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Preoperative Radiotherapy in Myxoid Liposarcoma

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Abstract

Myxoid liposarcomas are responsive to radiotherapy, particularly preoperative radiotherapy. The expected outcome of the preoperative radiation is a decreasing tumor size and major necrotizing area. With a good local control, organs can survive without any amputation. Preoperative radiotherapy can be given with or without chemotherapy. Conventional fractionation such as 25 x 2 Gy or hypofractionation of 5 x 5 Gy could be an effective way to treat preoperative myxoid liposarcoma.

Keywords: myxoid liposarcoma, preoperative radiotherapy, sarcoma, radiotherapy

Introduction

Sarcoma is a malignancy that originates from mesenchymal cells that could arise in some parts of the human body, such as vascular, fat, nerve, muscle, bone, and cartilage tissues. Liposarcoma is the most common soft tissue tumor, about 15-20% of total soft tissue tumor's incidence rate.[1] Myxoid liposarcoma is one of the liposarcoma subtypes.

Mainly, treatment for liposarcoma is an operative procedure. However, neoadjuvant therapies like neoadjuvant radiotherapy and neoadjuvant chemotherapy are necessary to maintain organ function. A complete and successful therapy depends on the characteristic and type of sarcoma.

Generally, liposarcoma has a less sensitive characteristic towards chemotherapy and radiotherapy. However, myxoid liposarcoma is known to have a decent response to preoperative radiotherapy, particularly in the extremities.

Epidemiology

The Myxoid liposarcoma subtype is found in 20-30% liposarcoma incidence rate.[2] Most common patients are young adults age 20-40 years old. In children, common liposarcoma incidence is rare, only 2% of total soft tissue sarcoma incidence. But, The Myxoid subtype is found in 70% of cases of liposarcoma in kids. The incidence rate of myxoid liposarcoma is 1/759.000. The probability of Myxoid liposarcoma is slightly higher in males.

Myxoid liposarcoma, mostly grow in proximal portions of the extremities, 2/3 from the total incident are found in the thigh, 70-80% are in intermuscular fascia and deep sited, subcutaneous area are rare. But, it might develop in some other body parts such as the retroperitoneal abdomen area, ankle, head and neck; and wrist.[1,5,9] Incidence in head and neck liposarcoma is 4-9% from total rate incident.

Etiology

Generally, the main cause of liposarcoma is still unknown, so is the myxoid liposarcoma. Others say that liposarcoma is related to genetic, environment, radiation, virus, and immunodeficiency. Some other[10] says that liposarcoma that originated from lipoma mostly is de novo, no causative factor.

Pathogenesis

Ultimately 90-95% of myxoid liposarcoma will

undergo a translocation between chromosome 12 and 16, t(12;16)(q13;p11), and not more than 5% cases are t(12;22), that result in an arising oncogene protein fusion Fused in Sarcoma – DNA damage-inducible transcript (FUS-DDIT3).

Clinical Symptoms

In this type of tumor, the emerging symptoms depend on the location of the tumor. The tumor is slowly growing and, usually, the patients have no pain. The tumor could grow to a bigger size and multifocal.[13] The pain sensation will come up if the tumor has a bigger size and if located in the extremities, which will cause a limited range of motion. Myxoid liposarcoma that grows in the head and neck site could show some symptoms such as dysphagia, voice changing, and dyspnea.

Metastasis

10-31% of myxoid liposarcoma could metastasize.[6] Not like other subtypes, myxoid liposarcoma can be hematogenically metastasized to other locations besides the lung, such as bone, soft tissue, and abdomen.[2,6,14,15] From the total cases of metastasized myxoid liposarcoma, 56% metastasized to bone especially the vertebrae.

Diagnosis

Unfortunately, myxoid liposarcoma is difficult to distinguish from other benign tumors because of its slowly growing mass. Nevertheless, to make the right diagnosis, biopsy and imaging are needed.

Diagnosis is made based on cytology of myxoid liposarcoma that is obtained with fine-needle aspiration biopsy, biopsy core, incision biopsy, excision biopsy. The gold standard is biopsy core.

Imaging should be done before the biopsy for deep-seated tumors so that we know the exact location of the tumor and the shortest range for taking the sample (sampling procedure).

In a histologic aspect, myxoid liposarcoma could form a myxoid tumor with a spindle cell-like type to hypercellular sarcoma.[11] The cell is tiny, round shape or oval, with some immature lipoblast signet rings in the myxoid stroma.[1] Myxoid tissue consists of gelatinous mucopolysaccharide matrices of sulfate and nonsulfate glycosaminoglycan.

