Radiation Medicine Program- Sarcoma Practice Guidelines

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1. Introduction

Soft tissue sarcomas (STS) are a heterogeneous group of rare malignant tumors derived from mesenchymal tissue and comprise just less than 1 % of adult cancers in the United States. In 2013, approximately 11, 410 new cases of STS were diagnosed in the USA, of which 6290 will be male and 5120 will be female (Source: Cancer Facts and Figures 2013 from the American Cancer Society http://www.cancer.org/acs/groups/content/@epidemiologysurveilance). The global incidence of STS is difficult to report due to the low prevalence of this disease.
Several risk factors have been identified for STS, however, there is no clearly defined etiologic factor. General screening in high-risk patients using imaging or laboratory tests is not supported by clinical evidence, however, a more detailed clinical evaluation at a lower threshold of intervention may be indicated.

Introduction	Description
Incidence	▪ Incidence*: o Global incidence is not available (source Globocan 2008 http://globocan.iarc.fr/) o Incidence in the USA: 11, 410 newly diagnosed cases in 2013 o 4, 390 estimated deaths
Etiology Including risk factors for the disease	▪ Age o 50 – 55 years ▪ Genetic predisposition: o Li-Fraumeni syndrome- associated with p53 mutation o Von Recklinghausen disease- neurofibromatosis o Retinoblastoma o Gardner's Syndrome o Carney's triad o Werner's syndrome o Gorlin's syndrome o Tuberous sclerosis o Basal cell nevus syndrome ▪ Industrial chemicals: o Manufacturing thorotrast

	○ Vinyl chloride and arsenic- hepatic angiosarcomas ○ Phenoxyherbicides ○ Chlorophenols ○ Dioxins ○ Phenoxyacetic acids ○ Certain herbicides ▪ Past medical history ○ Lymphedema associated with lymphangiosarcoma ○ Past radiation exposure increases risk ○ Certain viral infections, including human herpes virus 8 (HHV-8) and human immunodeficiency virus (HIV)
Screening	▪ General screening has limited use in STS given its rarity ▪ Deep lesions to the superficial fascia require investigation, especially with a history of growth ▪ Any superficial or deep lesion of skin or soft tissue in patients with a history of prior radiation (RT) increases risk ▪ Patients with predisposing genetic factors require detailed clinical evaluation
Presentation	▪ Signs and symptoms vary depending upon the location of the tumour ▪ In general, STS presents as a lump that gradually increases in size over a period of time ▪ Early stage STS may not cause signs or symptoms (painless mass) until growth into surrounding tissues or organs ▪ Pain on presentation suggests origin from or invasion of neurovascular structures ▪ In general, superficial lesions and those that develop in the head and neck region are smaller than those in the retroperitoneum and those originating deep to fascia
Work-up and Diagnosis	▪ Complete history and physical ▪ Pre-Biopsy – Adequate cross sectional imaging (CT +/- MRI) – Plain radiograph optional ▪ Biopsy and pathology assessment – Carefully planned along future resection axis

	– Core needle or incisional biopsy. Fine needle aspiration may be acceptable in institutions with sarcoma expertise – Should establish grade and histologic subtype ▪ Chest CT to assess for distant metastases ▪ Chest CT or chest x-ray for low grade T1 lesions for metastatic assessment ▪ CT abdomen/pelvis for abdominal lesions and certain histologies, mainly myxoid/round cell liposarcoma, epithelioid sarcoma, angiosarcoma, and leiomyosarcoma ▪ Consider MRI of total spine for myxoid/round cell liposarcoma ▪ Consider CNS imaging for alveolar soft part sarcoma and angiosarcoma ▪ Consider CSF bone marrow in cases of rhabdomyosarcoma

2. Natural History

Typical signs and symptoms of STS are dependent upon the location, size, depth and pathologic characteristics of the primary tumour. The most frequently observed symptom of extremity and superficial torso STS includes a painless mass. The average interval between the onset of symptoms and diagnosis is shorter for extremity and head and neck STS than for abdominal or retroperitoneal tumors. Some STS may be asymptomatic with growth, and could be large at presentation (i.e. retroperitoneal liposarcoma). The natural history of certain pathological subtypes is inconsistent with the general behavior of STS and will be described separately (i.e. angiosarcoma).

The major route of spread is local extension. Regional lymphatic spread is less common and distant metastases are present in approximately 10 % of cases at initial diagnosis.

Pathology/ Anatomical Location	**Description and Natural History**
▪ STS of extremity, trunk or head and neck	▪ Usually presents as a painless mass in the extremity and superficial torso ▪ Erythema and warmth may be present ▪ Large, slow-growing lesions may restrict joint motion ▪ Larger tumours may ulcerate skin and/or invade adjacent muscle compartments and bone, leading to fracture ▪ For head and neck STS specifically, commonly observed symptoms include nasal obstruction, cranial nerve dysfunction, and proptosis ▪ Associated mass effect in more sensitive head and neck locations including pain, odynophagia, pharynx obstruction and airway compromise ▪ Lesions of the extremity and superficial trunk are usually controlled at the local site and death results from lung metastases, usually occurring within 2 to 3 years of the initial diagnosis ▪ Local control is lower in head and neck lesions than in the extremity, and several histologies exhibit unusual patterns of disease relapse, including rhabdomyosarcoma, liposarcoma, and epithelioid sarcoma.

▪ Retroperitoneal or intra-abdominal STS	▪ Represents 10-15 % of STS ▪ Liposarcoma (30 % to 60 %) and leiomyosarcoma (20 % to 30 %) are the most common histologies ▪ Symptoms often develop late and are nonspecific ▪ May be quite large at presentation (i.e. liposarcomas) ▪ Growth rate a determinant of clinical response ▪ Nonspecific abdominal pain or a palpable mass ▪ Low grade tumours may grow at a slow rate without symptoms and may be quite large at presentation ▪ Anorexia and chronic subacute intestinal obstruction with subsequent weight loss may appear with large tumours ▪ Nausea, vomiting or heartburn may appear ▪ Have a greater propensity to recur locally than at a distant site many years after initial treatment ▪ Rate of local relapse of these often biologically indolent tumours is high (40 to 50 %)
▪ Gastrointestinal stromal tumours (GISTs)	▪ These tumours may arise anywhere in the gastrointestinal tract but occur more commonly in the stomach or small intestine ▪ Prognostic factors include site, size, mitotic index and mutation status ▪ Metastases occur within the peritoneum and liver ▪ Represent the first solid tumor to exhibit a consistent favorable response to molecular targeted therapy- targeting c-kit
▪ Desmoid tumours (Aggressive Fibromatoses)	▪ A benign locally aggressive tumour defined by over-expression of beta-catenin ▪ Originating in the deep muscular-aponeuroses, scar tissue and tendons ▪ Women are affected twice as frequently ▪ Usually occur during the third and fourth decades of life ▪ Also occurs in children ▪ Categorized as extra-abdominal (70 %), intra-abdominal

