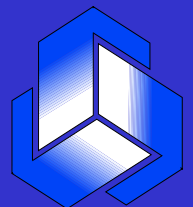


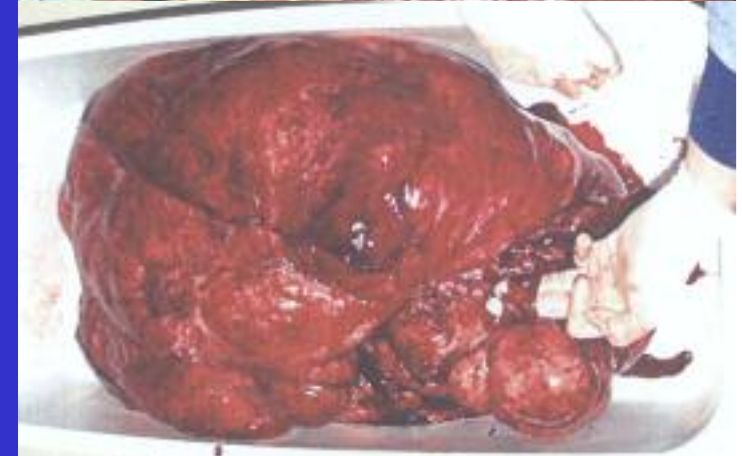
What adjuvant radiotherapy could improve outcome in primary retroperitoneal sarcoma?

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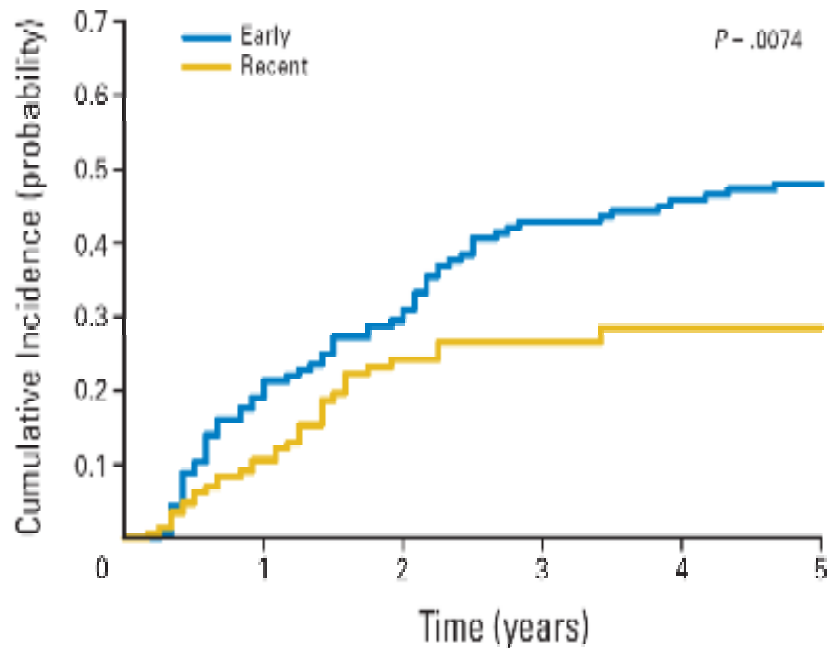
Retroperitoneal sarcoma (RPS)

- Frequently a slow-growing disease
- 5-year OS of 60% and 5-year LRFS rate of 50% (Lewis JJ Ann Surg. 1998, Hassan I Ann Surg. 2004, Bonvalot JCO 2009, Anaya Ann Oncol 2009)
- Locoregional recurrence is a frequent cause of death among patients with low-grade tumours
- the size and anatomical complexity of RPS often result in microscopic residual disease after surgery

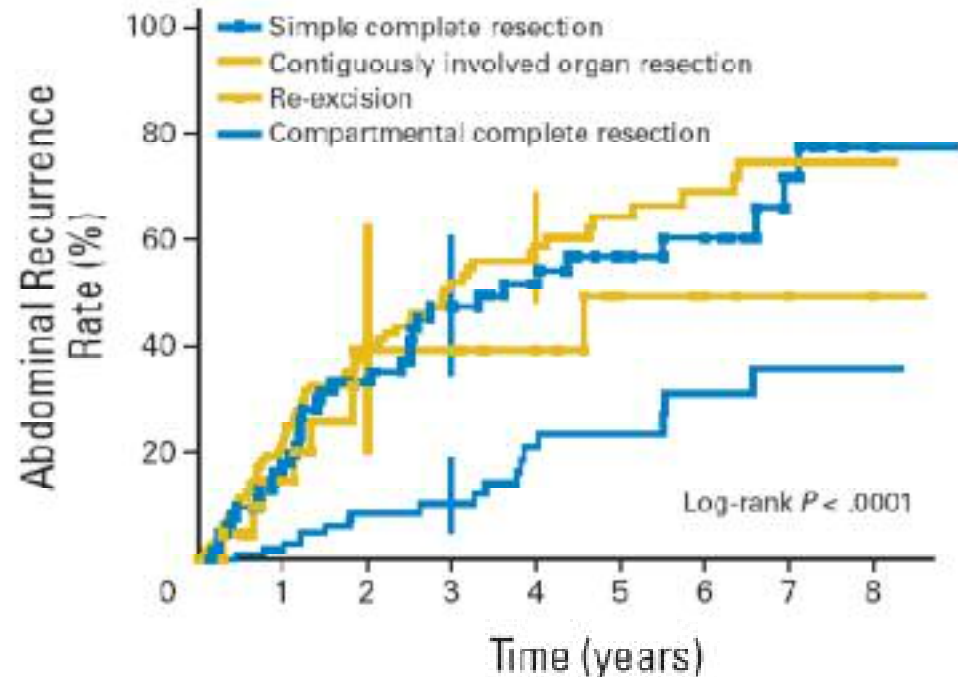


How to improve?

