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Prospective clinical study of pre-operative SIB-IMRT in preparing surgical boundary of extremity soft tissue sarcoma

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Abstract. – OBJECTIVE: To establish the pre-operative simultaneous integrated boost intensity-modulated radiation therapy (SIB-IMRT) technology in preparing the surgical boundary of extremity soft tissue sarcoma (ESTS), aiming to investigate its impacts towards the short-term local control and post-operative wound complications of ESTS.

PATIENTS AND METHODS: 16 patients with local advanced ESTS were prospectively collected and performed the SIB-IMRT technology to prepare the surgical boundary. The resection surgery was completed within 3-6 weeks after the radiotherapy. The efficacy was evaluated according to the changes of limb circumference, RECIST criteria and relapse-free survival; and the CTCAE 4.0 standard was used to evaluate the considerations of post-radiotherapy acute radiative skin injury.

RESULTS: The radiotherapeutic plan of pre-operative SIB-IMRT technology in preparing the surgical boundary of locally advanced ESTS was developed. Before and after SIB-IMRT, the difference of limb circumference was statistically significant ($p < 0.05$); after SIB-IMRT, 13 cases exhibited the decreased lesions, 7 cases exhibited the partial remission (PR), and 9 cases showed the stable lesions (SD); the median time of recurrence-free survival was 6.5 months, the efficiency of pre-operative SIB-IMRT was > 60%, with 13 cases of level 1 acute radiative skin injury, 2 cases of level 2 and 1 case of level 3.

CONCLUSIONS: The pre-operative SIB-IMRT was feasible, safe and effective in preparing the surgical boundary of locally advanced ESTS, which could reduce the tumor volume, and improve the short-term relapse-free survival time.

Key Words:
Simultaneous integrated boost intensity-modulated radiation therapy, Soft tissue sarcoma, Surgical boundary, Preoperative radiotherapy, Efficacy evaluation.

Introduction

The main treatment method towards the extremity soft tissue sarcoma (ESTS) is the surgical resection, while the post-operative recurrence rate is higher[1]. The recurrence rates of different surgical methods are not the same, among which those of wide resection and radical resection are 15-2% and < 5%, respectively. As the radical resection would often greatly damage the limb functions, the wide resection is set as the clinical surgical goal. When many ESTS patients receive the treatment, the tumor size would be large, and closely connect with the important surrounding anatomical structures such as nerves, blood vessels and bones. They could be identified as the locally advanced tumor patients[2]. This kind of patients exhibit no safe surgical boundary, thus, the wide resection could not be implemented. Therefore they lose the opportunity of limb salvage. So, it would be necessary to perform a variety of pre-operative neoadjuvant therapeutic techniques to reduce the tumor volume, thicken the pseudo-capsule and clear the tumor boundary, thus reaching the goal of tumor phase degradation[3]. With the rapid development of IMRT technology, it has been widely used in the esophageal cancer, lung cancer, breast cancer, head and neck cancer and other cancers[4]. The efficacy of pre-STS radiotherapy has been affirmed, but the conventional radiotherapy is still the main methods in may medical centers[5,6]. The conventional radiotherapy exhibits the disadvantages of high post-operative wound complication rate, long radiation treatment duration and relatively high complication

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Table I. General information of 16 patients with locally advanced limb soft tissue sarcoma.

Clinical feature		Cases (n)
Gender	Male	10
	Female	6
Age (years, mean)	14-66 (34.5)	
	≤18	1
	19~50	9
	>50	6
Site	Leg	5
	Thigh	6
	Upper arm	5
Staging	IIb	7
	III	9
Pathological types	Malignant schwannoma	1
	Synovial sarcoma	4
	Epithelioid sarcoma	1
	Ewing's sarcoma	2
	Pleomorphic sarcoma	2
	Fibrosarcoma	3
	Liposarcoma	2
	PNET	1
Resection method	R0 Resection	16

PNET, primitive neuroectodermal tumor

rate in the late stage of radiotherapy, etc.[7]. How to avoid the above disadvantages and make the locally advanced patients, who have lost the opportunities of limb salvage, reach the requirements of wide resection, are the still-needed-to-be-resolved problems. In this study, SIB-IMRT technique was used to perform the pre-operative radiotherapy towards the patients with locally advanced ESTS. STS is a solid tumor with irregular shape, and would usually exist only one direction or one edge that is adjacent to the vital structures such as nerves, blood vessels and bones. The application of SIB-IMRT technique could produce a "tumor-free area", as the safe surgical boundary, through improving the radiation dose towards the tumor-adjacent vital structures, creating the favorable conditions for limb salvage surgery. The patients that face the amputation could realize the limb salvage and effectively control the risk of local recurrence. Because of high dosage and smaller volume, it could reduce the radiotherapeutic toxicity such as fibrosis, while increase the dosage towards the small boundary of tumor, thus ensuring the requirements of wide resection. Currently, the SIB-IMRT technology has not been widely used in the therapeutic areas of STS yet at home and abroad. There is no report about the evaluation of its radiotherapeutic plan development and clinical efficacy, so we adopted a prospective clinical case observation research, aiming to explore the application of SIB-IMRT in the pre-operative radiotherapy and safe surgical boundary preparation towards the locally advanced STS, investigating its advantages in the radiotherapeutic plan design and clinical efficacy evaluation.

