of fat component in the tumour [13, 14]. Unfortunately, the tumour grade, which has a prognostic value, cannot be predicted by imaging.

Magnetic resonance imaging (MRI) offers no additional advantage over CT scan in evaluation of retroperitoneal tumours except for vascular involvement. Motion artifacts are common in MRI. MRI may be preferred in patients in whom intravenous contrast is contraindicated [8]. Usually angiography is not necessary before planning surgery. However, if involvement of a major vascular structure like aorta, inferior vena cava (IVC), superior mesenteric vessels or iliac vessels is suspected, an MR angiography or intravenous contrast angiography may help.

All patients with RPS should undergo a chest X-ray. If the chest X-ray appears suspicious or the tumour appears to be high grade, a CT scan of the thorax is indicated.

A biopsy is not essential if the patient is being planned for surgery. Biopsy becomes necessary if the tumour is inoperable or metastatic and neoadjuvant or palliative chemotherapy or radiotherapy is being planned [1, 2]. Another indication for biopsy is, if there is a clinical suspicion of lymphoma or germ cell tumour, as the treatment modality of these malignancies is different. When a biopsy is necessary, a CT guided core biopsy from a posterior route is preferred. In the biopsy, in addition to the histological diagnosis, the tumour grade should also be commented upon. Fine needle aspiration cytology is not preferred to diagnose a primary soft tissue sarcoma but can be used to diagnose a recurrence. A CT scan is useful in diagnosing recurrences. Recently positron emission tomography (PET) is being used to evaluate local tumour recurrence. As in other malignancies, PET can be used to assess the response to neoadjuvant chemotherapy

(NACT). In addition, PET is also useful to diagnose distant metastasis in patients with recurrence [15].

Pathology

The most common histologic types are liposarcoma, leiomyosarcomas, malignant fibrous histiocytomas (MFH) and malignant peripheral nerve sheath tumours [3, 4]. Liposarcomas most commonly seen in retroperitoneum are, the well differentiated and the de-differentiated types. De-differentiated sarcomas grow faster and have the ability to metastasize compared to well differentiated liposarcomas. The well differentiated liposarcomas are slow growing and may be difficult to differentiate from a lipoma. The more aggressive types of liposarcomas are the pleomorphic and the myxoid liposarcomas, which have a higher propensity to metastasize. Recent findings suggest that most of the cases diagnosed as MFH are in fact de-differentiated liposarcomas. Gastrointestinal stromal tumours are not included in RPS as they arise from the gut. Well differentiated sarcomas may convert to de-differentiated sarcomas after one or more recurrences [16, 17]. Well differentiated sarcomas have better outcomes in terms of recurrence, rate of metastasis and overall survival compared to de-differentiated sarcomas. High grade tumours are more likely to have distant metastases; chance of a positive resection margin and a significantly poor survival compared to low grade tumours [4].

Staging

The International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) staging

system is currently followed for RPS [18]. Histologic grade, tumour size, and depth are the primary determinants of this staging system [18]. This staging system applies rather poorly to RPS as all tumours are deep tumours and majority are over 5 cm in size. A post surgical staging system has been suggested which includes grade, completeness of resection and presence of metastasis (Table 1) [19].

Surgery

Enblock resection of the tumour with a surrounding margin of normal tissue (i.e. microscopically negative margins) is the preferred treatment and is potentially the only curative treatment. The advanced stage at presentation along with the anatomical location of the tumour presents a challenge in achieving resection with a negative margin. Thus, the results of treatment of RPS are inferior to those of sarcomas at other sites especially extremity sarcomas [1, 20]. The ability to achieve a negative margin depends on the relation of tumour to major vascular structures like aorta and IVC, invasion of adjacent visceral organs and the skeletal framework. Unresectability could be due to presence of metastatic peritoneal disease, invasion of spinal cord, invasion of major vascular structures and invasion of root of the mesentery.

Complete resection rates in several series for primary RPS vary from 43 % to 95 % [4, 12, 21–28], with a 95 % resection rate reported by Karakousis et al. [22]. In a study of 500 patients from Memorial Sloan Kettering Cancer Center (MSKCC), the complete resection rate was 80 % for primary tumours and only about 52 % for recurrent tumours [4].

Planning an incision and proper positioning of the patient before surgery improves the resectability rate [22]. The incisions useful for resection of retroperitoneal sarcomas are: 1) Thoracoabdominal incision for upper quadrant tumours; 2) midline incision for mid line sarcomas of the upper or mid abdomen; 3) midline incision with lateral incision into the flank in form of T, for flank sarcomas; 4) lower midline incision with bilateral transverse extensions from the lower end of the midline incision at the pubic symphysis for pelvic midline extension of tumour; 5) abdomino - inguinal incision for sarcomas of the iliac fossa, wall of lower pelvis and those extending to pubic bone; 6)

incision for internal hemipelvectomy for RPS involving the iliac bone and/or acetabulum.

