RADIOTHERAPY IN MANAGEMENT OF RETROPERITONEAL SARCOMAS

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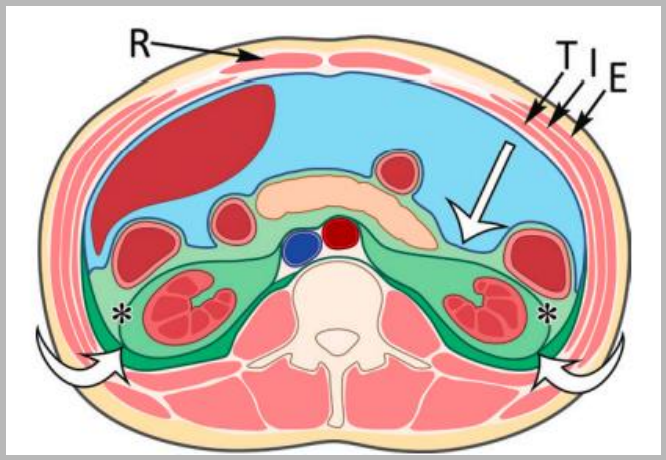
ONCOLOGÍA RADIOTERÁPICA

Medellín – 13-08- 2022



CONTENTS

- BACKGROUND
- NEOADJUVANT
- ADJUVANT
- DOSES
- OUR EXPRIENCE
- TAKE A HOME

Pathological heterogeneity: variable response to treatment

Timing of radiation treatment

1. Pre-operative versus Post-operative
2. Primary radiotherapy: radical versus palliative

Definition of at-risk target volume- the clinical target volume

Which radiotherapy technique to use?

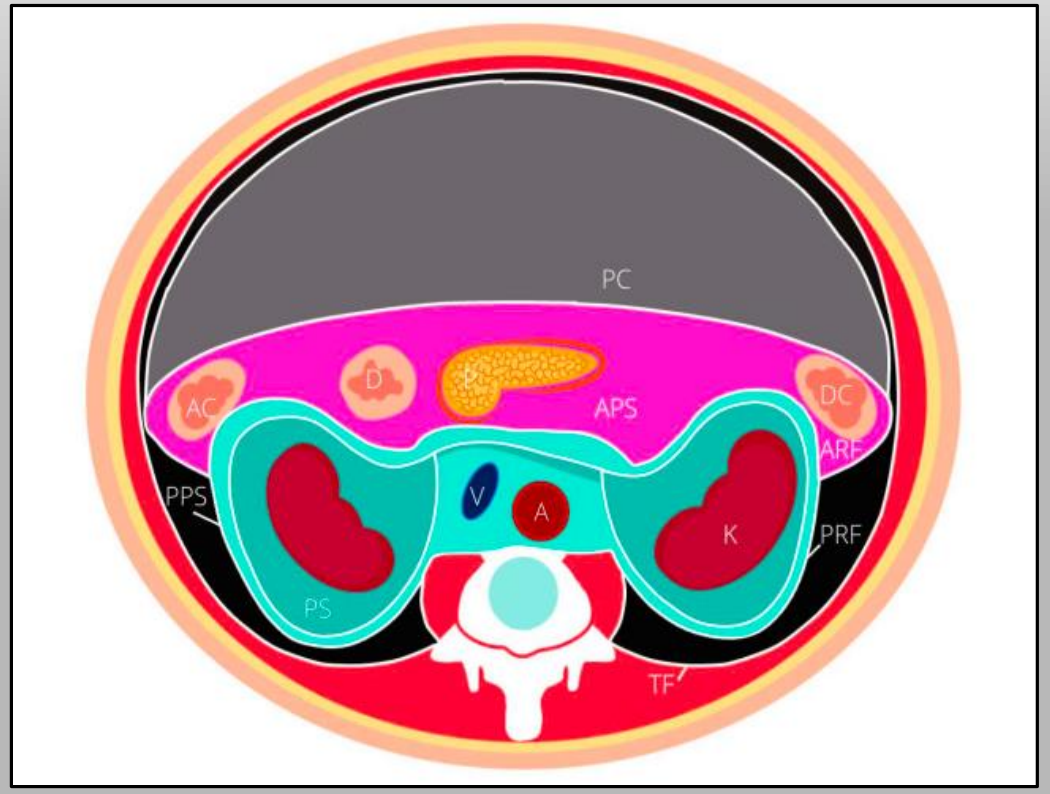
Can you further enhance therapeutic index and efficacy in combination with systemic therapy

BACKGROUND

- Soft-tissue sarcomas are biologically heterogenous tumors.
- Arising from mesenchymal cells, notably fat, nerves, blood vessels and connective tissues with over 100 subtypes.
- sarcomas account for < **1 %** of all adult malignancies.
- Retroperitoneal sarcomas are a distinct subgroup accounting for < **10%** of all sarcomatous tumors.
- There is no sex preponderance, and peak incidence is often the fifth decade of life.

Trans-Atlantic RPS Working Group Management of Primary Retroperitoneal Sarcoma (RPS) in the Adult: A Consensus Approach from the Trans-Atlantic RPS Working Group. Ann. Surg. Oncol. 2015, 22, 256–263.

BACKGROUND



Diaphragm superiorly, the iliopsoas inferiorly, the paraspinous muscle medially, the transversalis fascia of the abdominal wall laterally, and the psoas, quadratus lumborum, iliacus and transverse abdominis muscle posteriorly.

The retroperitoneum space is divided into 3 compartments: greater vessel, the posterior compartments and the lateral compartment.

1-Tirkes, T.; Sandrasegaran, K.; Patel, A.A.;Peritoneal and Retroperitoneal Anatomy and Its Relevance for Cross-Sectional Imaging. RadioGraphics 2012, 32, 437–451.
2-Coffin, A.; Boulay-Coletta, I.; Sebbag-Sfez, D.; Zins, M. Radioanatomy of the retroperitoneal space. Diagn. Interv. Imaging 2015, 96, 171–186

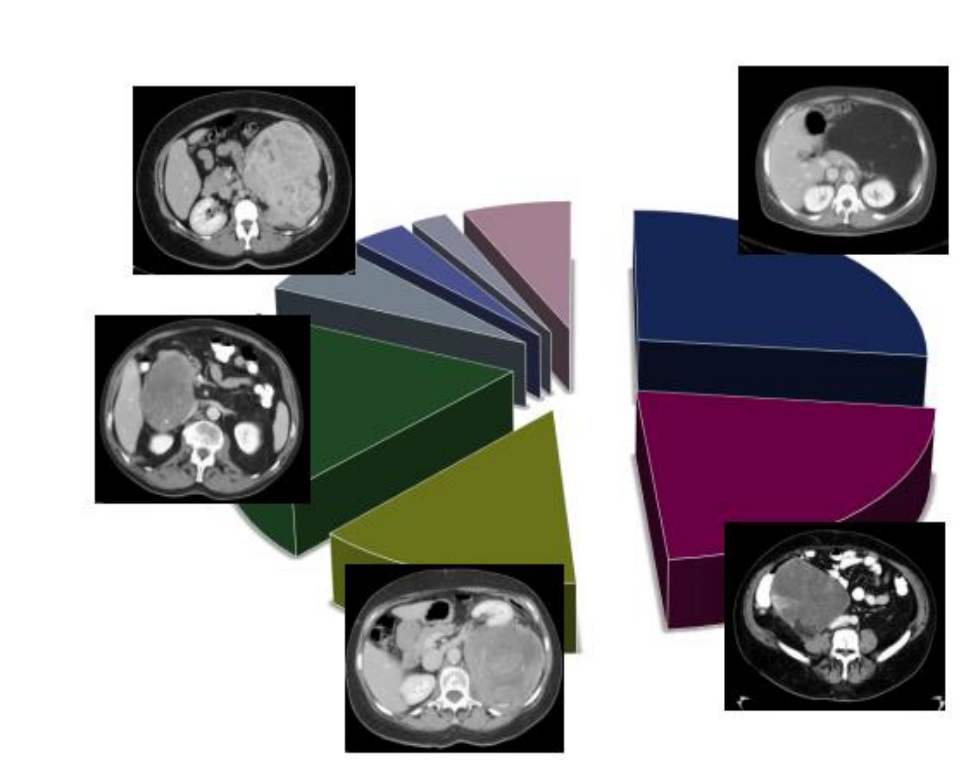
BACKGROUND

Table 1. Retroperitoneal compartments with associated spaces, borders and contents.