	(10 %), and those in the abdominal wall (20 %) ▪ Intra-abdominal forms are associated with Gardner syndrome ▪ Capable of local infiltration and destruction, hence the name “aggressive fibromatoses” ▪ Local recurrence following resection alone is quite common ▪ Biopsies are required to rule out malignant disease ▪ MRI is useful to determine infiltration into other organs and size of lesion ▪
▪ Rhabdomyosarcoma (non-pleomorphic)	▪ 5th most common cancer in childhood ▪ Classified into embryonal, botryoid, alveolar, and pleomorphic subtypes ▪ 70 % are classified as embryonal and 20 % alveolar, and the remainder are variants ▪ Alveolar subtype is characterized by translocations involving the FOXO1 gene: t(2;13)(q35;q14) generates PAX3 - FOXO1 and t(1;13)(p36;q14) generates PAX7 – FOXO1 ▪ Prognostic factors in rhabdomyosarcoma include: translocation positive, age less than 1 or greater than 10 years, lymph node or distant metastases, and site of primary ▪ Treatment involves multi-agent chemotherapy and local therapy with radiation and / or surgery ▪ Initial evaluation is similar to STS but should also include bone marrow examination
▪ Angiosarcoma	▪ Propensity of superficial angiosarcoma to occur in the dermal tissues of the head and neck, typically on the scalp (approximately 50 %) or facial skin ▪ Commonly present as purple, bruiselike lesions in elderly Caucasian men, with rare occurrence in patients of African origin ▪ Macules frequently become nodular, may coalesce, and

	may ulcerate ▪ Frank bleeding is an ongoing issue ▪ The apparent multifocal nature of this disease obscures accurate definition of margins for surgery and RT ▪ Meticulous clinical examination is the only real means of identifying areas of multifocal involvement that may exist ▪ Radial growth pattern within the dermis of the scalp and facial tissues frequently results in satellite lesions ▪ Individual patches may coalesce into flat masses of substantial size ▪ Involvement of the eyelid and periorbital tissues is particularly troublesome ▪ Also can present on the chest wall of women who have had prior radiotherapy for breast cancer ▪ Surgical resection in general is often very difficult due to wide infiltrative nature of these lesions; radiotherapy is offered to patients who have not previously had radiotherapy; otherwise, taxol-based chemotherapy is often first choice
▪ Liposarcoma	▪ Second most commonly encountered subtype of STS o Myxoid liposarcoma (MLS) the most common variant ▪ MLS has an unusual pattern of recurrence in soft tissues ▪ MLS may present multifocally or recur at two or more anatomically separate soft tissue sites (more frequently in the retroperitoneum and mediastinum) ▪ Bone metastasis more common than other STS ▪ More favorable survival independent of other prognostic factors such as grade, size and depth ▪ MLS is radiosensitive and may have favorable local control following adjuvant radiotherapy
▪ Synovial sarcoma	▪ Contain the characteristic chromosomal translocation t(X;18)(p11;q11) in 100% of biphasic and 96% of monophasic synovial sarcomas

		▪ Typically occurs in the para-articular areas of the tendon sheaths and joints ▪ Affects young adults ▪ 50% present in the lower limbs- especially the knee ▪ The remainder originate in the upper limbs ▪ Calcification may be apparent ▪ Little resemblance between synovial membranes and synovial sarcoma ▪ Rarely arise from synovial tissue ▪ Higher risk of lymph node metastases ▪ An increased potential for distant metastases with larger tumors (> 5 cm), local relapse, and age older than 20 years
Routes of spread	▪ Local	▪ Longitudinal spread within the muscle groups of origin, typically an extremity ▪ Invasion of contiguous structures and muscle may occur as growth progresses ▪ May envelope major neurovascular structures ▪ For extremity STS, barriers to tumour spread such as bone and major facial planes prevent axial spread beyond originating compartments ▪ Non extremity STS have similar patterns of spread, therefore, recognizing and accounting for facial planes in surgical and / or radiotherapy target volumes is required
	▪ Regional	▪ In general, lymph node metastasis is uncommon for STS except for epithelioid sarcoma, clear cell sarcoma, angiosarcoma and rhabdomyosarcoma ▪ Traditionally, lymph node involvement has been associated with an adverse prognosis ▪ Isolated lymph node metastasis may not be as deleterious a factor
	▪ Metastatic	▪ 10 % of cases present with overt metastasis ▪ Most common site is to lung ▪ Spread to bone may follow lung metastasis, but may be the

		first site of spread for myxoid liposarcoma (MLS) ▪ MLS may also develop isolated soft tissue metastases ▪ For retroperitoneal and intra-abdominal visceral sarcomas, the liver is more commonly the first site of metastasis

3. Treatment Philosophy by scenario:

Surgery is the main curative treatment modality for STS with the goal of achieving negative margins. Radiation may be used either pre- or post-operatively to reduce the risk of local failure for deep, high grade or large (> 5 cm) tumours. If fascial boundaries are compromised intraoperatively or margins are close (< 2 cm) or involved, re-excision and/or adjuvant radiation should be considered. Chemotherapy is reserved for certain high risk cases or chemosensitive tumours.

Scenario	Treatment Philosophy
Localized Disease	▪ Surgical excision is the primary treatment of STS ▪ Tissue preservation is achievable in most patients ▪ Inappropriate surgical violation of fascia should not occur as tumours can ordinarily be considered to involve either the deep or the superficial compartment but rarely both ▪ If the deep compartment is involved or has been contaminated (as is the case in an unplanned excision or misguided biopsy), reexcision, RT or a combination of the two may be required ▪ In general, adjuvant RT is recommended: o for deep tumours o if surgical margins are close (< 2 cm) or positive o tumours are > 5 cm ▪ Chemotherapy is mandatory in rhabdomyosarcoma, and may be considered in liposarcoma or synovial sarcoma ▪ Chemotherapy may also be considered in high risk cases of locally advanced, unresectable disease for the purpose of cytoreduction facilitating surgical resection ▪ Complete R0 surgical excision is also required for GIST at all sites ▪ Imatinib may be given neoadjuvantly to achieve cytoreduction to assist a complete resection (as above), or in the adjuvant setting in patients with large tumours, and / or with high mitotic index
Regional	▪ Certain histologies are associated with a higher propensity for lymph node metastases including epithelioid sarcoma, clear cell sarcoma, angiosarcoma, and rhabdomyosarcoma