Patients and Methods

Subjects

16 patients with locally advanced ESTS treated in our department from January 2012 to September 2013 were prospectively collected, including 10 males and 6 females, aged 14 to 66 years old, with a median age of 34.5 years old; the pathological type: 1 case of malignant schwannoma, 4 cases of synovial sarcoma, 1 case of epithelioid sarcoma, 2 cases of Ewing's sarcoma, 2 cases of pleomorphic sarcoma (malignant fibrous histiocytoma), 3 cases of fibrosarcoma, 2 cases of liposarcoma, 1 case of primitive neuroectodermal tumor (PNET); sites: 5 cases on the legs, 6 cases on the thighs and 5 cases on the upper arms; staging: 7 cases in stage II b, 9 cases in stage III; the 16 patients were all performed the pre-operative IMRT, followed by the R0 resection (wide resection). The general information of STS patients was shown in Table I. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Xinjiang Medical University. Written informed consent was obtained from all participants.

Inclusion Criteria

Pathological diagnosis confirmed the initially treated patients as ESTS; The staging was in the stage IIb-III according to the STS staging of American Joint Committee on Cancer (AJCC); The radiological assessment confirmed that there was not safe surgical boundary (adjacent to the major blood vessels, nerves and bones – locally advanced); No radiotherapeutic contraindications; Voluntarily accepted the pre-operative radiotherapy.

Exclusion Criteria

Combined with severe chronic diseases; Combined with other malignant tumors; with poor compliance; with the previous history of radiotherapy towards the affected extremity; with ulceration, sinus, infections and severe skin diseases in the radiation area.

Posture Immobilization, CT Simulating Positioning

As the extremities have a larger range of activities than the trunk, the positioning accuracy and stability would be critical. In order to ensure the accurate posture fixation and stereotactic positioning during the radiotherapy, the phantom was elaborated, and the plaster was used when necessary to ensure that the ESTS patients would maintain the stable extremity positioning during SIB-IMRT process. In this way, the radiation target volume could be precise and the positioning errors could be reduced as much as possible. According to the differences of tumor sites, a special SIB-IMRT position of leg and upper arm STS was designed, such as the supine position, the lower limb of healthy side flexed the hip and knee. Then, the leg of diseased side could be fully exposed to reduce the occlusion of the target volume by the healthy limb. The prone position, the shoulder joint expanded outwards, flexed the elbow, and the forearms were put behind the back to reduce the occlusion towards the trunk and the contralateral limb, so that the radiation area could be arranged easily to reduce the damages towards the internal organs. Before the CT positioning, the skin of radiation area should be marked with the lead wire to mimic the intended surgical incision, so that the delineation of skin and subcutaneous tissues-protected target volume could be facilitated. The iodine contrast agent was intravenously injected before the CT positioning scan, and the scanning range included the entire body, as well as the tumor (Figure 1).

Delineation of SIB-IMRT Target Volume

Marginal target volume (GTVs): at the adjacent of tumor and blood vessels, nerves and bones, the 1cm-wide boundary zone was drawn layer by layer from the pseudo-capsule towards intratumoral direction, with the vertical axis covering the both tumor poles. This target was

Figure 1. SIB-IMRT special position. ***A,*** Upper arm; ***B,*** Calf. ***C,*** Marked incision by lead wire.

the surgical boundary of SIB-IMRT; Tumor target volume (GTV): the layer by layer drawing imaging could expose the tumor; Clinical target volume (CTV): the partial subclinical lesions that were adjacent to the periphery of tumor, including the biopsy channels and the satellite lesions, based on results of GTV, this study extended 5 mm outwards along the x-axis and z-axis, and 3 cm outwards along the proximal and distal ends of y-axis, respectively; Planning target volume (PTV): on the basis of CTV, 3-5 mm were extended outwards along the 3 dimensions; Delineation of the involved organs, such as the bones, spinal cord, as well as the skins and subcutaneous tissues that were not marked by the lead wire were also delineated as the involved organs.

Development and Validation of SIB-IMRT plan

The patients were performed the treatment plan of high dose segmentation, short-treatment course and SIB-GTVs. GTVs 3.2-3.5 Gy/time; PTV 2.8-3.0 Gy/time, 5-7 fields, once/day, 5 times/week for 2-3 weeks to complete. Through the conversion of biological equivalent dose (BED), the pre-operative radiotherapy dose basically reached 50 Gy, which met the requirements of NCCN Guidelines.