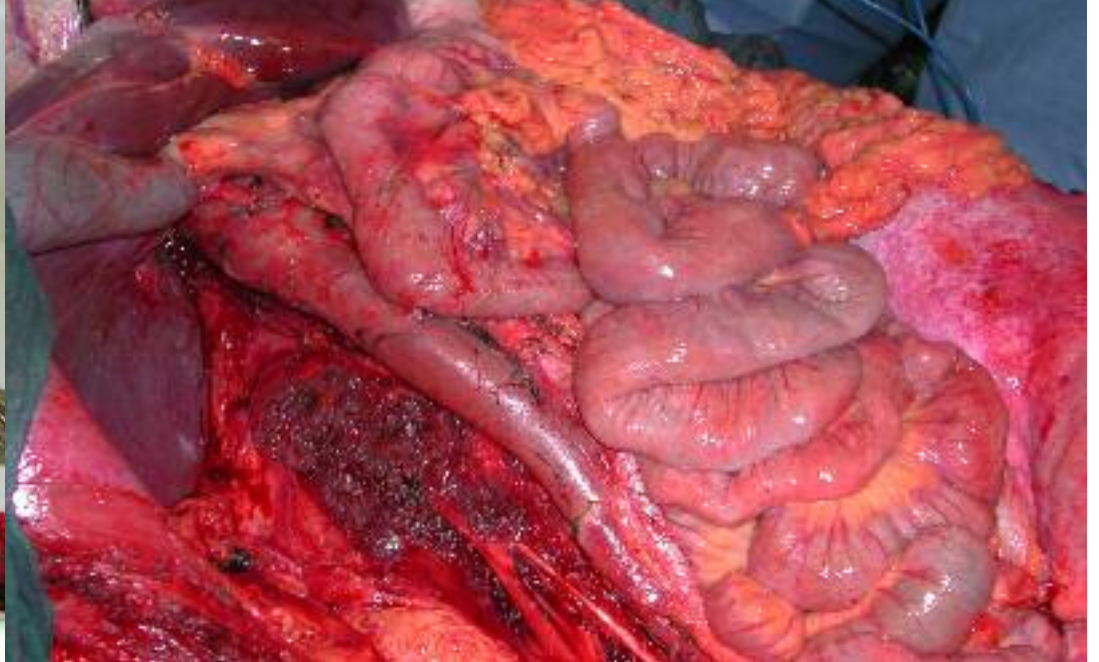
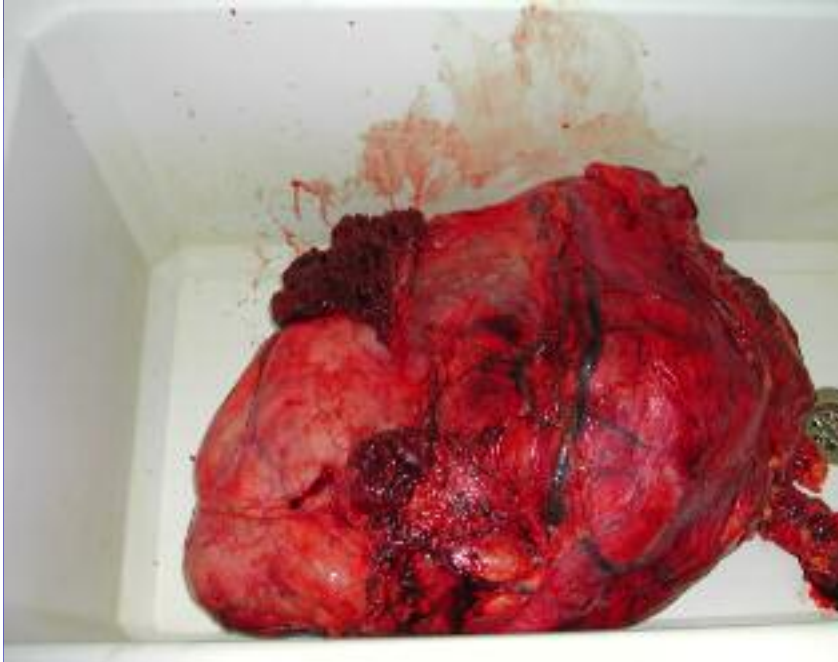
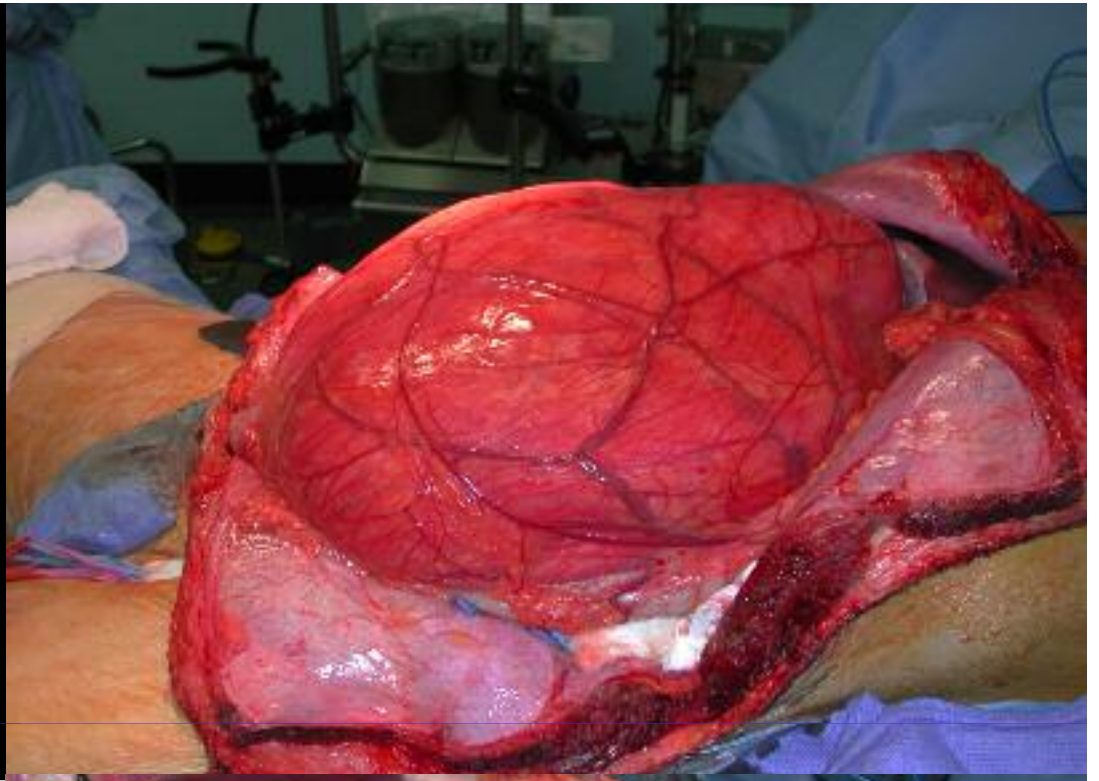
Aggressive surgery could be associated with a better local control