Round cells could be found in myxoid liposarcoma. Round cells constitute a round cell with an increasing cytoplasm-nucleus ratio.[18] The appearance of this round cell could be a prognostic factor and differentiating myxoid liposarcoma into 3 grades: low grade if there are no round cells, intermediate if there are 0-5% round cells, and high grade if the round cells are >5%.[19]

Imaging

Various types of imaging modalities could help us to diagnose and the liposarcoma stage. From a simple radiograph and ultrasonography through sophisticated modalities such as CT Scan and MRI.

In X-Ray, myxoid liposarcoma could appear normal or non-specific soft tissue mass. X-Ray could identify an invasion of myxoid liposarcoma into the bone.

In the ultrasonographic aspect, hypoechoic appearance with well-circumscribed will be seen in myxoid liposarcoma. Even though USG couldn't identify the fat adipose tissue, USG could help to identify the cysts that are found in CT Scan or MRI with an anechoic appearance that might show a septum which could lead us to suspect an unusual cyst.

CT scan is no longer useful for evaluating soft tissue sarcoma since MRI is found. In CT scan, myxoid liposarcoma is visualized as a big, well-circumscribed, hypodense mass because it consists of water and forms a cyst-like structure.

To diagnose myxoid liposarcoma, compared to CT scan, MRI is the best option for imaging modality. Myxoid liposarcoma is usually visualized as well-circumscribed, septa with multi lobule, intermuscular mass, and below subcutaneous.[21] Hypo-intensity imaging will be seen in T1-weighted because its primary components are myxoid matrices and fatless. About 10% of total tumor volume in myxoid liposarcoma is fat component that gives hyper intensity imaging in the T1 sequence, however, this kind of image is still rare. The mass is often lobular and multilocular. Edema is found around the mass. Heterogeneous density is found with contrast, but the myxoid component doesn't add up. The hyperintensity with heterogeneous intensity is found in T2-weighted.[21] Sometimes, very difficult to distinguish from benign cyst because of the cyst-like form with well-circumscribed are found in the imaging.[21] A bad prognosis of myxoid liposarcoma could be found, if the imaging of infiltrated bones, around the major vascular, non-capsule, and necrotizing tissue are seen in MRI.

Staging

The myxoid liposarcoma stages have the same stages with soft tissue sarcoma. According to the 8th AJCC, soft tissue sarcomas are classified based on the tumor location: core and extremity, retroperitoneum, head and

neck, abdomen, and the thorax.

According to the 8th AJCC (2017), the soft tissue sarcoma stages are based on TNM (Tumor Node Metastasis) and tumor grade. The grading system is complying with the French Federation of Cancer Centers Sarcoma Group/ Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC).

FNCLCC grading based on 3 parameter: differentiation (score 1-3), mitosis activity (score 1-3), and necrotizing spread (score 0-2). FNCLCC divides soft-tissue sarcomas into 3 grades.

Therapy

Surgery, radiotherapy, and chemotherapy are the main therapy in myxoid liposarcoma. To increase the patient's quality of life who is diagnosed with extremity liposarcoma, we need surgery as the main therapy combine with radiotherapy and neoadjuvant or adjuvant chemotherapy.

Surgery

The most important therapy in myxoid liposarcoma is surgery, with wide local excision, limited resection ≥ 10 mm. Resection R0 will increase the long term survival rate. Surgery with function preservation still plays a big role in increasing the patient's quality of life. But, if there is an invasion and close to the surrounding organs, amputation might be an unavoidable option. Metastasectomy radical could be performed when patients are diagnosed with single intraperitoneal metastasis.[25]

Chemotherapy

Compared to other soft tissue sarcomas, myxoid liposarcomas are known as chemotherapy-sensitive, particularly anthracycline-based combine with trabectedin. 65% of myxoid liposarcomas are responsive to this first-line combination, anthracycline and ifosfamide, whereas only 40% of other soft tissue sarcomas are responsive to this chemotherapy combination.[26,27]

Radiotherapy

Radiotherapy plays a crucial role in myxoid liposarcoma treatment. Radiotherapy Neo-adjuvant/ pre-operative and adjuvant/post-operative can be performed. The goal is to decrease the tumor size so that the limb salvage procedure can be performed and the limited resection/boundary incision is clean. Good local control is expected. Generally, pre-operative radiotherapy is given in conventional fractions with a total dose of 50 Gy, with fractions of 1.8-2 Gy/day.