Placement verification: before the radiotherapy, the patients were photoed the entopic lateral position verification film (EPID) by the radiotherapy machine, and compared with the planned DR images. The comparisons were performed towards the upper-lower, left-right, anterior-posterior positions of bony landmarks and anatomical locations. The error was less than 5 mm, the formal treatment could be started.

Surgical Program

The surgery was performed 3-6 weeks after the pre-operative SIB-IMRT. The incision was performed in the lead wire-marked area before the radiotherapy. The tumor-adjacent major blood vessels, nerves and bones (i.e. the surgical boundary identified by the SIB-IMRT technique), together with the tunica externa of blood vessels, nerve and periosteum, were performed the marginal excision, the electrotome was used to burn the bone surface to reduce the residual of tumor cells, while the rest sites of tumor were achieved the standards of wide resection (1 cm outside the pseudo-capsule of tumor) (Figure 2).

Evaluation Indexes

The following indexes were evaluated after SIB-IMRT: Changes of limb circumference: measured and compared the limb circumferences before and after SIB-IMRT; Efficacy evaluation of solid tumor: according to the RECIST guidelines[8], the changes of tumor sizes by MRI[9] were used to evaluate the efficacy of SIB-IMRT.

Tumor cell necrosis rate (TCNR): according to the Huvos method[10], the tumor was split from the maximum cross section for the multiple sampling to measure and calculate TCNR before and after SIB-IMRT. Each case had the representative biopsy specimens before SIB-IMRT (the tumor marginal tissues), 5 microscopic fields were randomly selected (40 × 10 times) to count the tumor cells, and the mean value M was used as the base. The specimen was cut from the maximum cross section after the surgery, and 10 tissues were randomly taken, among which 8 were from the surrounding sites and 2 were from the tumor center, each tissue was made 2 HE slices, and each slice was randomly selected 5 microscopic fields (40 × 10 times) to count the survived tumor cells, the average N was used; TCNR = (1-N/M) × 100%.

Recurrence conditions 6 months after the surgery: no recurrence within the 6 months after the surgery could be recorded as effectiveness.

Relapse-free survival time: the relapse-free survival time (months) was recorded from the first post-operative day to the end of follow-up in February 2014.

Acute radiation skin injury: according to the standards of CTCAE4.0 (Common Terminology Criteria for Adverse Events, 2009), the acute radiation skin injury was classified.

Follow-up Plans

The recheck was performed 1 month after the surgery, then rechecked every 3 months, the event starting point was defined as the first post-operative day, and the end point was defined as non recurrence within 6 months after the surgery. The follow-up time: from February 2012 to February 2014, with a total of 24 months.

Statistical Analysis

SPSS 18.0 was used for the statistical description (SPSS Inc., Chicago, IL, USA). Changes of limb circumference: mean ± standard deviation; MRI image changes: remission rate, etc; Relapse-free survival time: survival curves; Acute radiation skin injury: ratios of different injury levels.

Figure 2. The surgical procedure. ***A,*** Along with blood vessels, nerve sheath edge of outer membrane excision; ***B,*** Along with periost excision; ***C,*** No residual tumor on tumor bed after resection by naked eye; ***D,*** Safe surgical margin by SIB-IMRT.

The self-pair rank test was used to infer the differences of limb circumference before and after SIB-IMRT. $\alpha = 0.05$.

The sequential trial test was used to infer the effectiveness of surgical boundary of ESTS by SIB-IMRT technology: Non-relapse within 6 months after the surgery was viewed the effectiveness; while the relapse within 6 months after the surgery was viewed as the ineffectiveness.

Results

Delineation of Target Volume of ESTS Surgical Boundary

The target volume of each patient was composed by five parts: GTVs (produced marginal target volume), GTV (tumor target volume), CTV (clinical target volume), PTV (planning target volume), skin, subcutaneous tissues, bone, lung, spinal cord, testis and other protected organs. The delineation of upper limb STS target volume was shown in Figure 3.

Design of SIB-IMRT Planned Radiation Field

The computer simulation was used to design the radiation treatment field to make the conformity index better, and achieved the target coverage range of each isodose curve as much as possible. The results of this study showed that the conformity index of 5-7 ESTS radiation fields were better.

Distribution of SIB-IMRT Planed Isodose Curve

The plans and designs all achieved the required preset levels: PTV was covered by 95%

Table II. Changes of limb circumference before and after SIB-IMRT.

Changes of limb circumference (cm)	Minimum	Maximum	Mean ± SD	*p*
The limb circumferences before SIB-IMRT	26	95	52.84 ± 18.84	3.04×10^{-4}
The limb circumferences after SIB-IMRT	26	91	50.53 ± 18.56	
The average circumference shrank	0	6	2.31 ± 1.98	

isodose curve. There was no dose-cold spot within GTVs, and no dose-hot spot within the operative areas such skin and subcutaneous tissues, the dose-hot spots did not exceed 105% of the planned dose. The priority of designed plan was: GTVs, PTV, CTV, Skin and subcutaneous tissues. For example, the isodose distribution curve of STS behind the thigh was shown in Figure 4.