Gronchi et al. JCO 2009



Bonvalot et al. JCO 2009

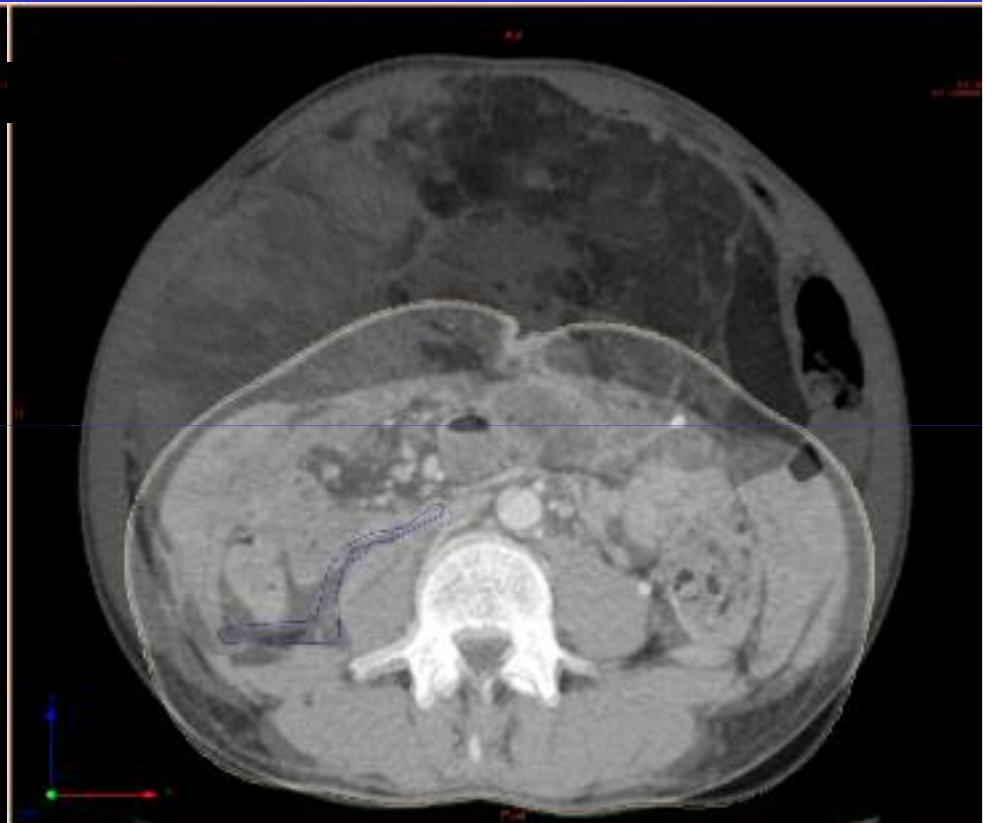


Addition of radiotherapy?

- Adjuvant radiation therapy reduces the likelihood of local recurrence of extremity sarcomas
- But there is no trial supporting its use for RPS as a standard
- Several retrospective studies have been reported with contrasting results, certain in favour of RT [Catton et al. 1994 ; Van Dorn et al. 1994 ; Heslin et al. 1997, Stoeckle 2001, Bonvalot et al. 2009].
- But radiotherapy for patients with RPS is complex (large treatment fields and proximity of critical anatomic structures) and can be toxic
- The local potential benefit does not translate into an ultimate survival benefit (lack of power?)