Compartment	Space	Borders	Contents
Greater Vessel	Greater Vessel Space	Superior: posterior mediastinum Posterior: vertebral bodies, psoas muscle Lateral: perirenal spaces and ureters	Abdominal aorta Inferior vena cava Lymphatics
Posterior	Posterior Space	Anterior: transversalis fascia	Psoas muscle
Lateral	Anterior Pararenal Space (APS)	Anterior: Parietal peritoneum and intraperitoneal space Posterior: anterior renal fascia and perirenal space	Pancreas head and neck Duodenum (parts 2–4) Ascending Colon Descending Colon
	Perirenal Space (PS)	Superior: diaphragm Anterior: Gerotas fascia and anterior pararenal space Posterior: Zuckerkandl fascia and posterior pararenal space	Adrenal gland Kidney Renal hilum with ureter, artery and vein
	Posterior Pararenal Space (PPS)	Lateral: lateroconal fascia Anterior: posterior renal fascia and perirenal space Posterior: Transversalis fascia	No major organs Fat pad ventral to quadratus lumborum

Dingley, B.; Fiore, M.; Gronchi, A. Personalizing surgical margins in retroperitoneal sarcomas: An update. Expert Rev. Anticancer Ther. 2019, 19, 613–631

BACKGROUND



- ✓ Liposarcoma:
  - •WDLPS well-differentiated liposarcoma.
  - •G II DDLPS dedifferentiated liposarcoma.
  - • G III DDLPS
- ✓ **LMS leiomyosarcoma.**
- ✓ SFT solitary fibrous tumor
- ✓ US undifferentiated sarcoma.
- ✓ MPNST malignant peripheral nerve sheath.
- ✓ FS fibrosarcoma.

Sbaraglia, M.; Bellan, E.; Dei Tos, A.P. The 2020 WHO Classification of Soft Tissue Tumours: News and perspectives. Pathologica 2020, 113, 70–84

BACKGROUND

Histological Types	Local Recurrence		Distant Metastases	
	Early	Late	Early	Late
WDLS	18–39%	60%	0%	8%
DDLS	33–58%	62%	9–44%	28%
LMS	6–16%	24%	55%	58%
SFT	4–8%		17%	41%
MPNST	20–35%		12%	15%

WDLS: well-differentiated liposarcoma; DDLS: dedifferentiated liposarcoma; LMS: leiomyosarcoma; SFT: solitary fibrous tumour; MPNST: malignant peripheral nerve sheath tumour.

1-Tan, M.C.; Brennan, M.F.; Kuk, D.; Agaram, N.P.; Antonescu, C.R.; Qin, L.X.; Moraco, N.; Crago, A.M.; Singer, S. Histology-based Classification Predicts Pattern of Recurrence and Improves Risk Stratification in Primary Retroperitoneal Sarcoma. Ann. Surg. 2016, 263, 593–600

BACKGROUND

- Surgery is the mainstay and only true curative treatment for retroperitoneal sarcomas.
- The standardized technique of extended en-bloc resection of the retroperitoneal tumor with all adjacent organs - Italian sarcoma group -significant oncologic improvement of local control.
- The technique entails a circumferential dissection from anterior to posterior in order to maintain vascular control, and good visualization with extended resection and peritoneal stripping in order for all surfaces of the tumor covered with healthy tissue.
- In principle, en-bloc wide resection is required to obtain appropriate negative margins with >5-10 mm of microscopic tumor-free tissue (R0 resection).
- Adjacent organs which are commonly sacrificed with the primary tumor include the ipsilateral segmental colon, adrenal gland, kidney, psoas muscle and abdominal wall.

Callegaro, D.; Swallow, C.J. ASO Author Reflections: Every Step Counts: Improved Survival of Retroperitoneal Sarcoma Patients During the Past 15 Years. Ann. Surg. Oncol. 2021, 28, 1710–1711

BACKGROUND

Sarcoma Subtype	Pattern of Spread	Mechanism of Failure (5-Year %)	Surgical Implications
WDLPS	Adipose infiltration Multilobulated Indistinct borders	LR (19–39%) >> MD (0%)	Extended en-bloc resection requiring ipsilateral retroperitoneal fat resection
DDLPS	Adipose and Visceral infiltration Multilobulated Indistinct borders	G2: LR (44%) > MD (10%) G3: LR (33%) << MD (44%)	Extended en-bloc resection requiring ipsilateral retroperitoneal fat resection
LMS	Distinct borders	LR (6–16%) << MD (55–56%)	En-bloc resection with vascular structures May preserve adjacent critical structures
MPNST	Distinct borders	LR (20–35%) > MD (12–13%)	En-bloc resection with associated neurovascular structures
SFT	Distinct borders	LR (4–8%) > MD (17%)	En-bloc resection May preserve adjacent critical structures

Gronchi, A.; Miceli, R.; Allard, M.A.; Callegaro, D.; Le Péchoux, C.; Fiore, M.; Honoré, C.; Sanfilippo, R.; Coppola, S.; Stacchiotti, S.; et al. Personalizing the approach to retroperitoneal soft tissue sarcoma: Histology-specific patterns of failure and postrelapse outcome after primary extended resection. Ann. Surg. Oncol. 2015, 22, 1447–1454.

BACKGROUND

Criteria for technical non-resectability:

- Involvement of the superior mesenteric artery, aorta, coeliac trunk, and/or portal vein.
- Involvement of bone.
- Growth into the spinal canal.
- Invasive extension of retrohepatic inferior vena cava leimyosarcoma into the right atrium.
- Infiltration of multiple major organs such as liver, pancreas, and or major vessels.

Ann Surg Oncol. 2021 November ; 28(12): 7873–7888. doi:10.1245/s10434-021-09654-z

BACKGROUND

- Imaging is not capable of distinguishing between more than 100 varieties of histological RPS subtypes.

- CT is the appropriate choice for assessing vascular and visceral involvement, including secondary lesions, usually in the liver and the lung.

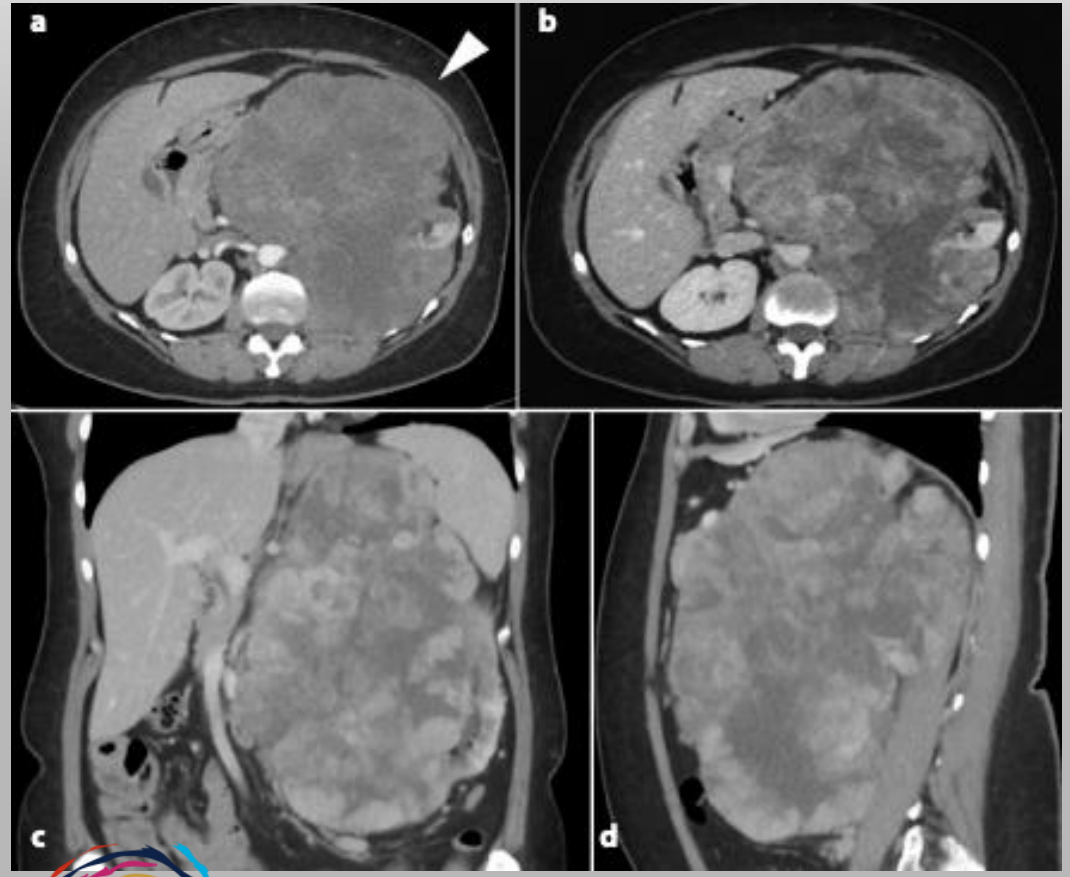
- About 21% of the lesions diagnosed as RPS at the CT scan turn out to be non-mesenchymal tumours at histopathology. Moreover, it has been shown that the CT alone is not able to provide the correct histopathological subtype, except for well-differentiated liposarcoma (WDLS) and angiomyolipoma.

- MRI-higher soft tissue contrast resolution, is of great utility when the pelvis is involved, - follow-up and every time CT insufficient to provide information — local tumor extent. But elecction —if bone, muscles or foramina are involved.