	▪ Isolated lymph node metastasis may not be as adverse a prognosis as traditionally thought and has been reclassified as stage III rather than stage IV disease in the 7th edition of the AJCC staging classification system ▪ However, treatment of the LN disease is required in all situations with surgery and / or RT if the patient is considered for curative management ▪ Aggressive approaches including regional lymph node dissection for both synchronous or metachronous nodal disease may result in prolonged survival ▪ RT is added where there is a high risk of recurrence within the surgically dissected tissues due to extracapsular nodal spread or for very large and / or multiple nodes. ▪ If RT is indicated, it should target the lymph node pathway and include the next echelon of apparently uninvolved nodal region
Metastatic	▪ In selected cases, pulmonary metastasectomy can offer prolonged disease remission ▪ Stereotactic RT delivered in a single high dose fraction or a small number of fractions may provide equivalent local control and overall survival (OS) for pulmonary metastases in a less invasive fashion. Optimal benefit is seen for patients presenting with one to three oligometastases peripherally located with no evidence of disease elsewhere ▪ Image guided intensity modulated radiotherapy (IG-IMRT) single dose fractions of 18-24 Gy have been used for sarcoma spinal metastases with high rates of local control, effective palliation, no spinal injury and minimal toxicity ▪ Soft tissue metastasis may be associated with long disease free survival (DFS), especially in selected cases of myxoid liposarcoma ▪ Treatment of metastatic bone disease is usually palliative, except in rare myxoid liposarcoma cases ▪ RT is indicated for management of symptoms of bone metastases and in cases with large malignant lesions adjacent to critical structures ▪ Surgery has an important role in the relief of obstruction or for

	mechanical problems, including fracture ▪ Debulking surgery in the chest, abdomen or elsewhere may prevent morbidity from intestinal obstruction, ureteral obstruction compressive syndromes, and respiratory embarrassment ▪ Doxorubicin-based systemic chemotherapy remains the first-line treatment for patients with metastatic disease (except rhabdomyosarcoma where multi-agent chemotherapy is offered) ▪ Other drugs including pazopanib, gemcitabine, ifosfamide or trabectedin may also be considered ▪ Imatinib remains first line therapy for patients with metastatic GIST
Recurrent	▪ 10 to 25 % of STS will recur locally ▪ Salvage treatment should be carefully considered as selected patients may enjoy long disease-free outcomes following the appropriate intervention ▪ Consider the dual goals of tumour control and normal tissue protection ▪ In patients with STS not previously treated with RT or chemotherapy, combined modality therapy should be used if they can be administered in a safe manner ▪ Treatment of previously irradiated lesions requires greater individualization ▪ Brachytherapy combined with a wide local excision may be used for lesions with a history of prior radiation treatment ▪ IMRT delivered preoperatively probably has an advantage in the treatment of previously irradiated lesions due to smaller doses and volumes involved ▪ Local recurrence with concurrent metastases following a short disease-free interval are best managed with palliative approaches
Follow up	▪ First F/U 4 to 6 weeks following primary treatment (surgery or surgery and radiation therapy) ▪ Every 3 to 4 months in the first 2 years ▪ Every 6 months for years 3 to 5 ▪ Annually thereafter ▪ For every examination:

	– Complete history and physical (H & P) – Chest imaging (plain radiograph or chest CT) – CT or MRI of the abdomen and pelvis (if retroperitoneal primary or GIST) – Consider baseline and periodic imaging of primary site based on estimated risk of locoregional recurrence – Evaluation for rehabilitation (occupational and physical therapy) o Continue until maximal function is achieved ▪ For very small gastric GISTs < 2 cm – Consider CT of the abdomen and pelvis with contrast every 3 to 6 months for 3 to 5 years, then annually – Consider endoscopic surveillance every 6 to 12 months for tumours with low risk endoscopic ultrasound features ▪ For GIST that is resectable with negative margins but with risk of significant morbidity, F/U includes monitoring with imatinib therapy and intervening with surgery if possible.

5. Radiotherapy- General Principles of Planning and Target Delineation:

Preamble:

- Intensity-modulated radiation therapy (IMRT) is a standard radiotherapy technique used for treatment of soft tissue sarcoma (STS).
- Anatomic location, size, depth (with respect to the superficial fascia) and pathological features dictate the management of STS.
- Invasion is typically in the longitudinal direction within muscle and confined to the compartment of origin. Suspicious peritumoural changes, henceforth referred to as edema, may harbor microscopic disease. Edema is most often pronounced in the cranio-caudal dimension, and should ordinarily be encompassed in the radiotherapy target volume.
- STS generally respect barriers to tumour spread such as bone, interosseous membrane, and major fascial planes and this concept should be exploited in tissue / function preserving radiotherapy planning, especially in extremity lesions.
- Retroperitoneal tumors commonly grow to a large size and initially displace but eventually invade adjacent organs and tissues.
- In the event of an 'unplanned' surgical resection with positive margins (surgical error), the RT target volume needs to generously include all disturbed muscle compartments in addition to any other tissues considered to be directly involved.
- For preoperative planning target volume definition, CT simulation imaging fused with MR imaging should be performed, idealy with the patient in the treatment position, to help guide delineation of the gross tumour volume (GTV) and clinical target volume (CTV). See figures 1 and 2.
- For postoperative planning target volume definition after assumed complete surgical resection, there is no GTV to delineate. The location of the original GTV following the operation (High risk target volume- HTV), should be recreated in the planning CT dataset using preoperative CT / MRI imaging if available (see figures 3 and 4).
- For preoperative cases, 50 Gy is ordinarily used and target volumes include the GTV and the $CTV_{50,}$ and should be delineated on every slice on the planning CT.
- For postoperative RT delivery, 66 Gy is ordinarily used (60 Gy can be used in margin clear, low grade cases) with an additional peripheral CTV volume for tissues with lesser risk of tumor infestation (see figures 3 and 4).
- For Intra-abdominal and retroperitoneal RT delivery, 50 Gy / 25 fractions to 50.4 Gy / 28 fractions is ordinarily used for preoperative delivery (see figures 5 and 6)

- For unresectable residual gross disease, 70 Gy in 2 Gy / fraction or equivalent dose fractionation is ordinarily used depending on the tolerance of the anatomic region.
- Suggested GTV and CTV_{50} for preoperative IMRT of extremity STS are detailed in Table 1.
- Suggested HTV and CTV_{66} for postoperative IMRT of extremity STS are detailed in Table 2.
- Suggested GTV and CTV (dose 50 to 50.4 Gy) for preoperative IMRT of retroperitoneal STS are detailed in Table 3.