Changes of Limb Circumferences After SIB-IMRT

The limb circumferences of ESTS patients, who accepted the pre-operative SIB-IMRT, varied different degrees of narrowing or consistent with the same before the radiotherapy. 13 patients exhibited the narrowed limb circumferences after SIB-IMRT, and 3 cases exhibited no changes. The circumference before SIB-IMRT: 52.84 ± 18.84, the circumference after SIB-IMRT: 50.53 ± 18.56, the average circumference shrank 2.31 ± 1.98 cm, and the seld-paired rank sum test revealed that there was difference in the limb circumference before and after SIB-IMRT, $p < 0.05$ (Table II).

Changes of Tumor Sizes Measured by MRI After SIB-IMRT

The enhanced MRI scan was performed to measure and evaluate the solid tumor effectiveness, based on the Evaluation Criteria of RECIST guidelines, among which o case of CR, 13 cases (13/16) exhibited the reduced lesions, 7 cases of PR (7/16), 9 cases of SD (9/16), and 0 cases of PD. The changes of some tumor size were not big, but MRI exhibited the significantly increased tumor necrosis range ($p < 0.05$) (Table III).

Postoperative Relapse-free Survival Time

At the end of follow-up, the shortest time of post-operative relapse-free survival was 2 months, while the maximum was 20 months, with the median of relapse-free survival time was 6.5 months, there were two cases occurring the lung metastases during the follow-up, but without local recurrence. The non-recurrence situation within 6 months of surgery was shown in Figure 5 A, with 10 cases of effective cases, and 6 cases of ineffective cases, and it could be seen that when the 16th patient was enrolled in the experiment, the experimental line touched the upper boundary, which could be explained as that the pre-operative SIB-IMRT produced ESTS boundary + R0 resection surgery could improve the relapse-free survival rate within 6 months after the surgery. The relapse-free survival curve was shown in Figure 5 B.

TCNR after SIB-IMRT

According to the Huvos grading method, the ratio of TCNR in this study was: 0 case of grade

Table III. Changes of tumor sizes measured by MRI.

Changes of tumor sizes (greatest dimension, cm)	Minimum	Maximum	Mean ± SD	*p*
The tumor size before SIB-IMRT	1.7	13.6	5.23 ± 3.50	0.158
The tumor size after SIB-IMRT	1.5	12.9	5.03 ± 3.28	
Percent of TNR before SIB-IMRT (%)	15	56	36.56 ± 13.69	0.008
Percent of TNR after SIB-IMRT (%)	20	65	41.25 ± 16.38	

TNR, tumor necrosis range

Table IV. Classification of TCNR and acute radiative skin injury after SIB-IMRT.

	grade I	grade II	grade III	grade IV	grade V
TCNR	0/16	12/16	3/16	1/16	
Acute radiative skin injury	13/16	2/16	1/16	0/16	0/16

TCNR, tumor cell necrosis rate.

I, 12 cases of grade II (12/16), 3 cases of grade III (3/16), 1 case of grade IV (1/16) (Table IV).

Acute radiative skin injury after SIB-IMRT

According to the grading standards of USA CTCAE4.0 acute skin radiative injury, among the patients of this research: 13 cases of grade I (13/16), 2 cases of grade II (2/16), 1 case of grade III (1/16), 0 case of grade IV and V (Table IV). the skin defect range of 1 patient was large after the tumor resection, then performed the skin flap graft with mesocarp and pachyderma, the post-operative flap necrosis was 1/2, while the wound healed after the local dressing, and the rest 15 patients prolonged the stitch removal time to 4-5 weeks, and the wounds all healed in the first stage.

Discussion

The STS treatment has now entered the era of comprehensive treatment, the clinical practice has proved that the only single treatment would often be difficult to obtain the best results. STS mainly depends on the surgical treatment, and the radiation therapy is an important supplement towards the local therapy. The overall effect of chemical treatment is still controversial except for the sure curative effects towards synovial sarcoma, Ewing's sarcoma and rhabdomyosarcoma. The target drug therapy has been developed greatly in recent years, but it's not the first-line treatment towards STS patients. In summary, the surgery and radiation therapy are still in the pivotal positions in the treatment of STS.