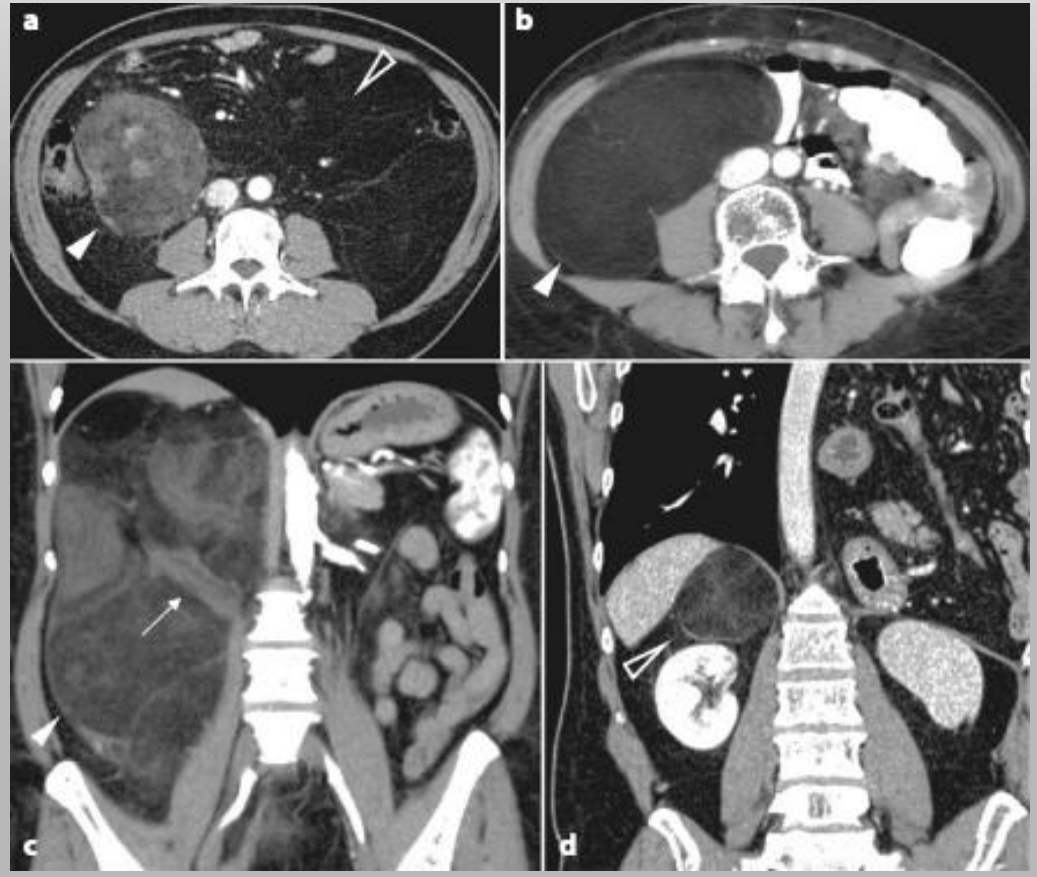
- MRI gives structural information through a precise assessment of the fat component inside the mass, of the internal necrotic areas and of the surrounding edema.

Morosi, C.; Stacchiotti,.; et al. Correlation between radiological assessment and histopathological diagnosis in retroperitoneal tumors: Analysis of 291 consecutive patients at a tertiary reference sarcoma center. Eur. J. Surg. Oncol. 2014, 40, 1662–1670

BACKGROUND



Leiomyosarcoma



Liposarcoma

BACKGROUND

- ✓ Currently imaging of the primary tumor during and immediately post radiotherapy should be avoided.
- ✓ Histopathological changes including necrosis, cystic change, haemorrhage, hyalinization, and fibrosis which occur following RT may cause tumors to increase in size resulting in pseudoprogression.
- ✓ With the exception of myxoid liposarcomas significant dimensional radiologic responses after preoperative RT are rare and have been reported as low as 0%.
- ✓ **Miki** - showed that 31% of tumors increased in size by more than 10% but this was not associated with deterioration in local recurrence free survival, event free survival or overall survival.
- ✓ Not correlation with recist and outcome measures and demonstrated that tumors could show significant reductions in size despite demonstrating predominantly viable tumor whereas stable or growing tumors could show dramatic histopathological response.

1-Miki Y, Ngan S, Clark JCM, et al. The significance of size change of soft tissue sarcoma during preoperative radiotherapy. Eur J Surg Oncol.2010;36:678–683

2--Canter RJ, Martinez SR, Tamurian RM, et al. Radiographic and histologic response to neoadjuvant radiotherapy in patients with soft tissue sarcoma. Ann Surg Onc. 2010;17:2578–2584.

NEOADJUVANT

- The role of preoperative radiation therapy is still being evaluated and debated, and clinical practice consequently varies across the world.
- Several retrospective studies investigated the outcomes of patients with RPS receiving preoperative RT.
- Surgeons hesitate to delay curative surgery (or enroll patients in a trial where curative surgery could be delayed) in the absence of strong evidence to support neoadjuvant RT and significant toxicity to surrounding structures.
- Using a case-controlled, propensity score-matched methodology to minimize selection bias, preoperative RT and port were associated with significantly improved overall survival compared to surgery alone.

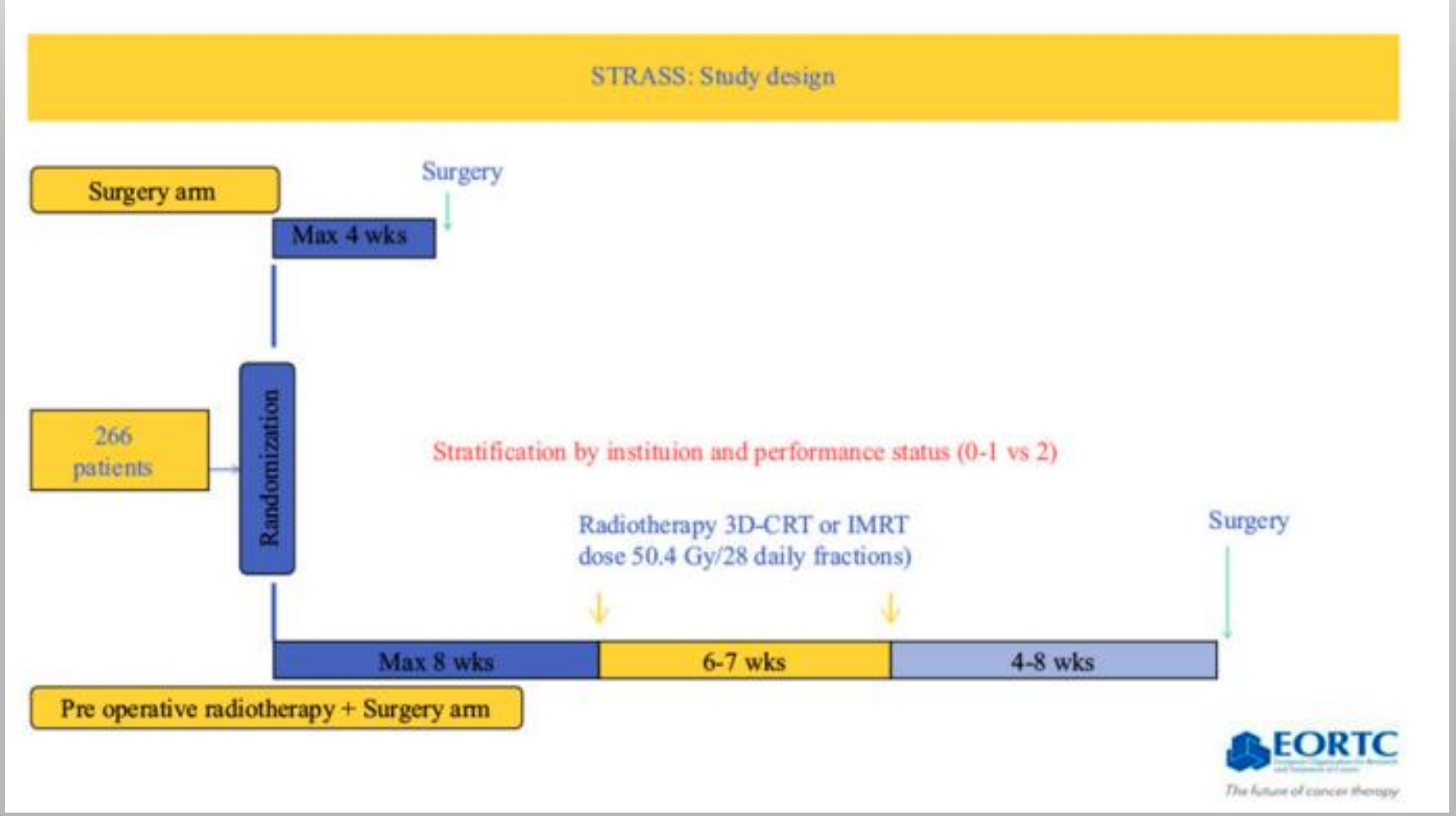
1-Smith, M.J.F.; Ridgway, P.F.; Catton, C.N.; Cannell, A.J.; O'Sullivan, B.; Mikula, L.A.; Jones, J.J.; Swallow, C.J. Combinedmanagement of retroperitoneal sarcoma with dose intensification radiotherapy and res ection: Long-term results of a prospectivetrial. Radiother. Oncol. 2014, 110, 165–171.
2- Cancers 2022, 14, 1831. https://doi.org/10.3390/cancers14071831

NEOADJUVANT

Study	Design	N	Population	Intervention and Comparator	Outcomes	Findings
			Radiotherapy			
STRASS Bonvalot 2020	e III RCT (1:1)	266	Resectable primary RPS	I: Neoadjuvant 3DCRT or IMRT (50.4 Gy in 28 fx of 1.8 Gy) + surgery C: surgery alone (en-bloc curative intent resection)	Primary: AFRS Secondary: tumor response, DMFS, ARFI, OS, safety, QoL	• No difference in ARFS on ITT analysis • 3-year ARFS 66% v. 59% on 1st sensitivity analysis ** • 3-year ARFS 72% v. 60% on 2nd sensitivity analysis ** • In LPS patients, failure reported for 40% receiving RT v. 60% surgery alone.