Table 1

Suggested target volumes for preoperative extremity/trunk/head and neck STS

Target volumes	**Definition and description**
GTV	Primary: All gross disease on physical examination and imaging. T1 weighted contrast enhanced MRI preferable. (Figure 1-2) Co-registration of the MRI and planning CT is facilitated by immobilizing the patient in the treatment position.
CTV_{50*} (The Subscript 50 denotes the radiation dose delivered)	Includes all areas at risk of subclinical spread defined by the distance from the GTV or edema.
	Includes the GTV + a 4 cm margin in the longitudinal dimensions and a 1.5 cm margin in the radial dimension limited to but including any anatomic barrier to tumor spread, such as bone and fascia (Figure 1-2).
	Suspicious peritumoural edema, best demonstrated on T2 weighted MRI, may contain microscopic tumour cells and should be contoured separately with an adequate margin (usually 1 to 2 cm).
	For cases of 'unplanned excision', margins should include: $_{postop}$GTV or any residual GTV + all surgically manipulated and disturbed tissues and violated fascia + 4 cm longitudinally and 1.5 cm radially limited to but including any barrier to tumour spread.
PTV_{50*}	CTV_{50} + 0.5 to 1.0 cm, determined by individual institutional protocols, procedure.

* Suggested gross tumour dose is 2.0 Gy/fraction to 50 Gy.

Table 2

Suggested target volumes for postoperative extremity/trunk/head and neck STS

Target volumes	Definition and description
HTV	HTV should identify the original site of the tumour. Important to review and import pre-surgical imaging when contouring on the CT simulation scan for RT planning to ensure adequate coverage of the original tumour extent.
CTV_{66*} (The Subscript denotes the radiation dose delivered)	CTV_{66} should encompass the entire HTV+ immediate area of surgical change with a 1 to 2 cm margin in the longitudinal plane and a 1.5 cm margin in the transverse plane. This may, but not always, include all surgically disturbed tissues, scars and drain sites.
PTV_{66*}	CTV_{66} + 0.5 to 1.0 cm, determined by individual institutional protocols and procedure. (Figure 1-3 and 1-4).
CTV_{56*}	Includes all areas at risk of subclinical spread defined by the distance from the HTV and additional disturbed tissues.
	Includes the HTV + a 4 cm margin in the longitudinal dimensions and a 1.5 cm margin in the radial dimension limited to but including any anatomic barrier to disease spread (Figure 1-4); additional disturbed surgical tissues and any scars or drain sites are ordinarily included with a 1 to 2 cm margin if they are not included in the CTV_{66}.
	Suspicious peritumoural edema should be contoured separately and included with an adequate margin. Like surgically disrupted tissue, it is best identified from a recent post-operative MRI scan.
	Discussion with the surgeon and review of surgical and pathology reports will facilitate the decision about whether or not a seroma, lymphocele, or hematoma should be included.
PTV_{56*}	CTV_{56} + 0.5 to 1.0 cm, determined by individual institutional protocols and procedure. (Figure 1-4).

***** High-risk subclinical dose: 2.0 Gy/fraction to 66 Gy; For lower risk subclinical regions 1.69 Gy/fraction to 56 Gy delivered to the $CTV_{56.}$

** Table describes single phase simultaneous boost technique. An alternate is the more traditional phased shrinking field technique that delivers 50 Gy in 25 fractions to all areas of subclinical disease followed by a boost to deliver the final 16 Gy in 8 fractions.

Table 3

Suggested target volumes for retroperitoneal STS

Target volumes	**Definition and description**
GTV*	Primary: All gross disease on physical examination and imaging.
CTV	Includes all areas at risk of subclinical spread defined by the distance from the GTV.
	Includes the GTV + a 2 cm margin in the longitudinal dimensions and a 0.5 – 2.0 cm margin in the radial dimension limited to but including any anatomic barrier to tumor spread and critical anatomy. For example, if the tumour is approximating an intact liver, 0.5 cm of the liver is included.
	2 cm margins are usually used posteriorly to include fatty tissues and vessels.
	Ipsilateral kidney may be sacrificed provided the contralateral kidney has acceptable function. In such a case, dose to the uninvolved opposite kidney should be kept as low as reasonably achieveable.
	Other organs at risk include the small bowel, liver, spinal cord and lungs.
PTV	CTV + 0.5 cm, determined by individual institutional protocols and procedure.

*****Suggested gross tumour dose range of 50 Gy / 25 fractions to 50.4 Gy / 28 fractions.

5. Case Example Figures

Figure 1. A patient with a T2bN0M0 Grade 3 dedifferentiated liposarcoma in the posterolateral thigh. This patient presented having had a previous unplanned excision of a superficial lesion where the fascia of the vastus lateralis was breached, but did not involve the deeper compartment originally. CT simulation used 2.0 mm slice thickness. Notice the area of violated fascia due to previous surgical error. Shown are representative slices.