The first step after exploring the peritoneal cavity is a medial visceral rotation to expose the tumour and the retroperitoneum. The dissection proceeds outside the pseudocapsule surrounding the tumour. Resection of an organ abutting the tumour is recommended rather than peeling off the organ from the tumour. This requires resection of one or more organs to achieve a negative margin. The commonest organ resected is the kidney followed by colon, adrenals, spleen and pancreas.

Major vascular involvement is considered as a criterion for unresectability, however aggressive surgeries have been performed in patients with vascular involvement. In a study of 141 patients with RPS, 17 % of patients undergoing surgery had major vascular involvement. The tumours were resected along with the involved vessels and the vessels repaired primarily or using a graft. The 5-year survival was 66.7 % in patients with a margin negative resection [29].

Partial resection offers no advantage over no resection with regard to survival except in patients with liposarcomas, particularly well differentiated liposarcomas [30].

Although aggressive surgery has improved the outcome of RPS the 5-year survival still varies from 36 % to 68 % [4, 21–26, 28] and the 10-year survival from 14 % to 50 % (Table 2) [4, 22, 23, 25–27].

Radiotherapy

The high recurrence rate after surgery has led to investigations into the use of combined modality treatment for these tumours. As the most common form of relapse in RPS is a local recurrence, adjuvant radiotherapy has been proposed to enhance the cure rates and improve the relapse free survival. Studies in extremity sarcomas have demonstrated improved local control rates when surgery was combined with radiotherapy [31].

Radiotherapy to the retroperitoneum is challenging because of the large field size and presence of important visceral structures like the kidney, liver, bowels and spinal cord. Radiotherapy has been used in the preoperative; post operative and intra-operative settings with some investigators using both intra-operative and preoperative or postoperative radiotherapy.

As these tumours are rare there are only a few small prospective trials and retrospective studies of radiotherapy in RPS. The current recommendations are mostly based on consensus guidelines and the few prospective or retrospective studies done till date.

The first randomized controlled phase III trial that provided evidence of use of radiotherapy for improving outcomes was

Table 1 The Dutch/Memorial Sloan-Kettering Cancer Centre Classification System [19]

Classification	Definition
Stage I	Low grade, complete resection, no metastases
Stage II	High grade, complete resection, no metastases
Stage III	Any grade, incomplete resection, no metastases
Stage IV	Any grade, any resection, distant metastases

Table 2 Resection rates, 5 to 10 years overall survival in some major published series for RPS

Series	Year	No. of patients	Complete resection	Overall survival (%)	
				5 years	10 years
Sindelar[20]	1993	—	80	45	NR
Karakousis[12]	1996	87	86	63	46
Catton [21]	1994	104	43	36	14
Singer [23]	1995	83	NR	60	50
Lewis [4]	1998	287	80	54	35
Stoeckle [24]	2001	145	65	49	NR
Gronchi [25]	2004	167	88	54	27
Van Dalen [26]	2007	143	55	39	21
Ballo [27]	2007	83	52	NR	44
Strauss [28]	2010	200	170	68.6	NR

by the National Cancer Institute, USA in which 35 patients with operable RPS were randomized to receive either surgery with postoperative external beam radiotherapy (EBRT) (20 patients) or surgery with intraoperative radiotherapy (IORT) and adjuvant EBRT (15 patients) along with misonidazole (a radiosensitizer). On a median follow up of 8 years, only 3 out of 15 patients in IORT plus EBRT arm had a local recurrence compared to 16 out of 20 patients in the EBRT group. The drawbacks of the trial were a small sample size, high local failure, and high toxicity of treatment [20]. Pawlik et al. [32] reported the combined data of two prospective trials of preoperative EBRT for localized intermediate or high grade RPS. In this study, 72 patients were treated with preoperative radiotherapy. 64 patients completed the planned radiotherapy; of which 57 (89 %) underwent surgery. 54 patients (95 %) had a R0 or R1 resection. The 54 patients who had a R0 or R1 resection after radiotherapy had a 5 year local recurrence free, disease free and overall survival rates of 60 %, 46 % and 61 % respectively. These results were favourable compared to the historical data.

A retrospective study by the French Cancer Federation Sarcoma Group [24] also concluded that postoperative radiation was associated with improved local control compared to the surgery only group. The 5-year local recurrence free survival rate was 55 % for patients treated by radiation and surgery compared to 23 % for patients who underwent only surgery. A retrospective analysis of 261 patients was conducted using the National Oncology Database [33]. Patients who underwent surgery with a R1 or R0 resection were included. Patients who had received adjuvant radiotherapy had a significant improvement in local failure free survival compared to patients who underwent surgery alone [33].

There is still a controversy regarding the timing of radiotherapy. There is no trial comparing preoperative with postoperative radiotherapy for RPS. The advantages of preoperative radiotherapy are that the abdominal viscera are displaced by the tumour and so are at a lower risk of

radiation injury, the effective radiation dose is lesser, the tumour is in situ and can be marked for treatment [34, 35]. Also the tumour bed is better oxygenated. The advantages of postoperative radiation are that high risk patients can be selected for treatment based on margin status and grade of tumour. Post operative radiation has several disadvantages as post resection normal tissues move into and become adherent to tumour bed and receive higher radiation dose and thus produce high treatment related toxicity.