The STS surgical approaches could be classified by two systems. The wide resection and radical resection are the ideal approaches[11]. Because STS is often adjacent to the important peripheral nerves, blood vessels and bony tissues, the radical resection would significantly damage the limb functions, therefore it's currently less used in the treatment of STS, the most widely used method is the surgical resection. The wide resection refers to the resection in the three dimensions of tumor, setting the normal tissues 1cm outside the tumor

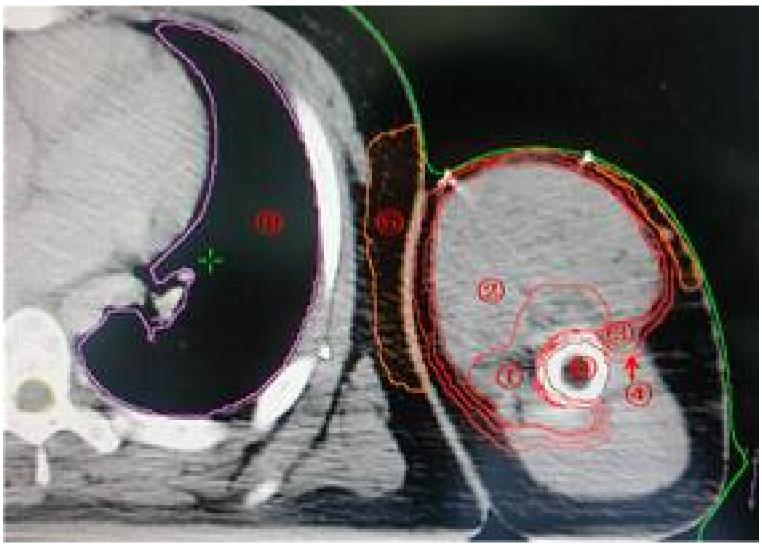

Figure 3. The target sketch from upper arm. 1) GTVs (produced marginal target volume), 2) GTV (tumor target volume), 3) CTV (clinical target volume), 4) PTV (planning target volume), 5) skin, subcutaneous tissue, 6) bone, lung, and spinal cord, testis, etc.

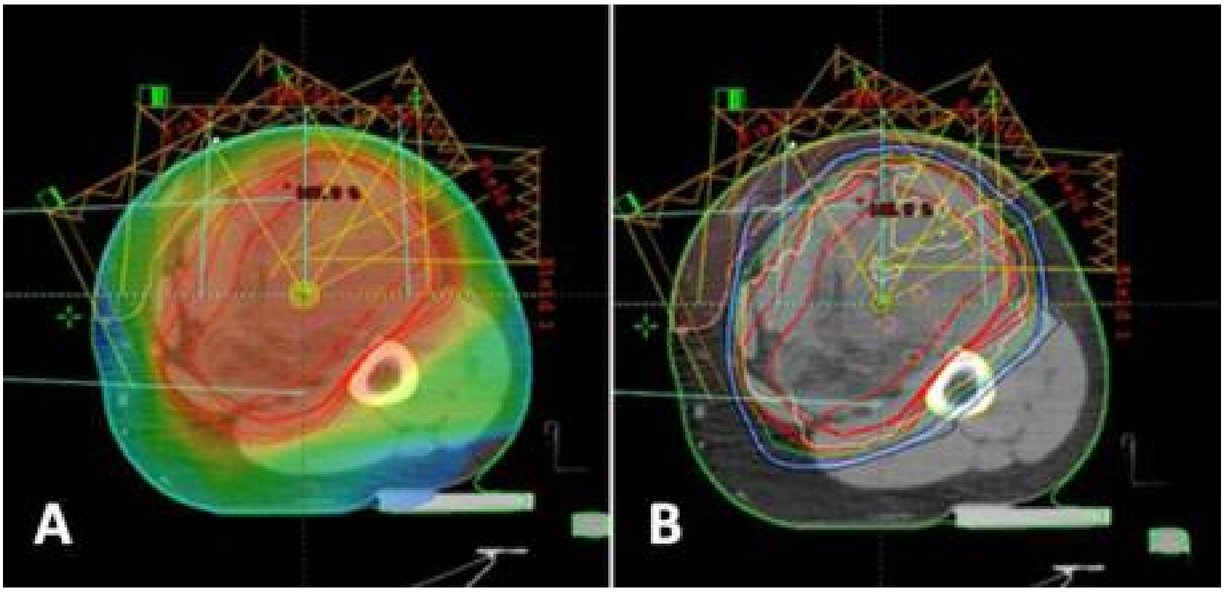

Figure 4. Distribution of the isodose curve. ***A,*** The distribution of hot dose point; ***B,*** Covering target zone in different isodose curve.

as the safe margin. STS is often adjacent to such important anatomical structures as nerves, blood vessels and others, this area could not achieve the required safe surgical margin of wide resection. In this study, SIB-IMRT technique was used to perform the pre-operative radiotherapy towards the locally advanced ESTS patients, aiming to make the safe surgical boundary to achieve the requirements of wide resection.