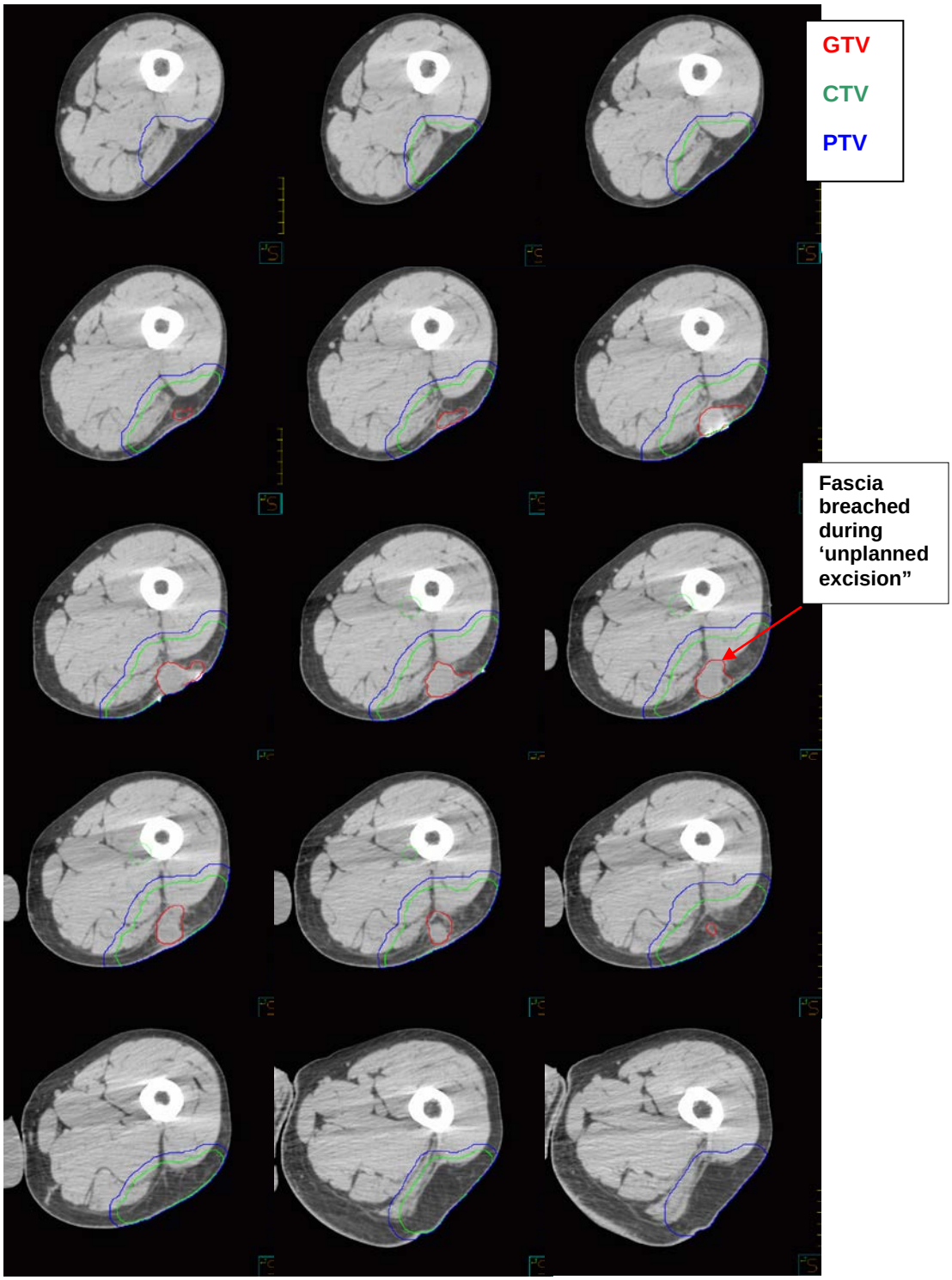


Figure 2. Example of GTV, CTV and PTV displayed in the sagittal view as well as an axial view of the disrupted fascia as a result of an unplanned excision with the corresponding planning CT target volumes.