Multiplanar - v10040.00
Patient ID: P00144481, CT3, 000 @ 110kVp/140 Beam, 100



Multiplanar - v10040.00
Patient ID: P00144481, CT3, 000 @ 110kVp/140 Beam, 100

Analysis of 110 patients with primary RPS operated by systematic “enlarged compartmental surgery” with or without radiotherapy between November 1997 and November 2008

	Surgery w/o radiotherapy		Surgery + radiotherapy	
	Patients	%	Patients	%
Histological margins				
R0	38	62%	20	41%
R1	23	38%	26	53%
R2	0	0%	2	4%
All	58	100%	52	100%

FNCLCC Grade	Surgery w/o radiotherapy		Surgery + radiotherapy	
	Patients	%	Patients	%
1	29	50%	17	31%
2	15	26%	15	29%
3	14	24%	20	40%
All	58	100%	52	100%

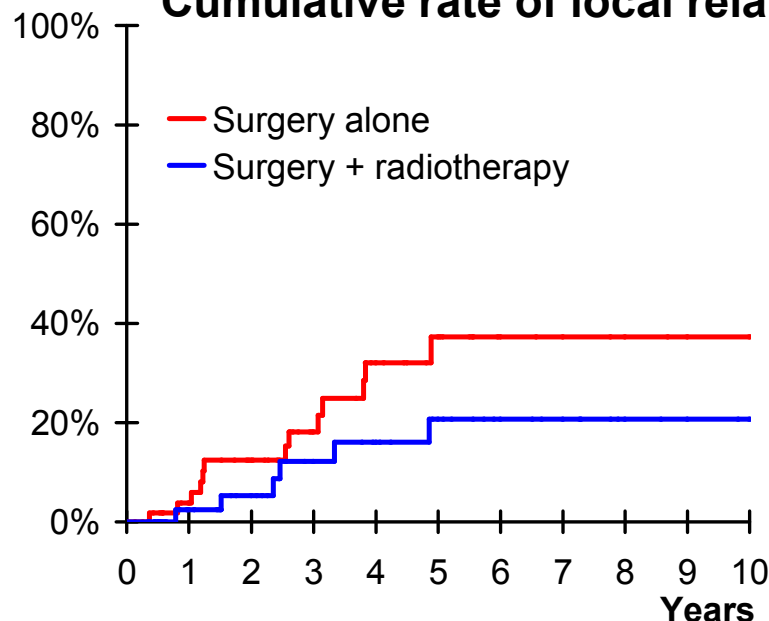
- Significant difference in margins distribution between the two groups of treatment: more R1 and R2 margins in the group with radiotherapy (Chi-square test for R0 vs. R1/R2 : $p = 0.03$).

- There are more patients with grade 3 tumours in group with S+R (40% vs. 24%), and less patients with grade 1 tumours (31% vs. 50%), although this difference is not statistically significant ($p = 0.11$)

- Surgical morbidity: 10% pts underwent a re-intervention.

Analysis of 110 patients with primary RPS operated by systematic “enlarged compartmental surgery” with or without radiotherapy

Cumulative rate of local relapse



- Median follow-up of 4.1 years
- Overall survival at 5 years: 78%
- In this prospective data base with systematic enlarged compartmental surgery performed by the same surgeon, the addition of radiotherapy seems to improve the local control, although it was performed in a significantly higher risk group

At risk

—	58	47	36	24	17	12	6	5	4	3	3
—	52	38	31	23	20	16	11	9	5	4	3

	Surgery w/o radiotherapy	Surgery with radiotherapy
At 2 years	12%	5 %
At 5 years	36%	20 %

Only one randomized study...

Intraoperative radiotherapy in retroperitoneal sarcomas. Final results of a prospective, randomized, clinical trial

- Group A: 20-Gy intraoperative radiotherapy (IORT) in combination with postoperative low-dose (35- to 40-Gy) external-beam radiotherapy
- Group B: postoperative high-dose (50- to 55-Gy) external-beam radiotherapy alone
- Median follow-up, 8 years

35 patients	Follow up	LR	Enteritis	Neuropathy
Group A: 15 pts IORT plus RT	45 months	6/15 (40%)	2/15	9/15
Group B: 20 pts RT control group	52 months	16/20 (80%)	10/20	1/20

....Only one published randomised trial,
but:

- Small sample size
- Radiotherapy versus radiotherapy!
- Significant treatment-related toxicities
- Old trial, no conformal radiotherapy
- High local recurrence rates in both arms
- This trial is not considered definitive and has not changed the standard of care

Pre or post op?