Compared with the conventional radiotherapy, IMRT has many advantages[12], including 1) the precise posture immobilization, improving the precision of radiotherapeutic localizationing, positioning and treatment; 2) the precise plan, accurate delineation of target volume, higher adaptation degree, much more uniform of dose distribution, and better protection towards the surrounding normal tissues. 3) Precise radiotherapy, the doses of the points inside the target area could be adjusted based on the needs to ensure maximum tumor dose, while reduce the radiation dose towards the surrounding normal tissues. 4) Individualized treatment plan, which could achieve the different dose levels in the same plan, and shorten the treatment time.

IMRT was proposed in the 1970s, and matured in the 1990s, and have been developed for

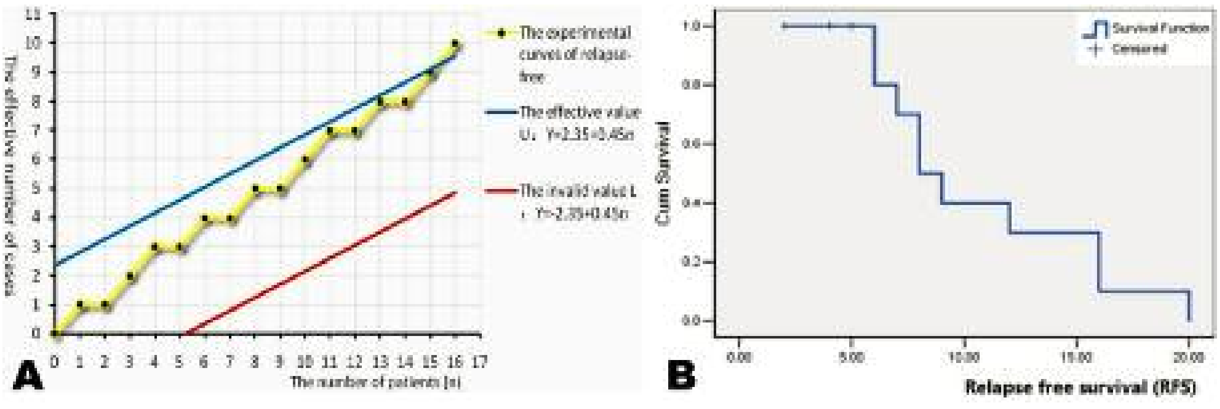

Figure 5. Limbs STS recurrence and post-operative relapse-free survival. ***A,*** Sequential trial of limbs STS recurrence after pre-operative SIB-IMRT. ***B,*** Post-operative relapse-free survival curves after pre-operative SIB-IMRT.

over 20 years[13]. However, there was a little study about the limb STS IMRT. In this study, the IMRT technique was used for the pre-operative radiotherapy towards the locally advanced STS patients, who could not achieve the safe surgical margins because of the adjacent vital structures, such as blood vessels and nerves, etc. The SIB technology was used to prepare the STS safety surgical boundary, through improving the radiotherapeutic dose towards the regions without the safe surgical boundaries without prolonging the treatment course, and there was no related research report domestically and abroad currently.

During the radiotherapy of malignant cancer, the posture immobilization is an extremely important part of treatment process and treatment planning design. The fixed position allows the patient to reduce the position offset during the radiotherapy process, so that the actual target range could be maintained as consistent as possible with the original plan. The posture immobilization is one of the key technologies which could ensure the efficacy, reduce the side effects of radiotherapy.

There are no vital organs adjacent to the limb radiotherapeutic regions except for the blood vessels, nerves, soft tissues and bones, so the conventional radiotherapy would be more used for the intra-operative radiotherapy previously; thus, there would be not too much need for the phantom fixation. Secondly, because the limbs have larger scopes of activity than the head, neck and trunk, it would be much more complex for the posture immobilization. In this study, the thermoplastic phantom was used for the posture fixation and positioning towards the radiotherapeutic limb. As the activity range of limbs are larger, and the tumors in the distal soft tissues could not be fixed stably only with the phantom, we chose the plaster as the auxiliary fixation to limit the minor movements of limbs inside the phantom; thus, the irradiation could be much more accurate and effective. The four limbs are the symmetrical organs, in order to reduce the occlusion by the trunk and contralateral limb, and reduce the damages towards the involved organs. We designed a special STS radiotherapy position of leg and upper arm, aiming to minimize the occlusion by the normal tissues in the radiation field, and avoid the adverse reactions of normal tissues by the irradiation. The clinical effects had been proven to be good.

The delineation and determination of target volume are an important part of ESTS IMRT, either the preparation of surgical GTVs or the delineation of planning target volume would directly affect the dose volume parameters of target volume and normal tissues and organs[14].

The study used SIB-IMRT technique to produce ESTS surgical margin. The research focused on the adjacent points of tumor and vessels and nerves –pseudocapsule, reaction zones and satellite lesions, just for achieving the requirement range of wide resection. Because SIB was used to improve the dose of this area, GTVs were specifically designed. Before the CT positioning, the post- radiotherapy surgical incision was designed and marked on the skin of radiation area with lead wire, because the biopsy channel should be resected, and the incision would be more spindle, the skin and subcutaneous tissues outside the spindle-shaped incision would be set as the protective organs, so that the dose towards this region could be reduced, and the radiation-induced skin damage, as well as the occurrence of post-operative wound complications, could also be reduced. The clinical practice proved that the delineation of target volume was feasible.