Myxoid liposarcoma is a responsive tumor toward radiotherapy with or without chemotherapy. The median percentage of necrosis is 92-95% and the mean rate is 76-77%.[28-30] Myxoid liposarcoma without round cell component are responsive to radiation with 5-year local control and achieving 98% post adjuvant and neoadjuvant radiotherapy.[6]

Short term complication such as post-operative wound infection is higher in pre-operative radiotherapy. A report says that wound complication is 35% for preoperative radiotherapy, whereas 17% for postoperative radiotherapy. However, long term complication such as fibrosis, joint stiffness, edema is found less in pre-operative radiotherapy than post-operative radiotherapy.[32]

According to Chowry, et al, an addition of congruent chemotherapy radiotherapy has increased myxoid liposarcoma necrosis to 82,3% with trabectedin congruent chemotherapy whilst, compared to 58,8% with radiotherapy only. Chemotherapy is responsive histologically but doesn't increase the disease-free survival and overall survival.[29]

First phase study chemo radiation congruent trabectedin and radiotherapy show a tolerated side effect. In 3 years, Relapse Free Survival (RFS), Disease-Free Survival (DFS) and Overall Survival (OS) is 92% (95%CI:76-100), 86% (95%CI:67-100), 93% (95%CI:79-100). In this study, trabectedin is given in 3 cycles/3 weeks with radiation dosage 45Gy/25 Fraction.[33] There is no other chemotherapy regimen that has the same effectiveness for treating myxoid liposarcoma.

Sometimes, to treat myxoid liposarcoma patients, pre-operative radiotherapy is given with 2 variants of dosage, hypo fraction 5x5 Gy and 5x4 Gy every day each and perform a wide local excision in 3-7 days in radiation's final days. 5-year local recurrence-free survival is 90%. 5-year overall survival is 68%. Within a follow-up period of 3-18 months, 34% metastasis was found. Acute toxicity was found in 21% of patients and only 9% having slow toxicity.[35] Pre-operative hypo fraction radiotherapy doesn't have higher wound complication than a conventional fraction.[36]

Spalek et al, perform a pre-operative hypo fraction radiotherapy to extremity myxoid liposarcoma with 5x5 Gy and followed by surgery 6-8 weeks after the last radiation procedure. In total 31% of patients are having pre-operative wound complications. No patients were found to have localized recurrence during the study, but 14% were having distant metastasis.

There is some pre-operative radiotherapy regimen for

soft tissue sarcoma which is given by hypo fraction:
10x3 Gy giving 97 % localize control for 5 years, with a lower complication level, which is 15%.
5x5 Gy given to soft tissue sarcoma, every day each, operative procedure performed in 3-7 days from the last fraction of radiotherapy. In resection limit case (R1), a booster dose is also given in 30 Gy into 15 fractions. The result is 3-year local recurrence-free survival is 81%.
8x3,5 Gy with ifosfamide congruent, giving localize control and good wound healing for myxoid liposarcoma. 91% of patients show no localize recurrence in 5 years.
A high level of local control in preoperative radiation toward myxoid liposarcoma is interesting to research. A trial for clinical phase II in an international prospective study for decreasing the pre-operative radiotherapy dosage with a total dose of 36 Gy (18x2 Gy) is still going on. This trial evaluated this type of liposarcoma pathologically. Clinical Trials.gov identifier (NCT number): NCT02106312.
Radiotherapy target for myxoid liposarcoma is the same as radiation target in pre-operative radiotherapy in other soft tissue sarcoma:[40,41]
1. Gross Tumor Volume (GTV) based on the pre-operative sequence of T1 in MRI with gadolinium contrast. MRI fusion and contrast CT scan recommended for delineating GTV
2. Clinical Target Volume (CTV) for intermediate – high-grade sarcoma is putting the gross tumor and clinical microscopic linear. CTV= GTV+3-4 cm longitudinal (proximal and distal). If the extension is reaching the outside compartment, the linear could limit to the end of the compartment and add 1,5 cm radially which is seen in the T2 MRI sequence in CTV. Clinical consideration is needed to put in the edema in CTV.
In the RTOG-0630 clinical trial, patients with preoperative radiotherapy with Image Guided Radiation Therapy technique is decreasing the slow toxicity in extremity soft tissue sarcoma. Slow toxicity that is evaluated is lymphedema, subcutaneous fibrosis, joint stiffness.[43] Radiotherapy with volume expansion target is obtained with the IGRT technique. Image guidance verification is performed every day. We use this volume target:
1. GTV: gross tumor based on MRI T1 contrast. MRI is performed in the last 8 weeks. If possible MRI fusion is done with CT planning.
2. CTV: gross tumor + microscopic risk in surrounding organ.
a. Intermediate-high grade tumor size ≥8 cm; CTV= GTV+3 cm heading to longitudinal with putting the edema that is seen in T2 MRI. However, the radial margin is 1,5 cm
b. Low grade tumor < 8 cm; CTV= GTV +2 cm and put in the edema. The radial margin is 1 cm
3. PTV: CTV + 5mm
According to Vakilian et al. study, myxoid liposarcoma with preoperative radiotherapy with 50 Gy dosage for duration median 37 days, giving an 8-69 % decreasing of tumor volume with median 42% from simulator CT until last MVCT radiation. Whereas if calculated from CT simulator until preoperative MRI result, a median of decreasing tumor volume is 67%. The reduction of this tumor volume is axially located.[44] The decreasing of tumor diameter with pre-operative radiotherapy is 39%.[7]
With the same dosage as preoperative radiotherapy which is 50 Gy in 25 fractions, other studies also show a median of decreasing myxoid liposarcoma tumor volume by more than 50%.[45,46]
Other studies are also evaluating pre-operative radiotherapy respond toward myxoid liposarcoma and soft tissue sarcoma:
1. Roberge, et al reported that the median of decreasing tumor volume in myxoid liposarcoma is 82,1%, and 13% for other subtypes of liposarcoma besides myxoid.[47]
2. Grange, et al, reported that the median of decreasing tumor volume in myxoid liposarcoma is 64,2%. Whilst the decreasing of tumor volume in total soft tissue sarcoma (19 from 68 cases are myxoid liposarcoma included) is 33%.[48]
Metastasis also has efficacy in palliative radiotherapy. Like other reports and studies. 63% resulting in an improvement in pain complaining, 50% improvement of motoric disorder in vertebrae metastasis and myxoid liposarcoma. The radiation dosage is 30 Gy divide into 10 fractions.[49] A case report has shown that metastasis intraperitoneal which is treated with radiation of 15x1,6 Gy at all over peritoneal cavity, and followed by booster 8x2 Gy in peritoneal residue lesion. The outcome, with this radiation dosage, is a complete metabolic response from peritoneal lesion based on the PET-CT scan result.