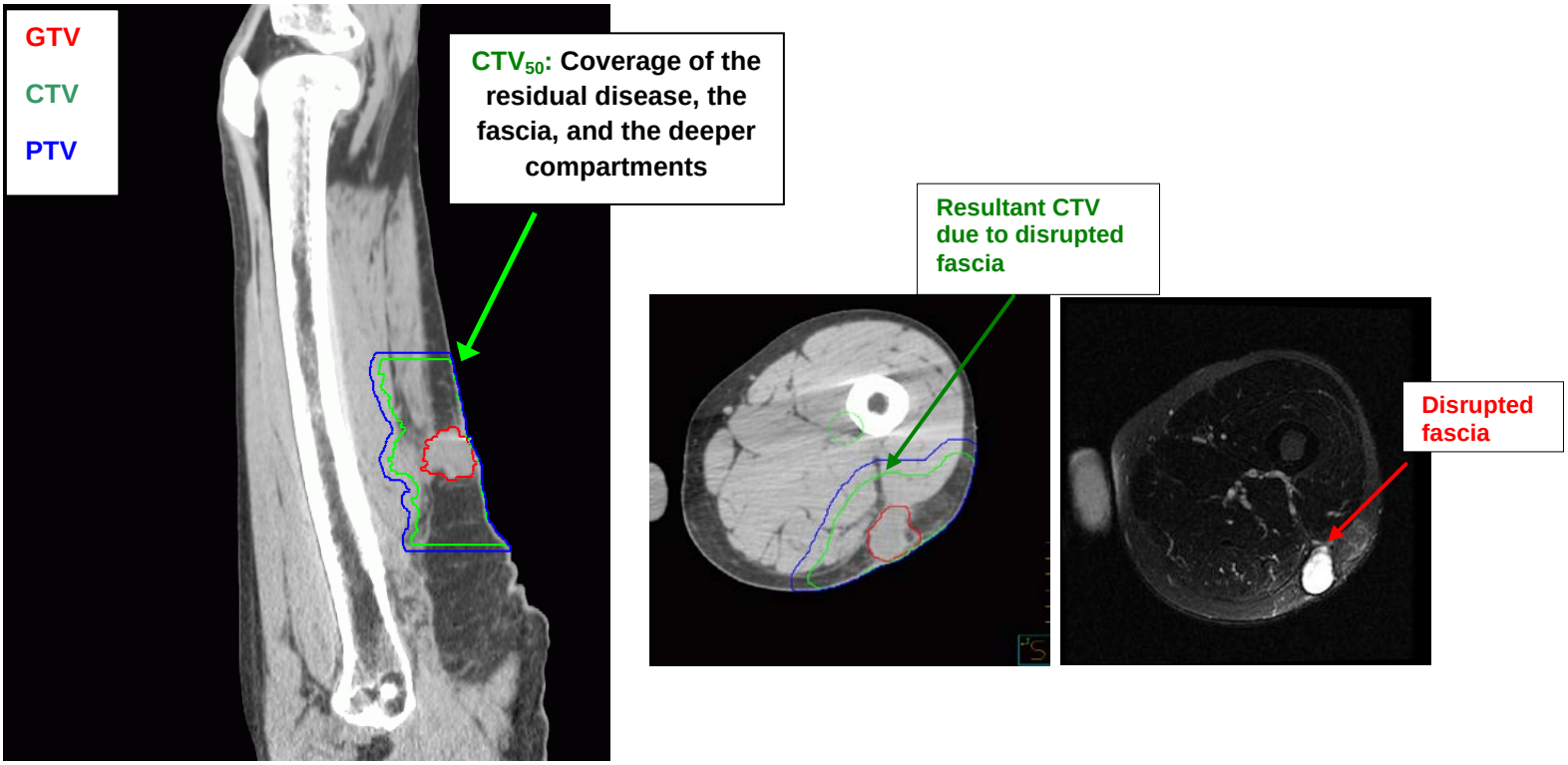
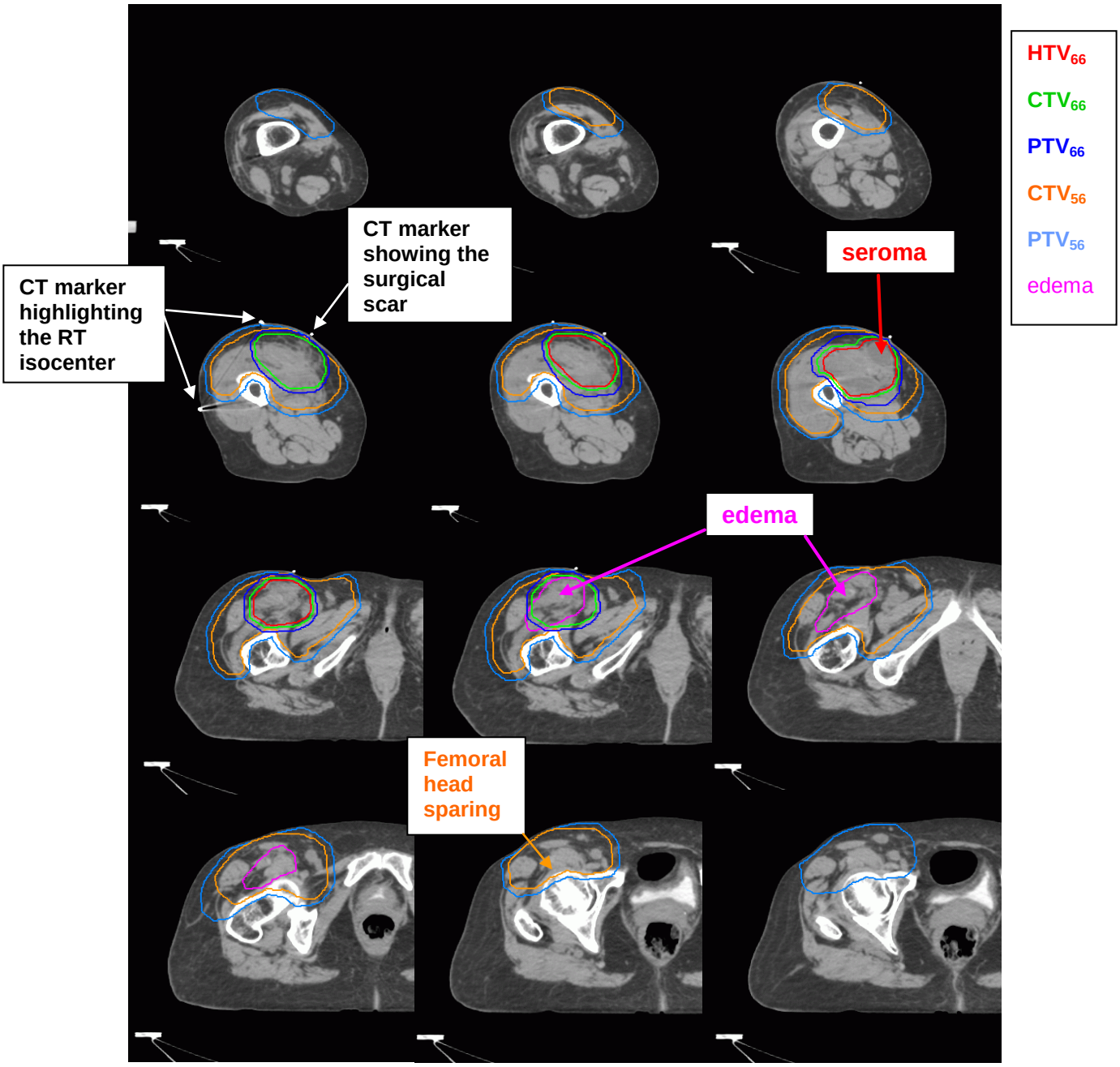


Figure 3*. A patient with a T2bN0M0 Grade 3 pleomorphic rhabdomyosarcoma in the left thigh. This patient received postoperative RT for negative but close margins. CT simulation used 2.0 mm slice thickness. Edema was contoured in the superior aspect of the HTV and included in the CTV_{56}. Shown are representative slices.



*CTV_{56} is limited by the femoral head and bone throughout the target. In some cases where the subcutaneous tissues hav been contaminated, bolus may be applied to the surgical scar for a component of the treatment (e.g. 50 Gy)

Figure 4. Sagittal CT simulation view of the radiotherapy target volumes for this postoperative STS case and corresponding preoperative and postoperative MRI. Note the CTV_{56} is defined by edema and the postoperative surgical changes. Where the target may appear coincidental in this scaled anatomic illustration, the usual margins were applied (e.g. 0.5 to 1 cm PTV expansion). In addition, the preoperative imaging was imported and co-registered with the postoperative RT planning CT dataset in order to appreciate the original tumour extent for delineation of the HTV.