- Experience on Limbs: Local control is equivalent (O'Sullivan et al, 2002)
- **In favour of preoperative RT in RPS:**
- The gross tumour volume (GTV) can be more clearly demarcated
- A higher dose can be administered
- The tumour is in situ and displace radiosensitive viscera such as bowel out of the radiation treatment volume
- RT can be administered with relatively little risk of injury to adjacent normal tissues

Pre op radiotherapy

- 2 single-center prospective non randomized studies
 - Jones JJ, Catton CN, O'Sullivan B, et al. Ann Surg Oncol. 2002.
 - Pisters PW J Clin Oncol. 2003
- 2 retrospective analysis of pre op radiotherapy +/- IORT
 - Gieschen HL, Spiro IJ, Suit HD, et al. Int J Radiat Oncol Biol Phys. 2001
 - Petersen IA, Haddock MG, Donohue JH, et al. Int J Radiat Oncol Biol Phys. 2002

Phase I trial of preoperative concurrent doxorubicin and radiation therapy, surgical resection, and intraoperative electron-beam radiation therapy for patients with localized retroperitoneal sarcoma

- 35 patients with primary or recurrent intermediate- or high-grade RPS
- Doxorubicin was administered each week for 4 or 5 weeks (initial bolus (4 mg/m²) followed by a 4-day continuous infusion (4 mg/m²/d)
- Pre op RX was administered in escalating doses: 18.0, 30.6, 36.0, 41.4, 46.8, or 50.4 Gy in 1.8-Gy fractions
- Pts with localized disease underwent surgical resection with IORT (15 Gy)
- **RESULTS:**
- At 50.4 Gy, 18% patients had grade 3 or 4 nausea
- Grossly complete resection (R0 or R1) was performed in 90% patients who had surgery
- IORT was feasible and successfully administered to 22 R0 or R1 patients
- **CONCLUSION:**
- Preoperative chemoradiation, surgical resection, and EB-IORT are feasible
- Preoperative external-beam radiation can be administered to a total dose of 50.4 Gy with continuous-infusion doxorubicin

Initial results of a trial of preoperative external-beam radiation therapy and postoperative brachytherapy for retroperitoneal sarcoma

- 46 patients underwent complete gross resection
- 41 patients had preoperative XRT (45 gy)
- 23 patients received post operative BT
- Preoperative XRT was very well tolerated and was associated with acute toxicity scores of ≤ 2 in all patients (RTOG score)
- BT related toxicity resulted in RTOG scores of ≥ 3 in 39.1%
- Late toxicity: death 4.3%, life-threatening illness 2.2%, all of whom had been treated with BT to the upper abdomen
- The 2-year OS 88% and DFS 80%
- **CONCLUSIONS:**
- Preoperative XRT was very well tolerated
- BT to the upper abdomen was associated with substantial toxicity
- The effect of BT on OS and DFS could not be assessed statistically

Long-term results of intraoperative electron beam radiotherapy for primary and recurrent retroperitoneal soft tissue sarcoma

- From 1980 to 1996, 37 patients with Primary or recurrence RPS
- All patients underwent **external pre op radiotherapy** (median dose 45 Gy)
- This was followed by laparotomy, resection, and **IOERT, if feasible**
- 20 patients received 10-20 Gy of IOERT with 9-15 MeV electrons.
- After pre op RT 78% pts underwent gross total resection

5 years	All type of resection +/- IORT (37 pts)	Complete resection + IORT (16/20pts)	Complete resection - IORT (13/17 pts)
OS	50%	74%	30%
LC	59%	83%	61%

CONCLUSIONS:

In selected patients, IOERT results in excellent LC with acceptable morbidity.

Use of intraoperative electron beam radiotherapy in the management of retroperitoneal soft tissue sarcomas.

- 87 patients with primary (n = 43) or recurrent (n = 44) RPS
- Between March 1981 and September 1995
- High grade in 54 pts (62%) and Low grade in 33 pts (38%).
- 77 tumors received pre op EBRT with a median dose of 48.6 Gy.
- All patients underwent maximal surgical resection with IOERT
- IOERT doses ranged from 8.75 to 30 Gy (median 15)
- **RESULTS:**
- The overall estimated 5-year survival was 47%
- The 5-year local control rate WAS 59%
- Gastrointestinal complications were recorded in 12 pts (Grade 3 or higher).
- Grade 3 peripheral neurologic toxicities occurred in 9 patients (10%)
- **CONCLUSION:**
RPS can be treated with an aggressive combined approach of EBRT, surgery, and IOERT, with acceptable toxicity

Messages from these studies

- Additional radiotherapy seems to improve local control in retrospective studies
- Preoperative EBRT is well tolerated and can be administered to a total dose of 50.4 Gy
- BT to the upper abdomen is associated with substantial toxicity and did not appear to have contributed to enhanced tumour outcome
- Additional boost of IORT seems to improve the local control (but small series, not randomized);
- In combined pre op EBRT and IORT, much of the toxicity may be related to the IORT
- Need for a randomized study with a control arm being surgery alone

Z9031

**A Phase III Randomized Study of Preoperative
Radiation Plus Surgery Versus Surgery Alone for
Patients with Retroperitoneal Sarcomas (RPS)**

Activation Date: 08/23/2004

Innovations in radiotherapy of RPS

- Focal boost dosing to the regions of attachment in the retroperitoneum (closest margins) BT IORT IMRT



IMRT: advantages

- Treatment of large retroperitoneal tumors volume
- Enhanced tumor coverage
- Better sparing of dose to critical normal structures such as small bowel, liver, and kidney
- IMRT should permit to enhance the prescribed dose without increasing dose in the OAR