Bonvalot, S.; Gronchi, A.; D.; Meeus, P.; van Coevorden, F.; Stoldt, S.; Stoeckle, E.;Rutkowski, P.; et al. Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092: STRASS): A multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2020, 21, 1366–1377.

NEOADJUVANT



NEOADJUVANT-EORTC-62092 (STRASS)

- Intensity-modulated RT (IMRT) or three-dimensional conformal RT (3D-CRT) was given to 50.4 GY in 28 daily fractions.
- The primary outcome was abdominal recurrence-free survival (ARFS), defined as local (abdominal) or distant progressive disease during pre RT, tumor or patient becoming inoperable, peritoneal metastasis found at surgery, macroscopic residual disease left at surgery, or local relapse after a macroscopically complete resection.
- A total of 266 patients were randomized, and at a median follow-up for 43 months.
- Median ARFS was not significantly improved by preoperative (RT 4.5 vs 5.0 years, HR=1.01, 95% CI=0.71–1.44).
- Overall survival (OS) was similar between the two groups—84.6% (95% CI=76.5–90.1) with surgery alone versus 84% (95% CI=76.3– 89.4%) with pre RT and surgery at 3 years and 79.4% (95% ci=69.1–86.5%) with surgery alone and 76.7% (95% CI=66.9–84.0%) with pre RT and surgery at 5 years.

NEOADJUVANT EORTC-62092 (STRASS)

- Unplanned subgroup analysis by histologic subtype and grade suggested preoperative RT might improve outcomes in liposarcoma and in low-grade RPS, but not for LMS and higher grade RPS.
- Of note, there were only 31 patients with high-grade RPS in the study.
- It should be noted that median follow-up is only 43 months, and additional follow-up may show different results, as local recurrences can occur beyond 5 years.
- The authors conclude that, at the present time, preoperative RT should not be considered standard of care for patients with newly diagnosed, localized RPS.

Preoperative radiotherapy in patients with primary retroperitoneal sarcoma: EORTC-62092 trial (STRASS) vs off-trial (STREXIT) results

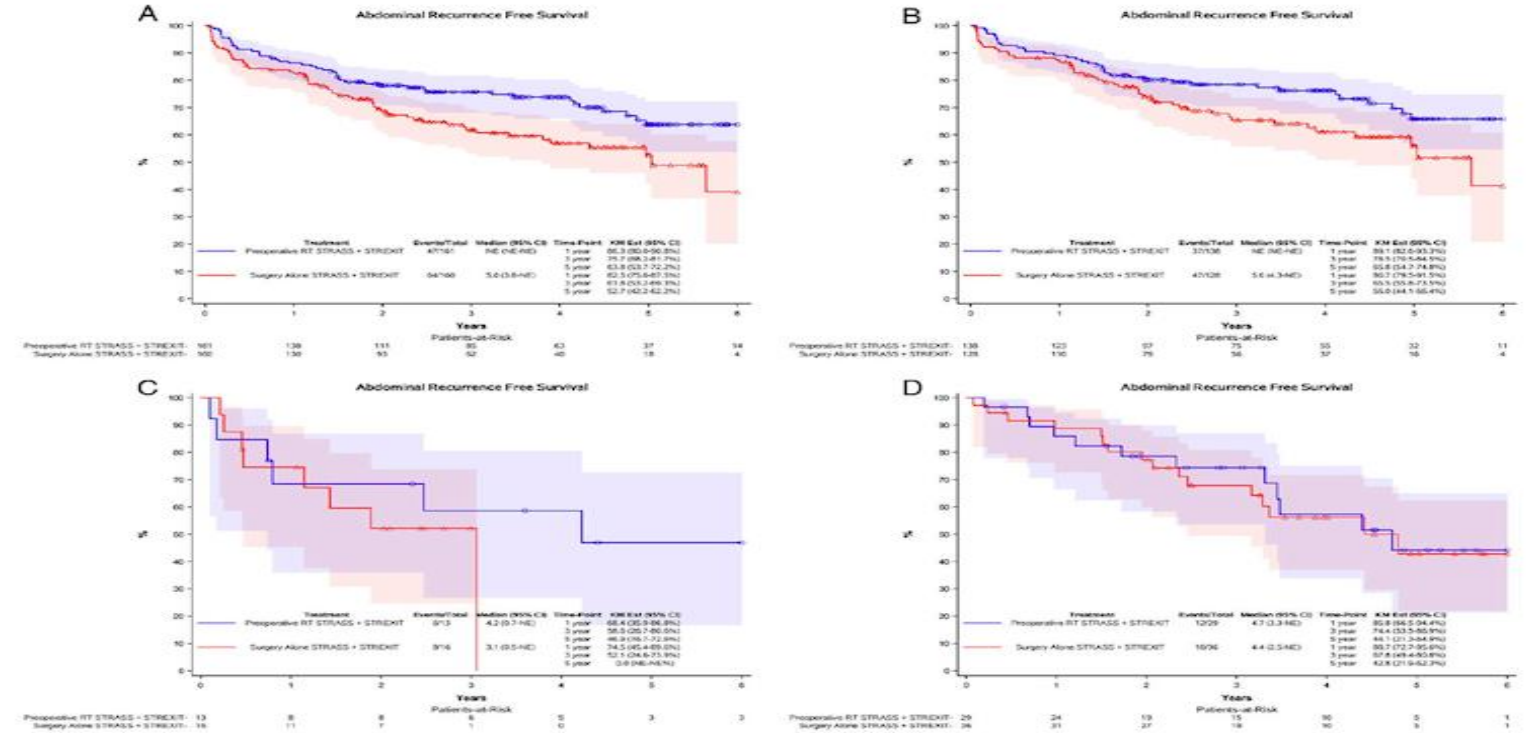
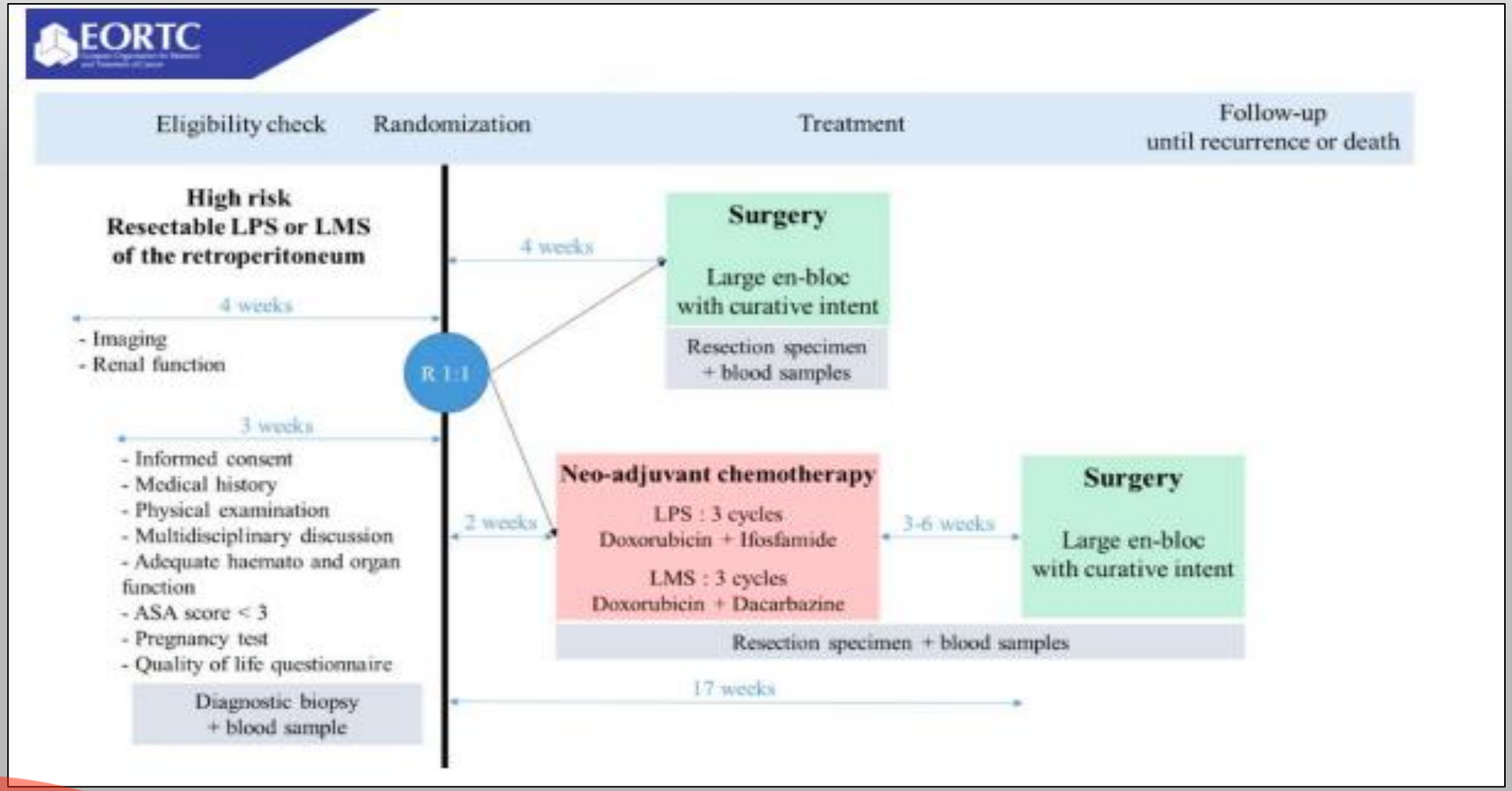