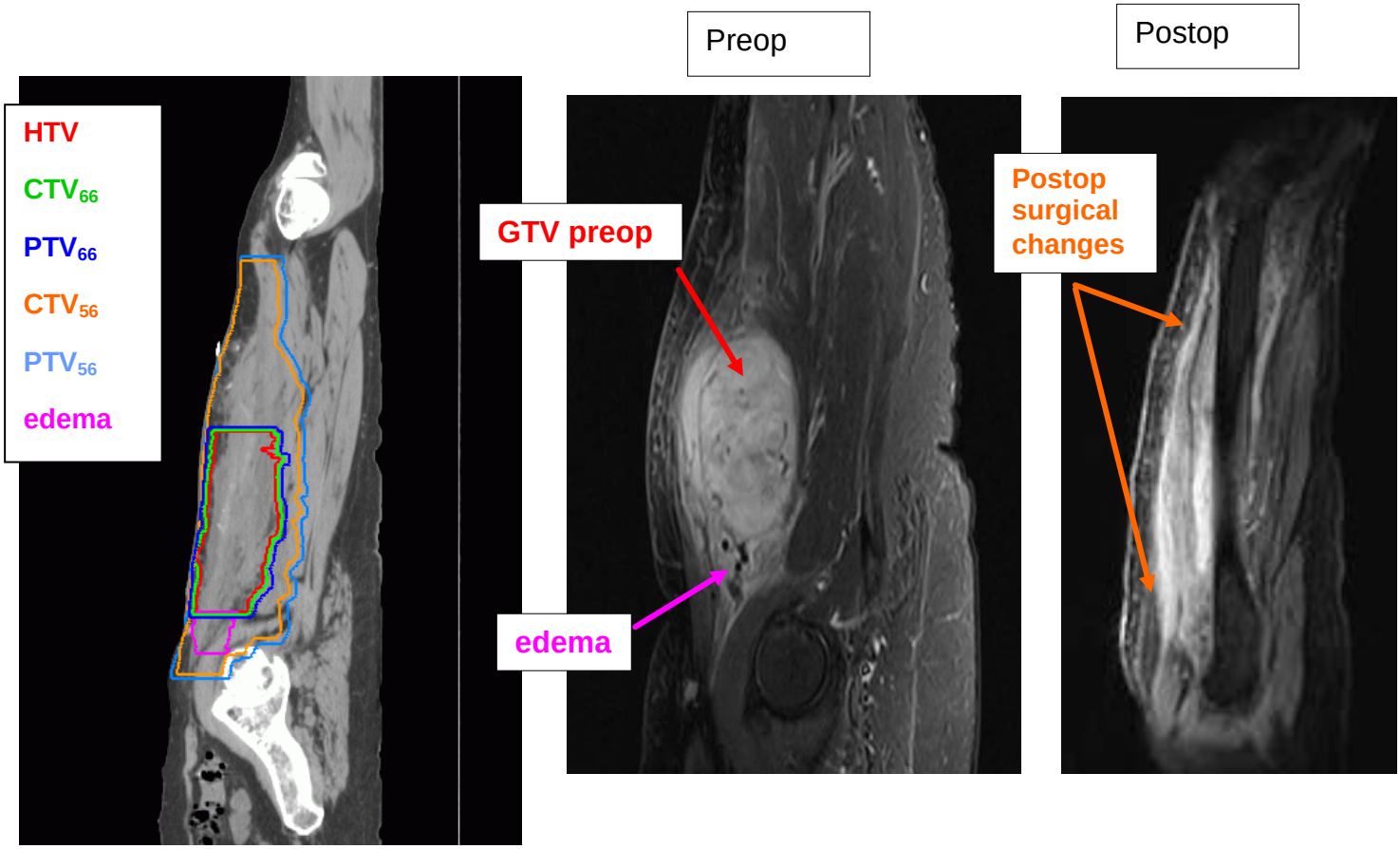


Figure 5. An example of a right sided T2bN0M0 grade 3 undifferentiated pleomorphic retroperitoneal sarcoma juxtaposed to the duodenum, the right kidney and the iliac vessels. CT simulation used a 2.0 mm slice thickness. Representative slices are shown. Note the small amount of liver included in the CTV and PTV in the first three axial slices. Multifocal areas of calcifications within the tumour aided in daily image guidance for targeted IMRT. 4D CT simulation is encouraged.