Energie: 6.00 MV
Mode: STEP

Suivant

Zoom -

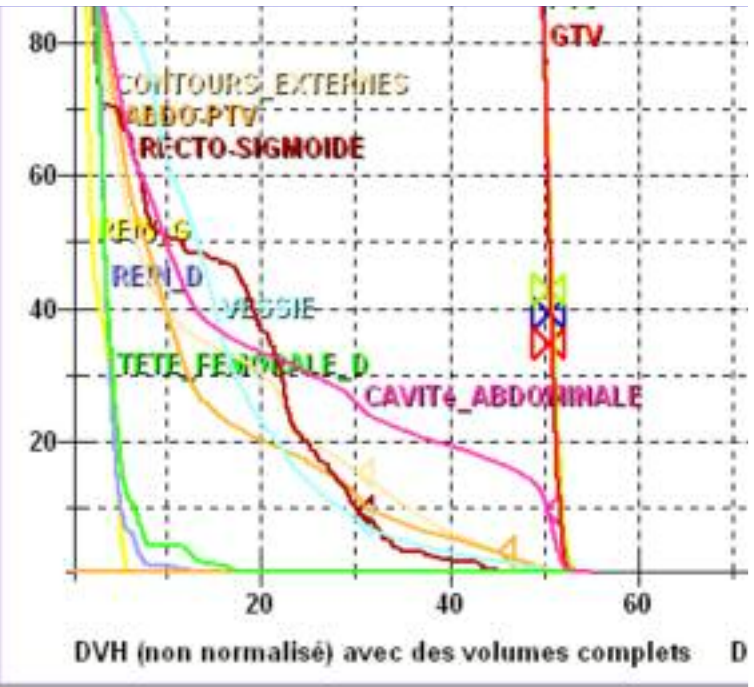
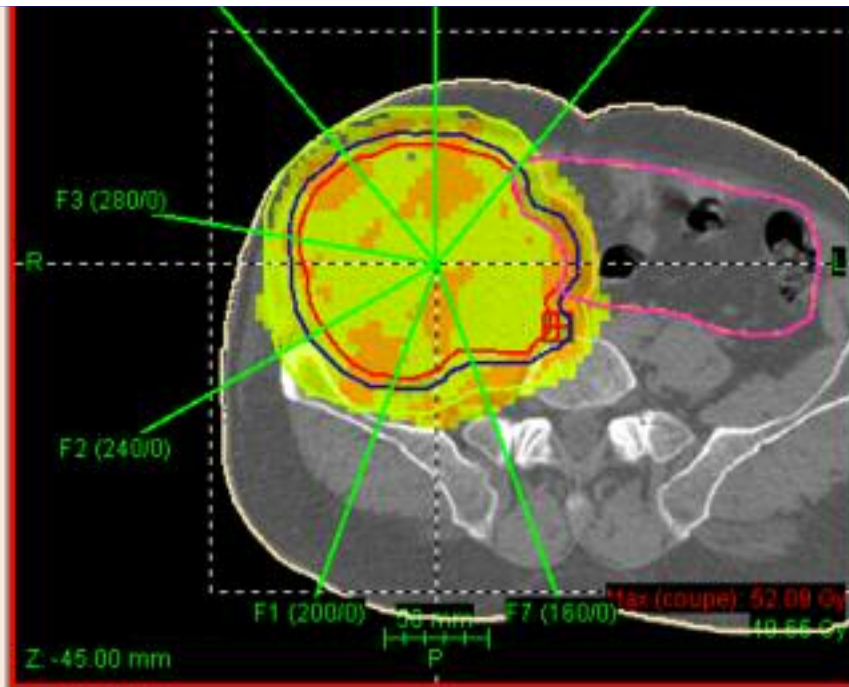
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