REVIEW ARTICLE

Retroperitoneal sarcomas: Anatomy, pathology and current trends in management'

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Abstract:
Soft tissue sarcomas are uncommon malignant mesenchymal tumors. They comprise 1% of all adult and 15% of all childhood malignancies. The annual incidence approximates to 2.7x106 population. They may occur sporadically or as part of genetic or hereditary syndromes with malignant predisposition, e.g. neurofibromatosis, Li-Fraumeni syndrome and Werner syndrome. These tumors are also related to environmental and occupational exposures to radiation, herbicides (chlorophenol, agent orange, dioxin), pesticides, cutting oil, saw dust, plywood, vinyl chloride, polyvinylchloride resin, asbestos and exposure to any kind of radiation including therapeutic radiation. Retroperitoneal sarcomas are rare among the soft tissue sarcomas and are highly malignant. They may be asymptomatic or present with non-specific symptoms. Because of their location, they can reach enormous sizes,weighing several kilograms before producing symptoms of compression or invasion of adjacent viscera. They may also be detected clinically or discovered radiologically as an incidental finding. Being aggressive and locally invasive, the tumor is already locally advanced involving several organs on presentation. They have the propensity to invade adjacent viscera and require extensive multivisceral resections for oncologically clear margins. Despite extensive resection, they still carry a high rate of local recurrence. The tumor may also metastasize to distant organs thus limiting long term survival. Due to multiorgan involvement, a multidisciplinary approach is required for optimum treatment. Surgery with grossly negative margins is the gold standard treatment for retroperitoneal sarcomas and is crucial for minimizing local recurrence and improving survival. Compartment resection involving a complete and radical resection of the tumor and contiguous viscera defines curative treatment and is a complex undertaking. The role of perioperative chemotherapy and radiation therapy is well-defined for certain types of retroperitoneal sarcomas. The prognosis of the disease decreases with increasing number of recurrences and worsening grade of the tumor.

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Abbreviations: STS; soft tissue sarcoma, RPS; retroperitoneal sarcoma, CNB; core needle biopsy

Introduction:

Soft tissue sarcomas are a heterogenous group of mesenchymal tumors and arise from connective tissues, nerves, fat cells and blood vessels. There are more than 70 histologic types of soft tissue sarcoma.[1] Retroperitoneal sarcomas represent only about 0.1-0.2% of all malignancies and 10-15% of all soft tissue sarcomas. They represent 40% of all retroperitoneal masses.[2] They are highly malignant tumors with a significant morbidity and a 5-year survival rate of 30-60%.[3] Sarcomas are the most common retroperitoneal

tumors characterized by an aggressive course, delayed symptoms and multiple local recurrences. Their location, delayed presentation, extensive local invasion and high rate of recurrence poses a therapeutic challenge. Usually asymptomatic and growing occultly for long periods, they cause symptoms once they reach a size of several kilograms by displacing and invading adjacent colon, spleen, kidney, pancreas and other viscera.[4]

Liposarcoma is the most common type, accounting for 40% of all retroperitoneal sarcoma, followed by leiomyosarcoma. The majority of tumors are low-grade but they still have the potential to recur locally, requiring re-resection. The grade of the tumor escalates with each recurrence till it finally becomes a high-grade sarcoma.[5,6] Liposarcomas have a propensity to recur locally, especially when de-differentiated, while leiomyosarcomas have a low local recurrence rate and tend to metastasize hematogenously.[7] Several genetic and environmental risk factors are identified and are associated with a particular type of sarcoma. Cutting oil and herbicide exposure is related to leiomyosarcoma and malignant fibrous histiocytoma (renamed as undifferentiated pleomorphic sarcoma), vinyl chloride with leiomyosarcoma and meat packing with dermatofibrosarcoma protuberans.[8] Similarly, paper and pulp mill workers are exposed to various types of tumors, including soft tissue sarcomas.[9]

Patients present with a palpable mass, abdominal discomfort or with symptoms related to the anatomical distortion or invasion of adjacent organs. Being locally invasive, sarcomas are already locally advanced at the time of presentation. The goal of treatment is to control the disease and decrease the chances of recurrence.[10] This requires a multidisciplinary approach where in surgical resection is the mainstay of treatment. Wide resection with tumor-free margins is the only curative treatment for retroperitoneal sarcoma ensuring local control and disease free survival. Wide resection entails extended en-bloc removal of the tumor and adjacent organs called 'compartmental resection'. This radical resectionis preferable over simple resection or debulking as it is associated with low recurrence and superior prognosis.[11] Survival decreases with metastasis and advancing grade of the tumor despite resection.[12]