Prognosis

Factors that predispose the prognosis of myxoid liposarcoma are age (first time diagnosed) >45 years old, tumor size >10 cm. high grade, deep sited tumor, operative incision boundary. Differentiated, mitosis, necrotize, proliferation index such as MIB-1 and Ki-67, overexpression p53 is the morphological aspect to

prognostic factors in myxoid liposarcoma.[11,14,19]

The amount of necrotizing tissue in liposarcoma after neoadjuvant therapy towards survival rate is still controversial. Some data shows that more than 90% of necrotizing tumors will increase the disease-free survival from univariate analysis, but, in multivariate analysis, the correlation of necrotizing tumors statistically not significant with the survival rate.[51] Necrotizing percentage correlates with the increase of local control with Hazard Ratio (HR),0.972 (95%CI:0.947-0.997),p=0.027, but there is no correlation between disease-free survival and distant metastasis-free survival. (p=0.706 dan p=0.207).[30]

In a previous study, patients with soft tissue tumor with 95% pathological necrotize after neoadjuvant therapy will have lower a localize recurrence rate and higher survival rate.[52]

There is still no study that evaluates the direct correlation between the increasing myxoid liposarcoma volume post-preoperative radiotherapy with survival rate. But, there is a controversy about the correlation between general post-radiotherapy decreasing volume tumor soft tissue tumor with histopathology response.

Roberge et al. reported that there is a correlation between a more than 50% decrease in tumor volume with responsive histopathology.[47] Whereas, Benz et al. reported that there is no correlation between decreasing volume tumor with pathology responsiveness.

Localized recurrence and distant metastasis often diagnosed within 5 years after first time diagnosed.[2] 5 years localize recurrence survival rate of myxoid liposarcoma is 82-96%, whereas overall survival is 86-93,9% .[6,7,11,14]

Five-year disease-free survival with radiotherapy preoperative is 78.6% (95% CI: 67.8–86.1), distant metastasis-free survival 84.7% (95% CI: 74.5–91.0), local recurrence-free survival 95.6% (95% CI: 86.9–98.6), overall survival 87.5% (95% CI: 77.2–93.3).[29]

Radiotherapy mainly gives the advantage of five-years disease-free survival about 96% compared to 82% with surgery only.

Conclusions

Myxoid liposarcoma is responsive to radiation. Preoperative radiation could be an option to maintain the organ function with a tolerated side effect.

Commonly the radiation dosage for preoperative radiation is 50 Gy into 25 fractions. The same goes for the conventional dosage, hypo fraction 5x5 Gy, and give a good local control with the operative procedure within a week or 6-8 weeks.

Myxoid liposarcoma response toward pre-operative radiation can be seen radiologically, post-radiation decreased tumor volume, and pathologically as a percentage of necrotizing tumor cell. There is no correlation between radiation responsiveness with survival rate. But, > 90 % of the necrotizing tumor has been reported to have a higher survival rate. Therefore, in myxoid liposarcoma cases, radiation is considered to avoid an aggressive operative procedure, especially in extremities.

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