Intraoperative radiation therapy (IORT) has the advantage of administering a large dose of radiation (unto 25 Gy) to the tumour bed. The abdominal organs are positioned out of the radiation field. It also has the advantage of delivering radiation to specific areas, which carry a high risk of recurrence [36–39]. IORT is usually combined with preoperative or postoperative radiotherapy. Few retrospective studies and a prospective trial have reported favourable outcomes with IORT [20, 37–39], whereas a study from MD Anderson Cancer Centre (MDACC) has not found any benefit from IORT [27]. IORT is also associated with a significant amount of toxicity. Toxicities of IORT include neuropathy, hydronephrosis, ureteral fistula and bowel obstruction.

The toxicity of radiotherapy has led investigators to focus on newer methods of delivery radiation like intensity-modulated radiotherapy (IMRT). A selective dose escalation is administered at the margins of the tumour with the aim of achieving an R0 resection with favourable results [40, 41]. Tzeng et al. [42] treated patients with neoadjuvant IMRT with a boost to the margins. The radiation dose was well tolerated with 88 % patients undergoing R0 or R1 resection.

Chemoradiation

Chemoradiation has also been studied in treatment of RPS, mostly in phase I trials. Chemotherapy has been used to increase the sensitivity of the tumour to radiation. In a phase

I study from University of Michigan, EBRT with Idodeoxiuridine was used [43]. In another study from MDACC 35 patients were administered doxorubicin with EBRT followed by surgery and IORT [44]. These studies reported acceptable toxicity with the combined modality. There is very little data to support routine use of chemoradiation for RPS.

Chemotherapy

There is no consensus regarding use of neoadjuvant or adjuvant chemotherapy. Neo adjuvant chemotherapy (NACT) is given with an aim to improve the resectability of the tumour. The advantages of NACT are a reduction in the size of tumours, probability of a margin negative resection and determining the tumour response to chemotherapy. In addition, any micrometastatic disease could be controlled. The disadvantages are that a tumour may not respond to chemotherapy and a potentially resectable tumour may become inoperable. Chemotherapy may also worsen the performance status of the patient. Several studies, most of them non-randomized have not shown any consistent benefit with NACT. In one large study, Meric et al. [45] reported results of 65 patients of RPS with NACT doxorubicin or ifosfamide, of these 23 had resectable RPS.

Similarly, there are few studies, most of them retrospective, which have studied the role of adjuvant chemotherapy. Because of the rarity of RPS, most of these studies have combined extremity sarcomas with RPS. A meta-analysis of 1,568 patients from 14 trials was published by the Sarcoma Meta-analysis Collaboration [46], evaluating the role of adjuvant chemotherapy for localized resectable soft tissue sarcoma of adults at various sites of the body. There was an improvement in the distant recurrence free interval and overall recurrence free survival, but not in overall survival. Any benefit seen was probably due to the inclusion of patients with extremity sarcomas. Similar results were seen in another recent meta-analysis of randomized controlled trials [47]. The role of either NACT or adjuvant chemotherapy in retroperitoneal sarcomas is still undefined.

Locally Recurrent Tumors

Local recurrence after surgery is quite high in RPS and could be as high as 50–85 % [4, 23, 28, 33, 48, 49]. High grade sarcomas have a higher incidence of recurrence even if resected with a R0 margin. Metastatic disease is uncommon. For recurrences that are potentially resectable, surgery remains the treatment of choice, although the chances of a margin negative resection remains low.

In addition complete resections are possible only in about 40–60 % of patients [3, 4]. The median survival of

completely resected recurrent sarcomas is 56 months compared to 27 months for unresectable ones [4, 32].

Recurrence decreases survival, but adequate resection is associated with an improved survival and hence surgery is preferred for recurrent disease

Prognostic Factors

Positive surgical margins are associated with a poor overall survival compared to negative margins and this is the most important predictor of local control in RPS. The 5 years survival decreases from 66 % to 48 % if surgical margins are positive [50] and local control rate decreases from 78 % to 52 % in patients with positive margins. In an analysis of 500 patients treated at MSKCC [4], the median survival of patients who underwent complete resection was 103 months compared to 18 months in patients undergoing incomplete resection. In another series by Catton et al. [21] the 5 years and 10 years local control was 50 % and 18 % in patients with complete resection compared to 14 % and 5 % in patients with incomplete resection.

High tumour grade is also associated with a higher recurrence rate. After complete excision with negative margins, one of the important predictors of recurrence is the tumour grade. Ferrario et al. [3] reported a 5 years survival rate of 84 %, 50 % & 39 % respectively for grade I, II, and III tumours. High grade tumours also have a high rate of distant metastases.

In the MSKCC study [4], the median survival of patients with high grade tumours was 33 months compared to 149 months for those with low grade tumours.

The size of the tumour does not appear to affect survival unless the tumour is in operable. Recurrent tumours carry a poorer prognosis as the rate of complete excision is low.

So the main prognostic factors associated with poor prognosis are unresectable disease, positive surgical margins, a high histologic grade and recurrent tumours.

Disclosures None.

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