Discussion:

Anatomically, the retroperitoneum is a highly complex region located on the posterior abdominal wall. Itharbors different organs and structures from the vascular, digestive and urinary systems. It is bounded posteriorly by the spine and its musculature, anteriorly by the posterior parietal peritoneum, superiorly by the thoracic diaphragm and inferiorly by the pelvic diaphragm. Its lateral limits are the abdominal wall muscles between the tip of the twelfth rib and the anterior superior iliac spine.[13] Retroperitoneum is further divided into various poorly demarcated spaces. Broadly, there are three major retroperitoneal compartments: anterior and posterior pararenal spaces, sandwiching the perirenal space between them. The 'anterior pararenal' space exists between the posterior parietal peritoneum anteriorly and the anterior layer of Gerota's (renal) fascia posteriorly. It contains the duodenum, pancreas, root of mesentery and ascending and descending colon. The 'posterior pararenal' space is bounded anteriorly by the posterior Gerota's fascia and posteriorly by the transversus abdominis and quadratus lumborum muscles and the thoracolumbar fascia overlying them. The 'perirenal space' lies within the layers of Gerota's fascia and contains the adrenals, kidneys and ureters. The Gerota's fascia from both sides fuses together in the midline in front of aorta and inferior vena cava, enclosing these major vessels in a space behind it called the 'retrorenal space'. The above spaces are separated from one another by fascial planes containing loose areolar tissue. The white line of Toldt is the embryonic fusion line between the posterior parietal peritoneum and the anterior visceral peritoneum of the colon. Access to these retroperitoneal spaces can be made by making an incision along the white line of Toldt, as for medial visceral rotations.[14]

Being an extensive space with ill-defined bound-

aries, devoid of any osteo-fascial limits, the retroperitoneal tumors can attaingigantic sizes before producing symptoms of abdominal pain, fullness, vomiting, early satiety and weight loss. The patient may notice ballottement, increasing girth and a palpable abdominal mass. Increasing tumorsize may also lead to weight gain and visceral obesity.[15] Tumors smaller than 5cm are seldom detectable.[16] Retroperitoneal sarcoma may infrequently produce compressive symptoms of gastrointestinal and urinary tracts and blood vessels. Gastric outlet obstruction and acute pancreatitis due to external compression have been reported.[17] Similarly, compression of colonic vasculature can cause ischemic colitis.[18] The tumor may rupture causing hemoperitoneum and present as acute abdomen.[19] Retroperitoneal sarcomas are occasionally discovered incidentally on imaging for unrelated causes.[20]

Epidemiologically, retroperitoneal sarcoma are associated with genetic and environmental risk factors. Several hereditary syndromes are characterized by development of soft tissue sarcoma, e.g., Li-Fraumeni syndrome, von Recklinghausen syndrome, familial retinoblastoma, familial adenomatous polyposis coli and Noonan syndrome. Identification of such syndromes is mandatory for optimal treatment, genetic counseling and screening of relatives for the tumor.[21] Occupational exposures have a strong association with soft tissue sarcoma. The groups at increased risk include farmers, railroad workers, wood workers, mechanics and workers who are exposed to asbestos, impregnating agents, chlorophenols (used in pesticides, herbicides, disinfectants, cutting oils and wood preservation) are a few examples of exposures.[22] Retroperitoneal tumors may be both primary and secondary. Primary tumors arise from retroperitoneal tissues. Two-thirds of these are malignant and include liposarcoma, leiomyosarcoma, malignant fibrous histiocytoma, malignant germ cell tumor and malignant paraganglioma. Benign retroperitoneal tumors include: paraganglioma, neurofibroma, neurilemoma, lipoma, teratoma and desmoid tumor. Secondary tumors are metastatic to the retroperitoneum having their primary some where else, e.g., malignant melanoma, testicular tumors.[23]