The commonly used pre-operative radiation dose of STS was 50 Gy, 1.8-2.0 Gy/time within 5-6 weeks. Fakhrai et al[15] studied the neoadjuvant radiotherapy in treating the high level limb sarcomas, the pre-operative radiotherapy doses was 50 Gy, 2 Gy/time within five weeks, and 6.5 weeks after the radiotherapy, the surgical borders were ≥ 1.2 cm, while no adverse reaction was found after the radiotherapy. Iwata et al[16] applied the pre-operative radiotherapy with a total dose as 51 Gy, 1.7 Gy/time, twice/day, with the interval as at least six hours, and completed with three weeks, the recurrence-free survival was superior to 50 Gy, 2 Gy/time conventional fractionation, and completed within 5 weeks. 112 cases of locally advanced patients were performed the radiotherapy, with the median dose as 50 Gy, 2 Gy/day, 5 times/week for 5 weeks, the three-year recurrence-free survival was 68%[17].

Among the previous studies of STS external radiotherapy, it would be mostly applied as 2 Gy conventional fractionation, five times/week for five weeks, with a total dose as 50 Gy. Such program needed 5 weeks before the surgery, and because the radiation-induced acute skin reaction period would be avoided, thus the surgery could only be performed 3-6 weeks after the radiotherapy, so the STS patients had to wait at least eight weeks, the waiting time was long, thus the patient's compliance would reduce during this period, and the outcome would be certainly affected.

This study used the SIB program to prepare the surgical marginal GTVs, the GTVs biological equivalent dose (BED) = 46-57.6 Gy, and the dose had reached the requirements of NCCN guidelines (50 Gy). During the planning, PTV was covered by 95% isodose curve, so that GTVs were small, without cold spot inside the GTVs target volume, and the dose distribution was much more uniform. This study used the large dose fractionation, doing the course shortened, reducing the patient's waiting time, and improving the patient's compliance. Since the boundaries of tumor and blood vessels, nerves and bones were the difficult parts of the surgery, this study used the SIB-IMRT technology to improve the dose of this area, reducing the doses of the rest target volumes. Based on the premise of not violating the "4R" principle of radiobiology. The high-dose target volume could be reduced, and the post-radiotherapy adverse reactions were also reduced. The inspection of domestic and international literatures revealed no similar study to this research.

The locally advanced ESTS would have the difficulty to achieve the requirements of radical radiotherapy. In this work, the SIB-IMRT technique was used to perform the pre-operative radiotherapy towards the locally advanced ESTS patients, with the main purpose to produce the safe surgical margin, and perform the surgical resection after the pre-operative radiotherapy, aiming to achieve the purpose of local radical treatment.

The selection of surgical timing would mainly impact the intra-operative surgical procedures and post-operative wound complications. The STS NCCN guidelines requires: the surgery should be performed 3-6 weeks after the radiotherapy, because the acute radiation reactions within this time would be more serious. It's also not recommended that the interval should be too long for the surgery because of the appearance of fibrosis in the latter stage.

Chen et al[18] reported that the surgery was performed 3-4 weeks after the neoadjuvant radiotherapy of IIb/III STS, and the wound could heal in the first stage. Baldini et al[7] reported those 4-6 weeks after the pre-operative radiotherapy 50 Gy, the surgical resection of STS was performed, and post-operative wound complication rate was 35%. In Roeder et al[19] report, the authors considered the radiation-induced acute toxicity, 25 cases of STS patients received the pre-operative radiotherapy, with the total dose as 50 Gy and 2 Gy conventional fractionation. The surgical resection was performed 4-6 weeks after the radiotherapy. Eckert et al[20] reported that the patients, who received 50-56 Gy pre-operative radiotherapy, were performed the surgery 4 weeks after the radiotherapy.

In this research, the patients were performed the surgery 3-6 weeks after the pre-operative SIB-IMRT. According to the grading standards of USA CTCAE4.0 acute radiation skin injury, 13 cases (13/16) were of grade I, 2 cases (2/16) were of grade II, 1 case (1/16) was of grade 3, and o case was of grade IV and V, showing that there was patients had the severe acute radiation skin injury than grade IV-V, and 3-6 weeks could make the acute skin radiation injury restore to the normal levels. According to the skin wound healing process: the proliferation of granulation tissues started from the 3rd day of trauma and the fibroblasts produced the collagen fibers on the 5th-6th day. With the increase of collagen fibers, the scar formation appeared, and 1 month after the trauma, the scar was fully formed. Therefore, we chose the stitch removal 1 month later, and the patients all healed in the first stage.