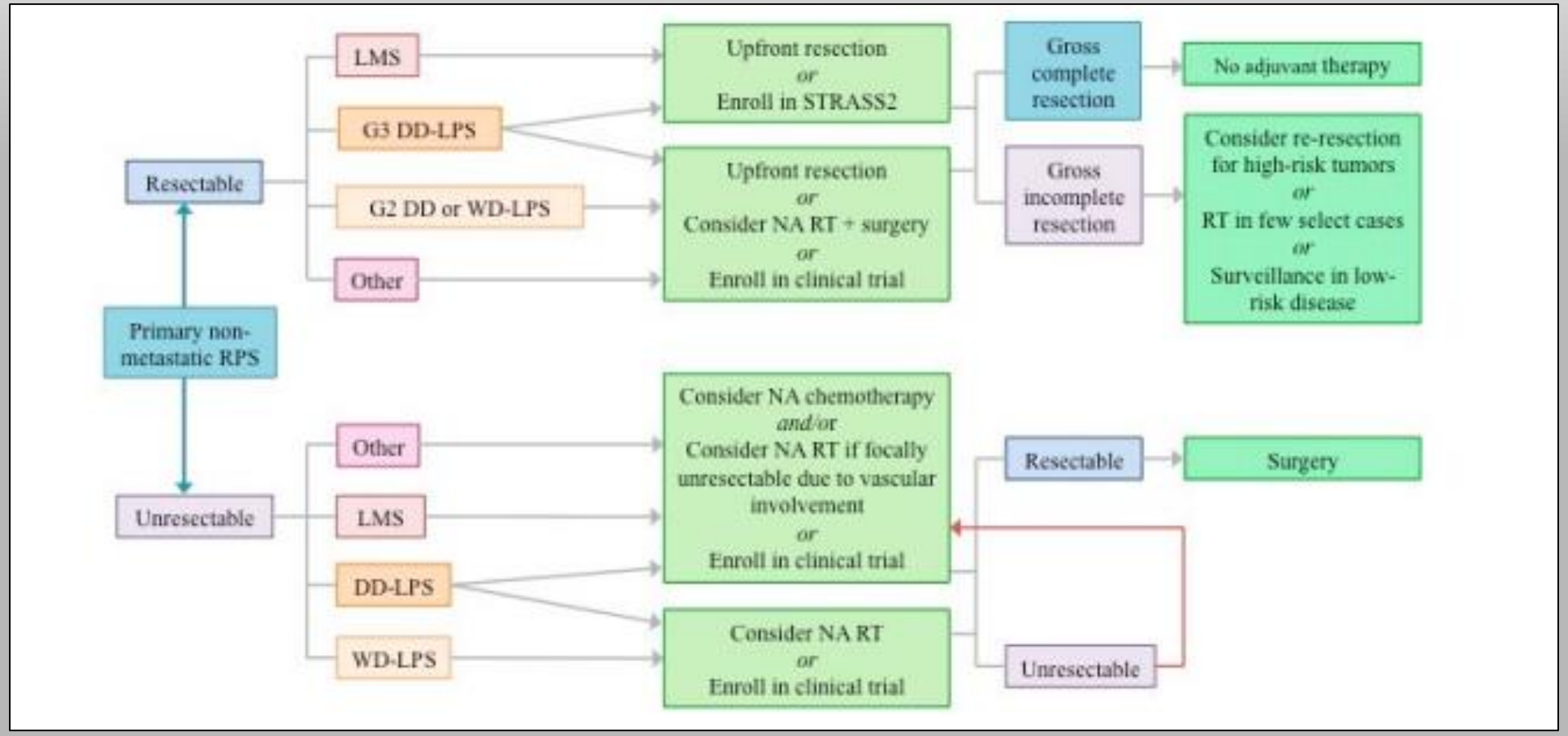
FIGURE 2. Abdominal recurrence-free survival curves in the pooled cohort subgroup analyses according to treatment (blue: preoperative radiotherapy + surgery; red: surgery alone). A, Patients with liposarcoma. B, Patients with G1-2 dedifferentiated liposarcoma and well-differentiated liposarcoma. C, Patients with G3 dedifferentiated liposarcoma. D, Patients with leiomyosarcoma.

Ann Surg. 2022 Jul 14. doi: 10.1097/SLA.0000000000005492

NEOADJUVANT- STRASS 2



NEOADJUVANT



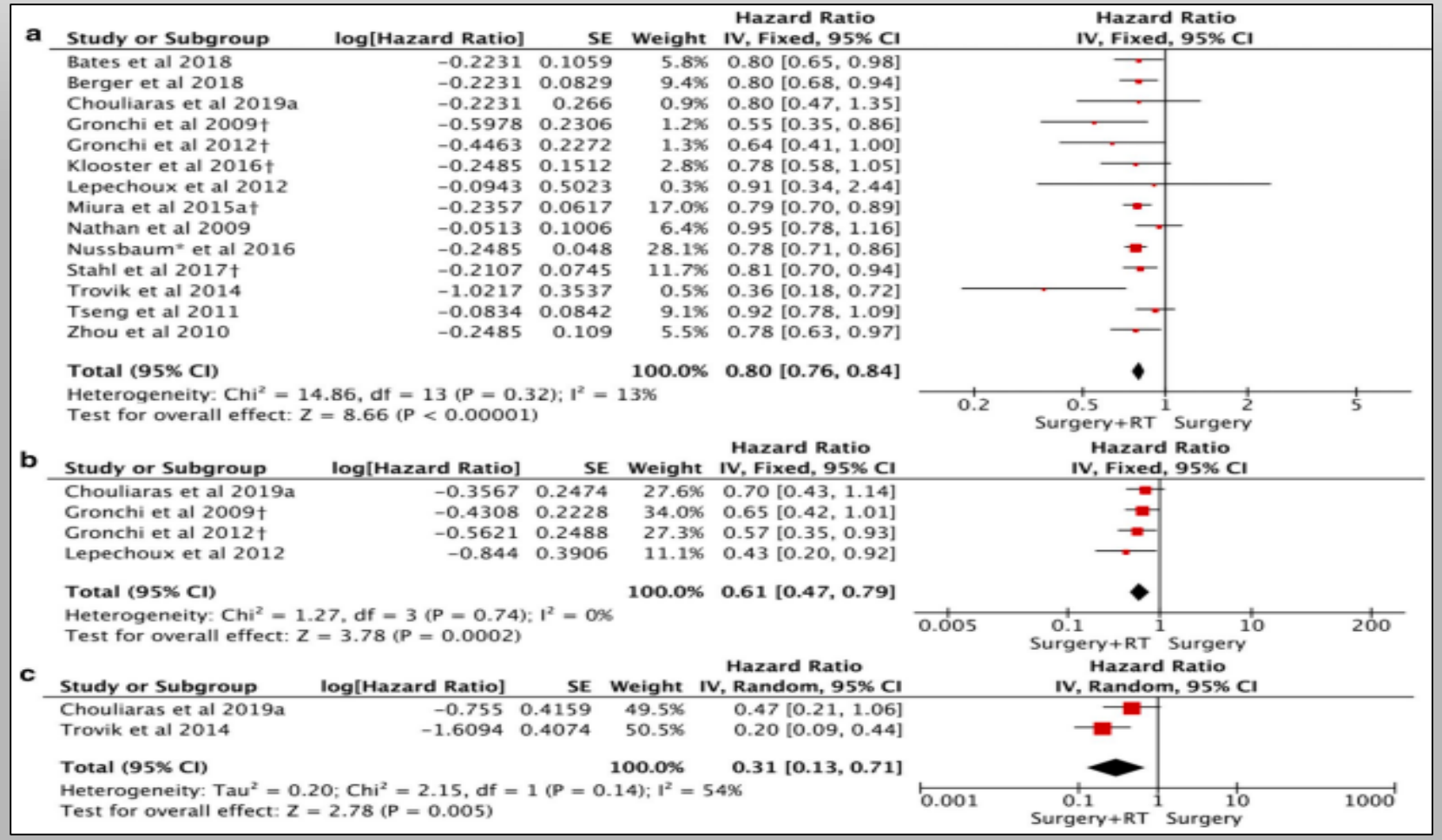
Cancers 2022, 14, 1831. https://doi.org/10.3390/cancers14071831