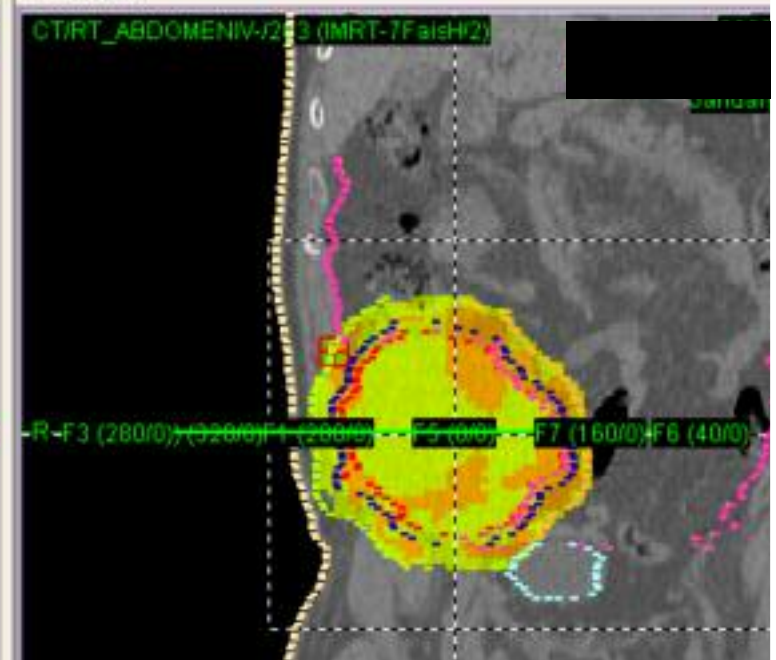
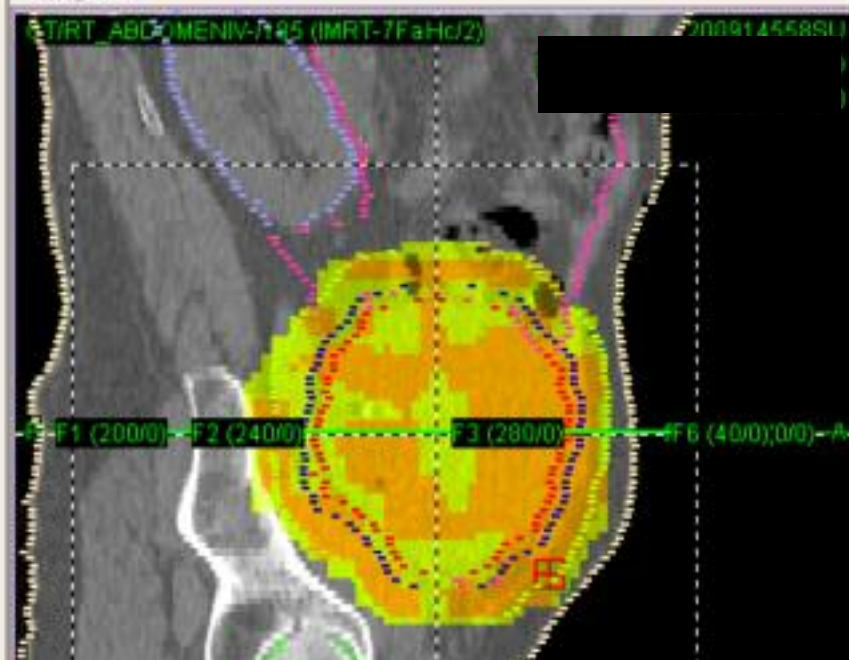
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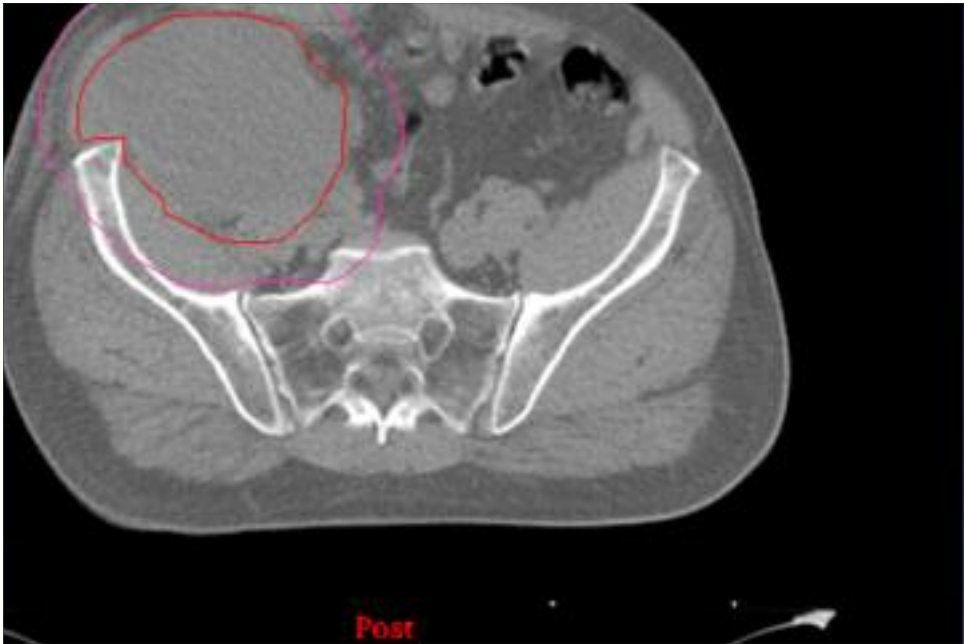
Sagittal