Previously, the standard treatment of local recurrence controlling towards ESTS was the amputation[21]. In the recent years, with the advances of surgical reconstruction techniques, the appearance of multidisciplinary treatments and the improvement of adjuvant therapy, many patients who were supposed to have the amputation retained their limbs, and minimized the functional loss.

A randomized controlled trial in the early year showed that the limb salvage radiotherapy was an effective treatment towards the high-level ESTS, with the local recurrence rate as only 15%, and exhibited no significant difference from the amputation group in the overall survival time and disease-free survival time[22]. Another study[23] showed that the limb amputation could not improve the ESTS metastasis control rate and disease-related survival. These results suggested that: the limb salvage surgery was an effective treatment towards ESTS, and the amputation could only be considered when the adequate resection margin could not be obtained.

The resection margin status is a reference to predict the local recurrence, the local recurrence rate was 13% when the cutting edge was <1 cm, while when the cutting edge was ≥ 1 cm, the local recurrence rate was 0[24]. According to the STS NCCN guidelines, the cutting edge ≤ 1 cm was set as the small edge, while the > 1 cm margin was set as the standard of wide resection. In this study, the 16 patients all exhibited the close relationship between a side edge of STS and the blood vessels, nerves and bones. The rest edges of tumor were normal muscle tissues, skins, or subcutaneous tissues, so these regions could realize the boundary of > 1 cm wide resection. When the tumor was adjacent to the edges of blood vessels, nerves and bones, SIB-IMRT technique could be used to prepare the 1 cm-wide surgical margin, and the surgery could resect the tunica externa of blood vessels, nerves and periosteum together, thus making the marginal resection of anatomical structure meet the wide resection requirements by the physical means of SIB- IMRT.

The efficacy of STS presurgical radiotherapy has been initially recognized. Jones et al[25] studied and showed that the surgical treatment of retroperitonealal STS after the pre-operative conventional external radiotherapy exhibited the 2-year overall survival and disease-free survival as 88% and 80%, respectively, higher than the pure surgery group. McBride et al[26] showed that the pre-operative radiotherapy + surgical resection could reduce the local recurrence rate of STS. Pawlik et al[27] study showed that the rates of 5-year local control, disease-free survival and overall survival of pre-operative radiotherapy + STS were 60%, 46% and 61%, respectively, and the result was better than the historical data of pure surgical treatment. Moore et al[28] reported that the local recurrence rate after the pre-operative 45-56Gy radiotherapy was 38%, lower than the pure marginal resection group. Al-Absi et al[29] referred that in the system evaluation of radiotherapy before and after the locally resectable STS, the pre-operative radiotherapy-induced delay of surgical time would not bring the fatal metastasis and diffusion, and the risk of post-operative recurrence of the patients who received the pre-operative radiotherapy was lower.

This research compared the changes of limb circumference before and after SIB-IMRT, the average circumference shrank 2.31 ± 1.98 cm, p <0.05; therefore, it could be thought that there was difference in the limb circumference before and after SIB-IMRT, indicating that the pre-operative SIB-IMRT could shrink STS, so that the purpose of stage reduction could be achieved, and the unresectable tumor could be turned into resectable.

This research used the enhanced MRI scanning, with RECIST as the standard, to evaluate the reactions after SIB-IMRT. The results showed that: the lesions of 13 cases (13/16) reduced, 7 patients were of PR (7/16), 9 cases were of SD (9/16). From the above data analysis, although there was no CR patient, and PR only had 7 cases, 13 patients exhibited the tumor shrinkage, and no one was worsened, indicating that through the pre-operative SIB-IMRT, the primary lesions of 16 patients had been well locally controlled.

This study used a prospective sequential trial design and evaluated the impacts of pre-operative IMRT with a wide resection towards the short-term relapse-free survival of locally advanced ESTS patients. A large number of domestic and foreign literatures did not mention the specific relapse time after the marginal resection. There was a domestic study which reported that the median time of recurrence was 7 months[30]. Combined with this research, the relapse-free median survival time was 6.5 months, while the follow-up was relatively short, the study set the relapse-free 6 months after the surgery as the effective indicator of sequential test. It could be seen that the 16th patient reached the upper effective cut-off line when entered the sequential test experiment. We could conclude that: the pre-operative radiotherapy, with the SIB-IMRT technology to produce the surgical border of ESTS, could realize the short-term local control towards the locally advanced patients. In order to get the long-term results, the number of cases needed to be increased, and the follow-up period needed to be extended for further verification by the randomized controlled design.

Conclusions

To sum up, our data show that the pre-operative SIB-IMRT can reduce the tumor limb circumference and tumor lesions, simultaneously increase the percent of tumor necrosis range and improve the short-term relapse-free survival time. The pre-operative SIB-IMRT was feasible, safe and effective in preparing the surgical boundary of locally advanced ESTS.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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