ADJUVANT

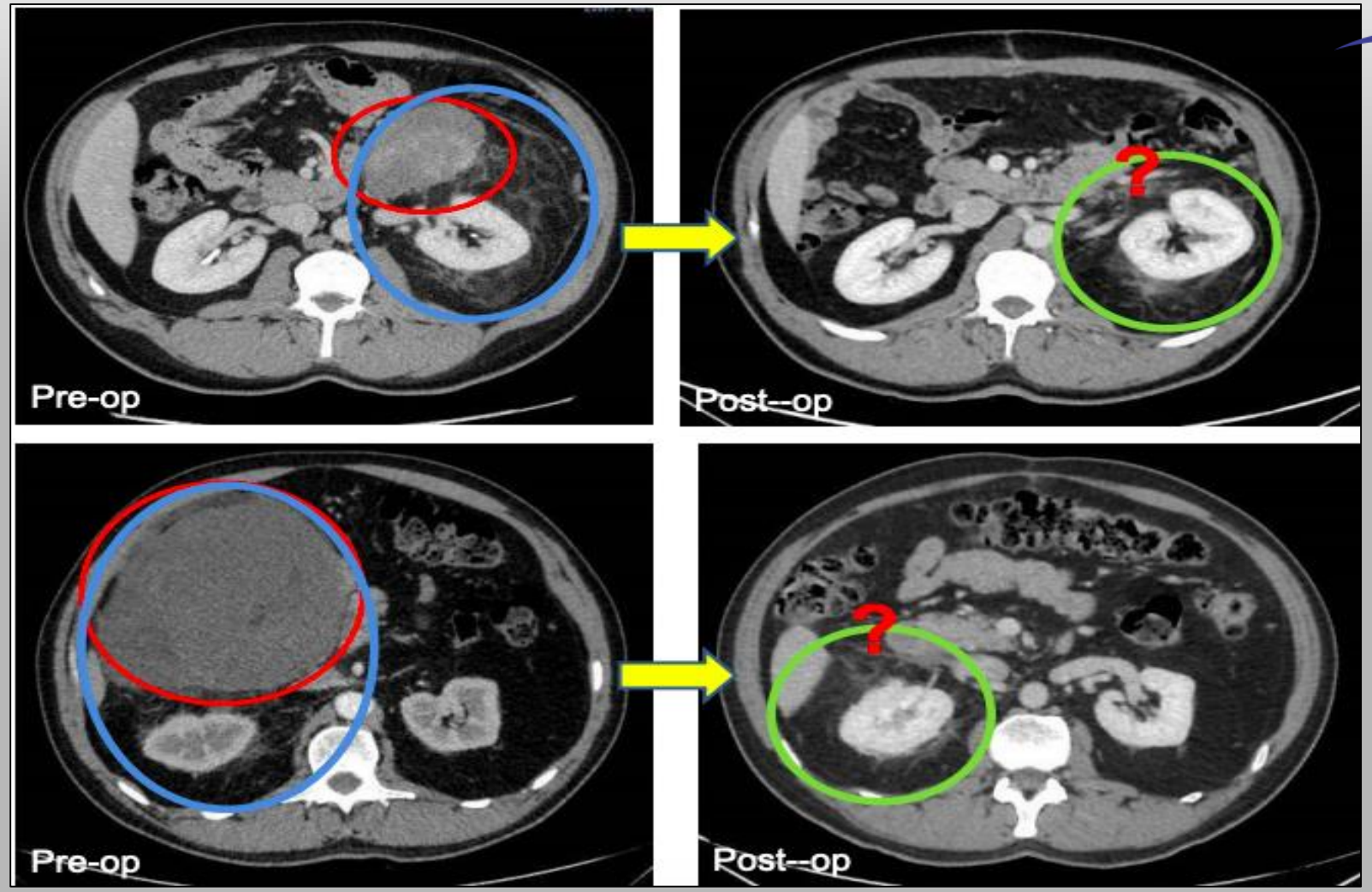
- Insufficient evidences to compile treatment guidelines due to the different conclusions based on limited retrospective clinical studies (RCSS).
- Retrospective and included a limited number of patients who underwent either complete or partial resection.
- Wide range of radiation doses were used (14–62 GY) depending on target volumes and the radiation tolerance of the normal critical.
- Possible benefit of RT in TX of RPS when adequate doses of RDT can be safely delivered- but in post operative limited dose tolerance for critical structures.

Li et al. Radiat Oncol (2021) 16:196

ADJUVANT



Li et al. Radiat Oncol (2021) 16:196


Pre-op
Post--op
?
Pre-op
Post--op
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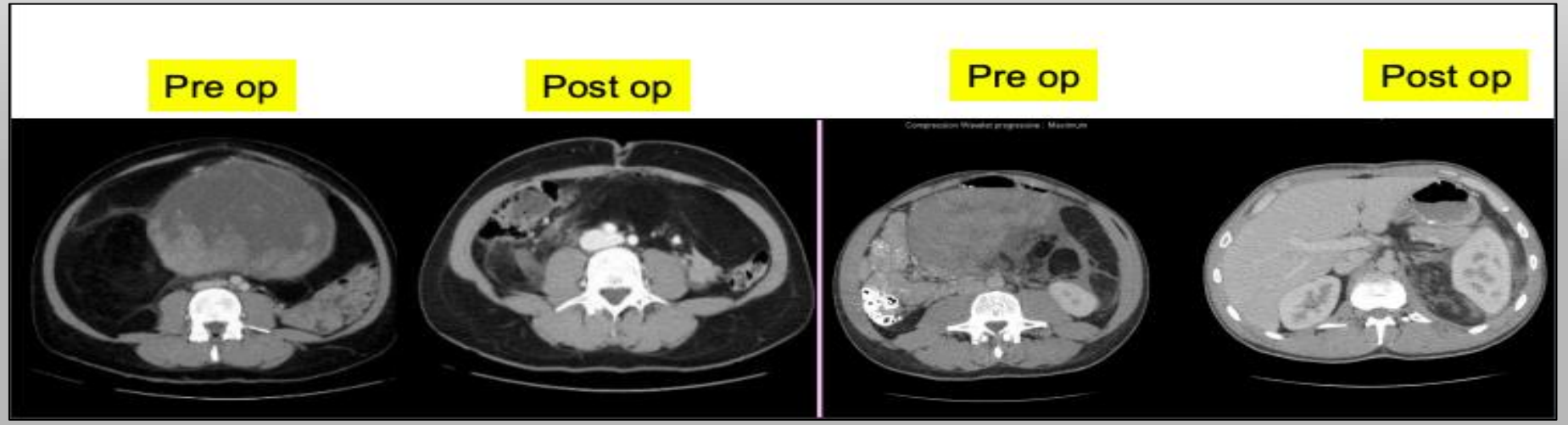
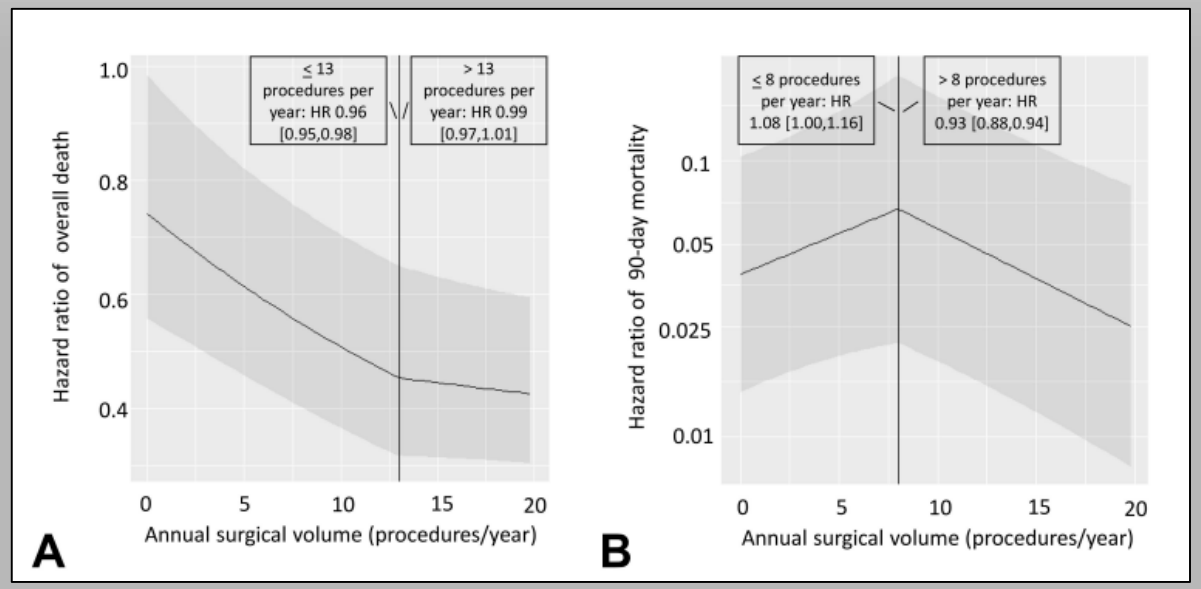
ADJUVANT



- Adjuvant postoperative RT has been shown to have a small benefit on local disease control, other than by delaying LR.
- Postoperative RT has been progressively abandoned due to the high morbidity rate, the poor benefit on cancer control and the growing interest in preoperative RT protocols.