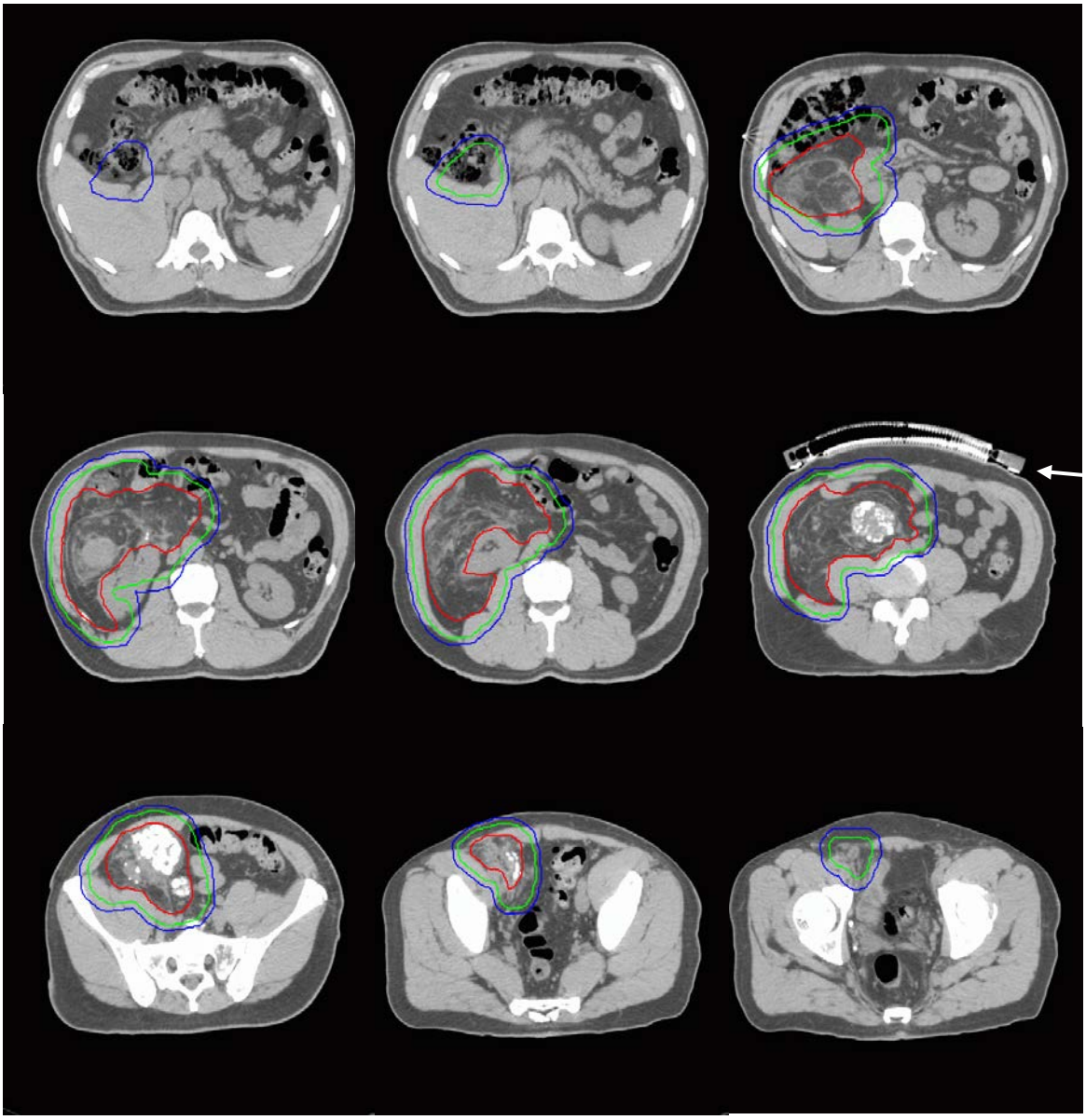
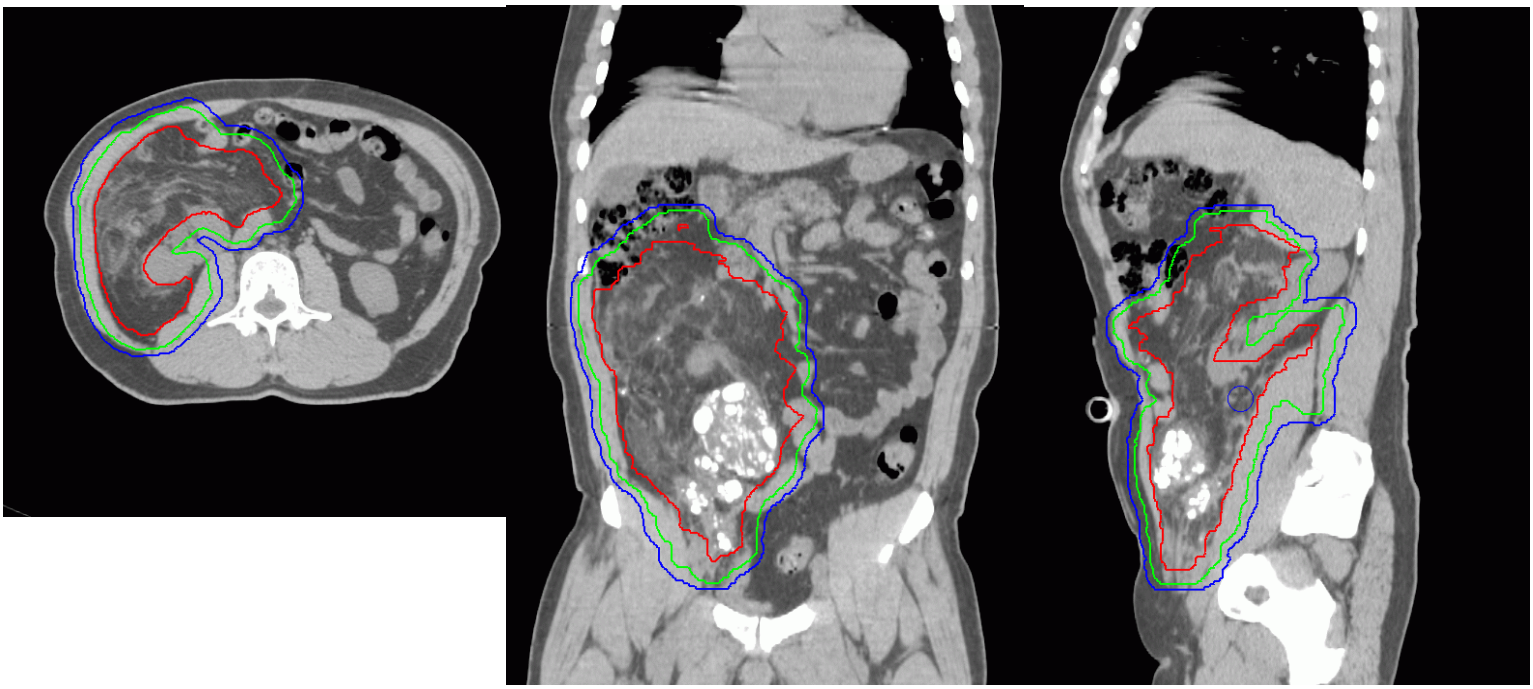


Figure 6. An axial, coronal and sagittal display of the right sided retroperitoneal sarcoma. Note the bowel displacement by the tumour, one of the major advantages of preoperative radi



6. Influential Phase III Clinical Trials

Trial Name	Result
Amputation or limb sparing plus RT **NCI, Bethesda (1)**	▪ Randomized (1:2) 43 cases of high-grade extremity sarcoma to amputation (at/above joint proximal to tumour) or to limb-preservation surgery plus RT ▪ Adjuvant-RT: 50 Gy to entire at risk area plus 10-20 Gy to tumour bed ▪ Local recurrence 4/27 (RT arm) vs 0/16 (p=0.06) ▪ Surgery plus RT led to no difference in survival: 5-year OS 83% vs. 88% (p=0.99)
Timing of RT **NCIC CTG, Canada (2)**	▪ Randomized 190 cases of extremity sarcoma to pre- or post-operative RT. Both arms received 50 Gy to 5 cm expansion. All post- operative patients had phase 2 (16 – 20 Gy to 2cm tumour bed expansion) whereas only positive margins of pre-operative group received phase 2 treatment ▪ Primary end point of wound complication: 35% pre-op vs 17% post-op at median follow up of 3.3 years (P=0.01). Lower limb more at greater risk. ▪ 2 year fibrosis rates 31.5% (pre-op) vs 48.2% (P=0.07) ▪ No difference in 5 year local recurrence rate or OS
Brachytherapy vs observation **MSKCC, New York (3)**	▪ Intraoperative randomization after complete excision of superficial trunk or extremity tumours to brachytherapy or observation. ▪ 164 patients (40% of those eligible) had catheters inserted with treatment, starting at day 6 postoperatively ▪ Iridium 192 wires delivering 42 -45 Gy over 4-6 days ▪ 5-year LCR: 82 (RT arm) vs 69% (p=0.04) ▪ 5-year DSS: 84 vs 81% (p=0.65) ▪ No significant difference in low-grade tumours. ▪ Increased wound complication (p=0.03) when brachytherapy commenced within 5 days of surgery. No significant difference when RT start changed to >5 days post surgery (p=0.67)
Post op Radiation	▪ 1980s, single-institution RCT comparing postoperative EBRT with IORT

retroperitoneal STS **NCI, Bethesda (4)**	and EBRT ▪ 15 patients received 20 Gy IORT with electron fields, followed by 35-40 Gy postoperative EBRT ▪ 20 received 35-40Gy extended-field EBRT with 15 Gy EBRT boost ▪ 40% vs 80% LRR ($p<0.001$) in favour of adding IORT ▪ At expense of significantly higher radiation enteritis and neuropathy in IORT arm ▪ No significant difference in median survival (45 vs 52 months) ▪ Small numbers, high toxicity and higher than expected LRR in control arm have limited the impact of this trial

8. References:

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