The differential diagnosis of retroperitoneal sarcoma includes lymphoma, desmoid tumors, GIST, germ cell tumors and benign lesions. Although the space contains pancreas, adrenals, kidneys and ureters, tumors arising from them are generally not classified as retroperitoneal tumors. However, they may get involved by the retroperitoneal sarcoma requiring resection. Sarcomas may involve aorta or inferior vena cava necessitating graft reconstruction. They may also arise primarily from aorta, inferior vena cava, iliac vessels, renal and gonadal veins.[24-26]

Initial evaluation of retroperitoneal sarcoma includes: history, physical examination, appropriate imaging studies and histology. Precise anatomical information regarding the location, extension and relation with adjacent viscera is of paramount importance for devising a surgical plan. Imaging differentiates RPS from other retroperitoneal masses. Contrast enhanced CT is the most usefuland most widely used imaging modality in the diagnosis and staging of RPS.[27,28]

Malignant tumors are larger in size (>5cm) and are characterized by irregular margins, cystic areas of necrosis among solid areas and absence of calcification on CT scan.[29] Lipoma is usually uniform while liposarcoma has varying density on CT scan. CT findings also include invasion of the adjacent viscera by the tumor.[30] MRI is used in a select group of patients allergic to iodinated contrast agents used in CT scan. It is also used when there is uncertainty about the diagnosis or when evaluating the involvement of structures not well visualized on CT scan, like major nerves and spine. MRI not only accurately identifies the origin of the lesion, but also defines tumor morphology and provides vascular details. MRI is also useful in identifying small recurrences on follow up.[20] PET scan is increasingly been used for the diagnosis of soft tissue sarcoma. It is good in diagnosing primary and recurrent tumors, and differentiating between low- and high-grade tumors but it can not differentiate benign from low grade malignant tumors.[31] PET is not only used for clinical

assessment and treatment planning but is also useful in predicting prognosis of RPS.[32]

Percutaneous core needle biopsy (CNB) biopsy is required for pathological diagnosis andis now the standard of care.[33] Core needle biopsy is performed under ultrasound or CT guidance targeting solid areas and avoiding cystic, necrotic areas, viscera and major vessels.[34] Core needle biopsy is required if neoadjuvant therapy is being considered or tumor other than sarcoma is suspected, e.g., a benign tumor or metastatic tumor like malignant melanoma as these may have different management strategies. Biopsy is also needed to differentiate RPS from tumors that may not require resection, e.g., lymphoma and germ cell tumor. Core needle biopsy is also known to have complications like bleeding, visceral injury, infection and recurrence of the tumor in the needle tract but these do not affect overall survival.[35] Regardless of these facts, centers specializing in soft tissue sarcoma surgery recommend core needle biopsy of retroperitoneal sarcoma in order to histologically classify and grade the tumor, thus helping in treatment planning.[27,36] Some tumors may require pre-operative angioembolization.[37]

The treatment of retroperitoneal sarcoma is multimodality and involves surgery, radiotherapy, chemotherapy and oncolytic viral therapy. Surgery is the cornerstone of treatment for retroperitoneal sarcoma. Complete, radical resection of the tumor and adjacent organs ensuring tumor-free margins and intact capsule is mandatory for long term results.[38] Three types of tumor resections have evolved over time as described below: simple resection, compartmental resection with resection of involved organs, compartmental resection with resection of uninvolved organs. Although other types of resections are also being practiced, the literature strongly supports the last type of extended resection that ensures wide and tumor-free margins.[11,39] Detailed pre-operative evaluation including three dimensional reconstruction of the tumor using CT or MRI is crucial for planning surgery. Compartment resection is performed through a midline laparotomy incision. The tumor is cleared circumferentially and resected en-mass with adjacent organ sabutting the tumor. Such extensive resection may require medial visceral rotation (Cattell-Braasch and Mattox maneuvers) on the side of the tumor to expose the retroperitoneal viscera and vasculature and assess their involvement in the tumor process.[20,40]