Tseng, W.H.; Martinez, S.R.; Do, L.; Tamurian, R.M.; Borys, D.; Canter, R.J. Lack of survival benefit following adjuvant radiation in patients with retroperitoneal sarcoma: A SEER analysis. J. Surg. Res. 2011, 168, e173–e180.

IDENTIFYING THE MINIMUM VOLUME THRESHOLD FOR RETROPERITONEAL SOFT TISSUE SARCOMA



Transatlantic Australasian RPS Working Group (TARPSWG):

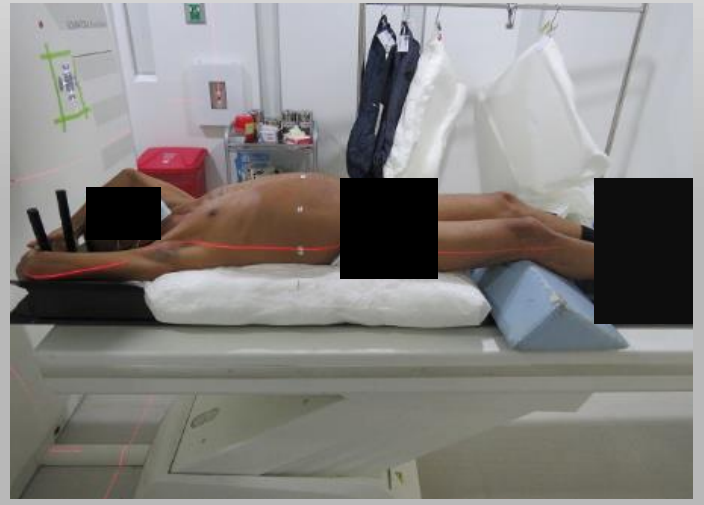
- Minimum annual institutional surgical volume of 10–20 RPS cases/y - appropriate for a center to be considered one of RPS expertise.
- High volume is closely associated with imperative elements such as confirmation of histologic diagnosis by an expert sarcoma pathologist.
- Sarcoma-specific tumor board.
- Surgeon with specialized training in resection of RPS + radiologist, pathologist, medical oncologist, and radiation oncologis.

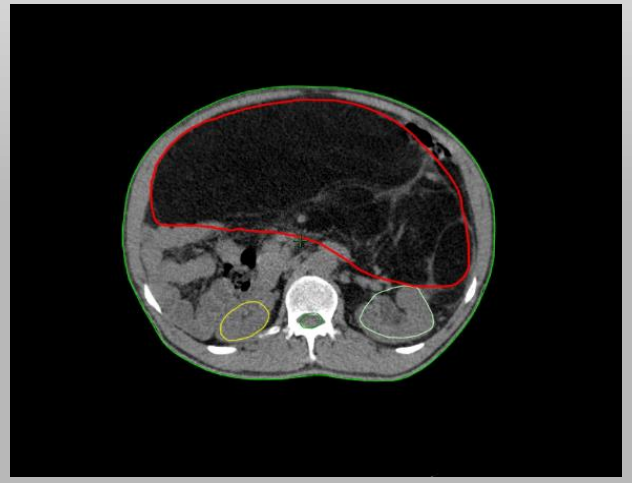
1-J Am Coll Surg. 2020 Jan;230(1):151-160.e2
2-Ann Surg Oncol. 2021 November ; 28(12): 7873–7888. doi:10.1245/s10434-021-09654-z.

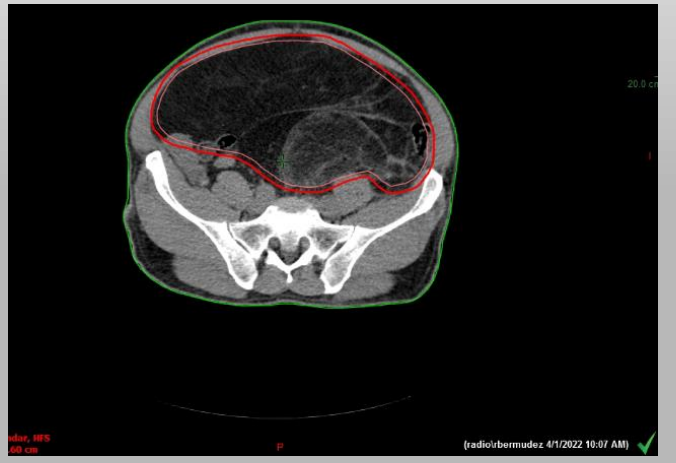
OUR EXPERIENCE

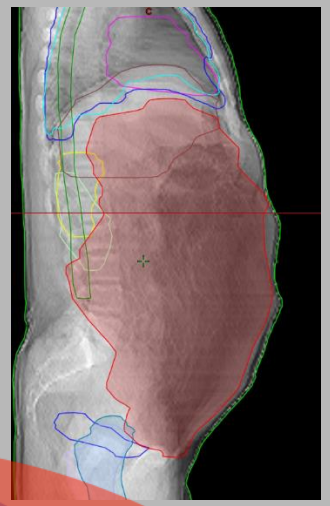
- CT simulation is performed in the supine position slice thickness 3MM.
- Vacuum fix bag + wings board.
- No specific bladder or bowel preparation. Not oral and intravenous contrast.
- NOT use of 4DCT reconstructions or respiratory gating.
- Conebeam-CT: 3/week.
- Doses.
- N cases 2020-2021: 6 / p year: 450-480 patients
- N cases 2022: 4

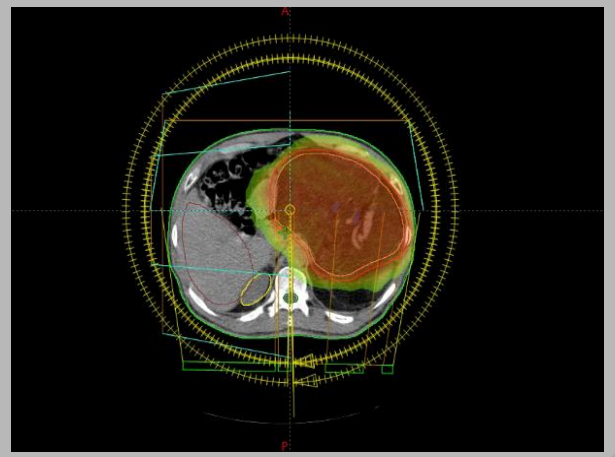
OUR EXPERIENCE

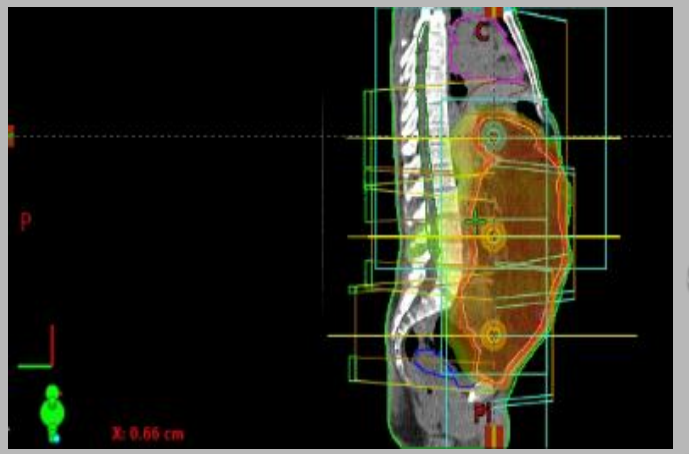












ASOPROCÁNCER
Asociación Pro Congreso de Cancerología

DOSES

Target volumes if 4D motion is assessed (recommended for all upper abdominal tumors)
iGTV: contour GTV incorporating 4D motion; this accounts for internal margin (IM)
ITV = iGTV + 1.5 cm (CTV expansion) for upper abdominal tumors
Edit ITV at interfaces:
Retroperitoneal compartment, bone, kidney, liver: 0 mm
Bowel and air cavity: 5 mm
Under skin surface: 3-5 mm according to institutional preference
If tumor extends to inguinal canal, expand iGTV by 3 cm inferiorly
PTV = ITV + 5 mm (if frequent IGRT with volumetric imaging will be performed)
PTV = ITV + 9-12 mm (if no IGRT with volumetric imaging will be performed)