The retroperitoneal compartments do not have distinct boundaries and contain vital organs and major blood vessels. These structures border the growing retroperitoneal tumors and thus get invaded ordisplaced by them. Since the tumors are closely related to the adjacent viscera, wide resection with clear margins is usually impossible without simultaneous resection of adjacent viscera abutting the tumor. Adequate resection is the single, most important prognostic factor in the treatment of retroperitoneal sarcoma. In order to ensure tumor-free margins during surgery, adjacent organs and structures including colon, kidney, spleen, duodenum, tail of pancreas, adrenal, psoas muscle, thoracic diaphragm and major blood vessel(s) like portal vein or inferior vena cava may need resection. Ipsilateral colon, kidney and psoas muscle are most likely to be resected along with the tumor, being closely related to it. Such extended multi-visceral resection is called 'compartmental resection' of the retroperitoneal sarcoma. It improves local control and has low morbidity.[41-42]

Survival is inversely proportional to histologic grade of the tumor, stage of the disease, resectability and completeness of resection. The same factors also determine the chance of recurrence. Primary disease has a better prognosis than recurrent disease.[43] Following surgery, patients are followed up at regular intervals per year for 4-5 years with physical examination and thoraco-abdominal CT scan for recurrence. Thence onwards, annual follow up isrecommended.[27] Although retroperitoneal sarcoma poses a formidable problem in terms of extensive surgery needed, the 5 and 10 year survival may reach 65% and 56% respectively with meticulous surgical technique.[44] Neo-adjuvant or adjuvant radiotherapy (RT) and systemic anti-cancer therapy are added selectively to the treatment

protocol based on histologic type of the soft tissue sarcoma.[45] Neoadjuvant RT is preferred in patients with resectable disease. It may also be the primary treatment in unresectable disease. In resectable soft tissue sarcoma, the tumor size is large, making for an excellent and well-defined target for RT. The large tumor displaces the bowel and other viscera away from the radiation field, thus minimizing radiotoxicity. It also reduces the risk of tumor seeding during surgery. Peritumoral edema following RT assists in tumor resection. On the contrary, following resection of a large retroperitoneal sarcoma, the intestines tend to fall back into the residual space, making it difficult to target the operative field exclusively. Adjuvant RT for preventing local recurrence is therefore discouraged in post-operative cases due to complications like radiation enteritis, intestinal obstruction and fistula formation.[27,46]

Intra-operative RT improves local control and minimizes toxicity but studies are limited.[47] Peri-operative chemotherapy involving anthracyclines, ifosfamide and adriamycin have shown promising results in improving survival in patients with soft tissue sarcoma, including retroperitoneal sarcoma. These drugs are also used as first-line treatment in unresectable and metastatic disease.[48] Second-line agents have been used for advanced soft tissue sarcoma for patients who are not candidates for chemotherapy. These include pazopanib, trabectedin, eribulin and anlotinib.[49] Anlotinib, a novel tyrosine kinase inhibitor, has shown promising results in advanced and metastatic soft tissue sarcoma with improved survival benefit. It may be used alone or in combination with chemotherapy.[50,51] Virotherapy using oncolytic viruses has emerged as a promising treatment for many solid tumors and shown encouraging results in soft tissue sarcoma. This form of immunotherapy is being used in soft tissue sarcomas (STS) and bone sarcomas.[52,53]

Unresectable or metastatic disease is treated initially with chemo-radiotherapy. If the tumor becomes resectable, it is treated as a primary tumor. Palliative treatment is offered if the tumor remains unresectable.[54] If the primary tumor is resectable and has a resectable metastasis, it should be considered for surgical removal, although this has questionable survival advantage.[2] Surgery is also the ideal treatment for local recurrence and pulmonary metastasis. Recurrent disease is treated with surgery, with or without neoadjuvant systemic therapy or intra-operative radiotherapy.[55]

Conclusion:

Retroperitoneal sarcomas are challenging because of their rarity, location, aggressiveness and advanced stage on presentation. Their treatment is multimodal, complex and associated with a high rate of recurrence. The ability to completely remove soft tissue sarcoma is still the overriding therapeutic factor in survival outcome. The best chance of cure requires an aggressive approach at the primary surgery since the prognosis declines with each recurrence. For optimal results, the tumor must be resected enmasse with adjacent organs, without breaching the capsule or rupturing the tumor. Low grade tumor, compartment resection without rupturing the tumor and negative resection margins are associated with low recurrence and improved overall survival rates. Although a specialist center is required for dealing with the soft tissue sarcoma, a general surgeon must be aware of these tumors and their treatment protocol as they are likely to come across such tumors in their practice.

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Zafar Ullah Khan, conceived the idea, collected the data, references and wrote the article.

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