Target volumes if 4D motion is NOT assessed and tumor has a significant component below the pelvic brim
GTV: contour gross tumor volume
CTV = GTV + 1.5 cm for tumors below pelvic brim
Edit CTV at interfaces:
Retroperitoneal compartment, bone, kidney, liver: 0 mm
Bowel and air cavity: 5 mm
Under skin surface: 3-5 mm according to institutional preference
If tumor extends to inguinal canal, expand GTV by 3 cm inferiorly
PTV = CTV + 5 mm (if frequent IGRT with volumetric imaging will be performed)
PTV = CTV + 9-12 mm (if no IGRT with volumetric imaging will be performed)

Target volumes if 4D motion is NOT assessed and tumor is in the upper abdomen (Note: 4D motion assessment is strongly recommended in this situation)
GTV: contour gross tumor volume
CTV = GTV + 2-2.5 cm in cephalocaudal directions, 1.5-2 cm in radial directions
Edit CTV at interfaces:
Retroperitoneal compartment, bone, kidney, liver: 0 mm
Bowel and air cavity: 5 mm
Under skin surface: 3-5 mm according to institutional preference
If tumor extends to inguinal canal, expand GTV by 3 cm inferiorly
PTV = CTV + 5 mm (if frequent IGRT with volumetric imaging will be performed)
PTV = CTV + 9-12 mm (if no IGRT with volumetric imaging will be performed)

Dose:
50.4 Gy in 1.8 Gy fractions or 50 Gy in 2 Gy fractions

Table 4 Organ at risk dose constraint recommendations for preoperative radiation therapy for retroperitoneal sarcoma

Organ at risk	Dose constraint (reference)
Liver	Mean dose < 26 Gy to planned residual liver
Stomach and duodenum	V45 ≤ 100% (61); V50 < 50%; maximum dose 56 Gy
Kidney, if 1 will be resected	V18 < 15% remaining kidney
Kidney, if both will remain	Mean dose < 15 Gy (61); V18 < 50%
Spinal cord	Maximum dose 50 Gy (61)
Small bowel and large bowel contoured as peritoneal cavity (58)	V15 < 830 cm^3 (60) V45 ≤ 195 cm^3 (61)
Small bowel contoured as individual loops	V15 < 120cc (61); V55 < 20 cm^3
Large bowel contoured as individual loops	V60 < 20 cm^3
Rectum	V50 < 50% (61)
Testicles	As low as possible; V3 < 50% for fertility; maximum dose < 18 Gy; consider cryopreservation in young men (62)
Ovaries	Maximum dose < 3 Gy for fertility (63); Consider cryopreservation in young women (62)
Bladder	V50 ≤ 100% (if necessary)
Perineum (including anus and vulva)	V30 < 50% if possible
Femoral head	Maximum dose < 50 Gy if possible; V40 < 64% (64); mean dose < 37 Gy (64)

Int J Radiation Oncol Biol Phys, Vol. 92, No. 3, pp. 602e612, 2015

DOSES

Hypofractionated Radiation Therapy for Unresectable or Metastatic Sarcoma Lesions

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1. Palliation or symptom relief .
2. Definitive intent for an unresectable.
3. Primary.
4. Oligometastatic disease.
5. Oigoprogressive disease where the goal of RT was to delay or prevent the need to change or reinitiate CT.

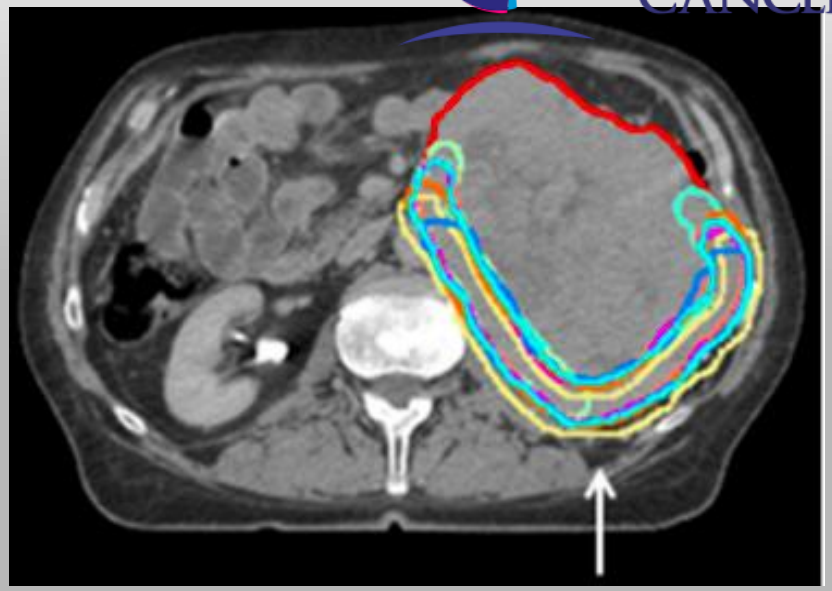
Variable	Value or n (%) N = 73
35 Gy/15 fx	1 (1)
36 Gy/12 fx	7 (10)
37.5 Gy/15 fx	44 (60)
37.5 Gy/17 fx	1 (1)
38.25 Gy/17 fx	2 (3)
39 Gy/12 fx	1 (1)
40.05 Gy/15 fx	1 (1)
42 Gy/12 fx	1 (1)
42.5 Gy/17 fx	7 (10)
45 Gy/15 fx	6 (8)
Dose per fraction GTV	
<3 Gy/fx	21 (29)
3 Gy/fx	38 (52)
>3 Gy/fx	14 (19)

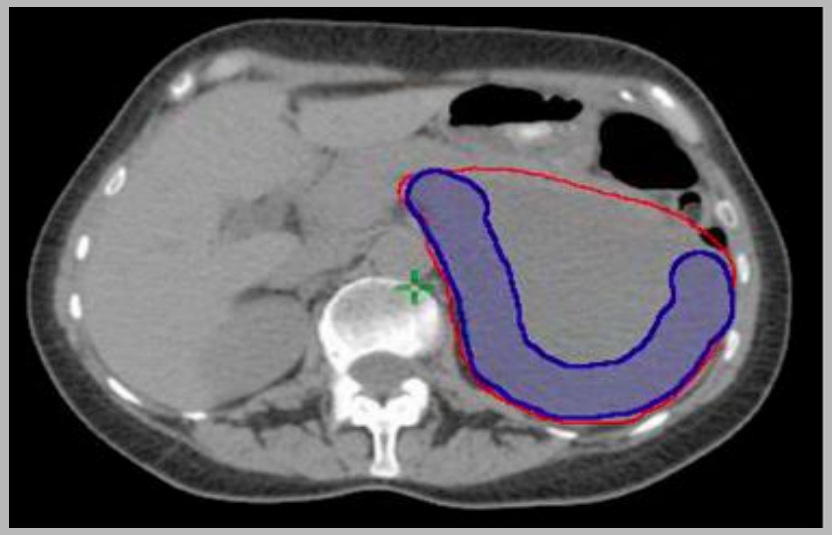
D. Boyce-Fappiano et al. Advances in Radiation Oncology: May–June 2022 10.1016/j.adro.2022.100913

DOSES

Retroperitoneal Sarcoma (RPS) High Risk Gross Tumor Volume Boost (HR GTV Boost) Contour Delineation Agreement Among NRG Sarcoma Radiation and Surgical Oncologists

HR GTV boost should be considered for visceral organs with a retroperitoneal component where potential morbidity of en bloc resection is considered significant or prohibitive.





Ann Surg Oncol. 2015 September ; 22(9): 2846–2852. doi:10.1245/s10434-015-4633-x.

DOSES

- Recommended pre-operative dose is 50-50.4 GY in 1.8-2 GY fractions- J surg oncol. 2018;117:93–98.
- Ongoing preoperative hypofractionated trials.
- Treatment with hypofractionated doses should be the first option in unresectable patients or palliative management

TAKE- HOME MESSAGES

- Retroperitoneal sarcomas are highly complex and heterogeneous diseases in time and in space.
- Considering retroperitoneal sarcoma as a robust system would provide us with a framework for future research strategies, and future cancer therapies may be judged on their ability to help control the robustness of tumors.
- Ct is the most useful and widely available imaging modality in staging and restaging of RPS, whereas MRI is a problem-solving imaging method in terms of disease detection characterization and anatomical definition.
- STRASS into perspective not for all subtypes for WDLPS and grades I and II DDLPS only.

TAKE- HOME MESSAGES

- G3 DDLPS and lMS do not seem to benefit from pre op RT.
- Meta-analysis showed RPS patients who underwent ART had better prognostic outcome than those who underwent surgery alone.
- The necessity of histology- and site-specific studies, reducing the duration of neoadjuvant therapy and subsequent delays to surgery, and mitigating or circumventing the toxicity associated with standard-course photon-based radiotherapy.

XXI Congreso Colombiano de Cáncer

Thank you

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