Frontal



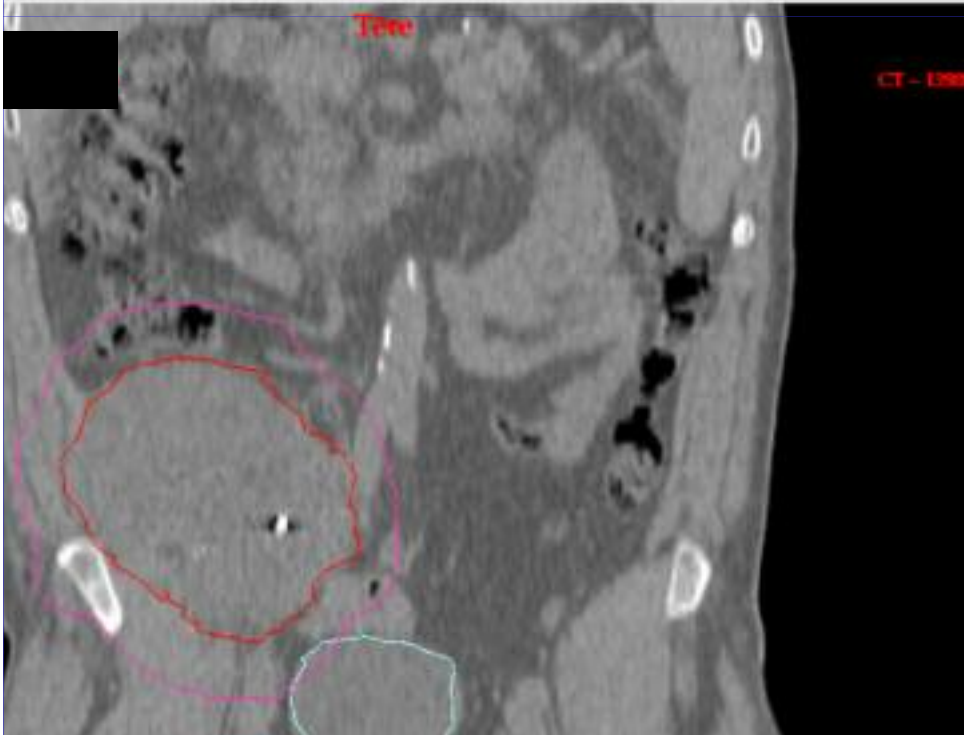
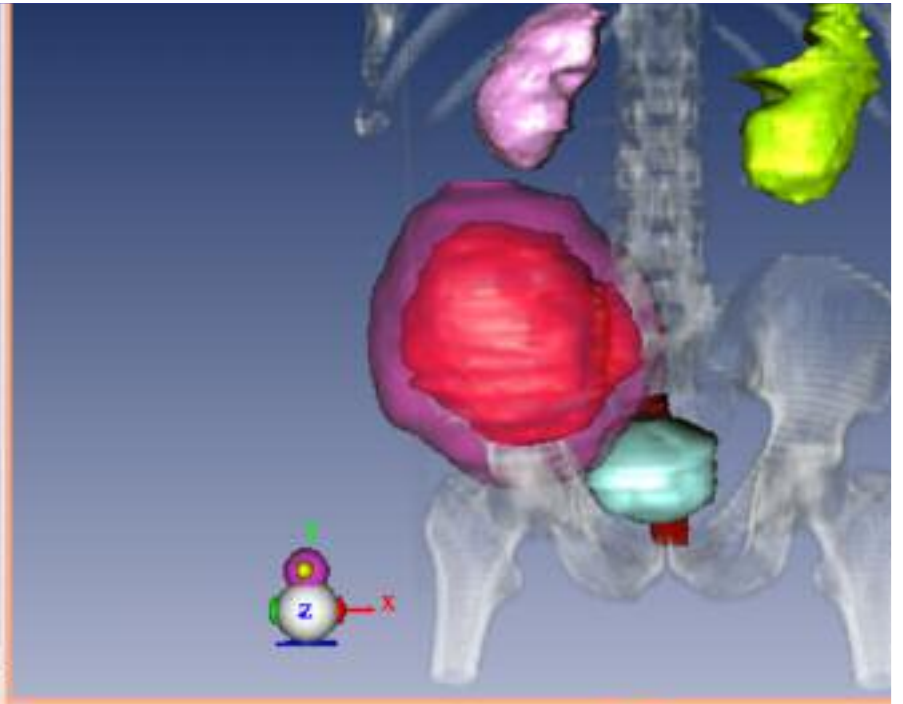
Normalisation

objectif (diff. relative)



Post

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Tête

IMRT for preoperative posterior abdominal wall irradiation of retroperitoneal liposarcomas

- 18 patients received pre-op RT: 50 Gy in 25 fractions of 2 Gy/day.
- The Clinical Target Volume (CTV) has been limited to the posterior abdominal wall (region at higher risk for local relapse)
- A Three-Dimensional conformal (3D-CRT) and an Intensity Modulated (IMRT) plan were used
- **RESULTS:**
- All patients completed the planned treatment
- The acute toxicity was tolerable
- IMRT allows a better sparing of the ipsilateral and the contralateral kidney.
- **CONCLUSIONS:**
- Preop RT is feasible and well tolerated
- The rate of resectability is not compromised by limiting the preop CTV to the posterior abdominal wall
- A better critical-structures sparing is obtained with IMRT

A phase III randomised study of preoperative radiation plus surgery versus surgery alone for patients with retroperitoneal sarcomas
62092/22092 EORTC-Study

Objective

- Multicentric, high-volume centers, randomized phase III study
- to evaluate the contribution of preoperative conformal radiotherapy to expert surgery in primary RP-STs

Schema

- Investigational Arm: pre-operative radiotherapy at the dose of 50.4 Gy/28 daily fractions of 1.8 Gy
- Control Arm: Surgery
- **Assessment of stratification factors**
 - • Institution/ Modalities of conformational radiotherapy (with or without IMRT)
 - • Grade

End points

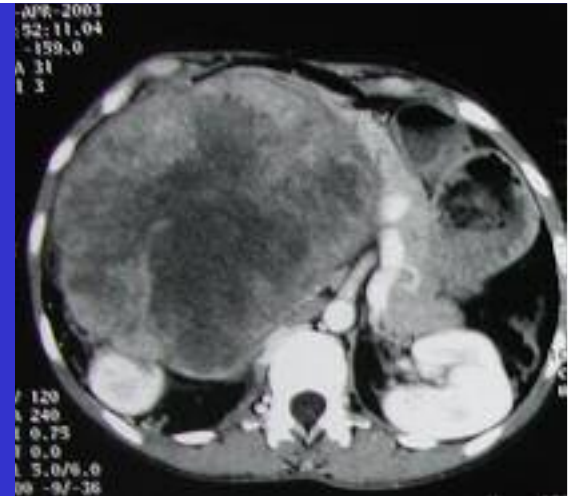
- **Main end point**
- Local disease-free survival at 5 years
- **Secondary end points**
- Evaluation of possible complications yearly
- Patterns of recurrence (local recurrence, sarcomatosis, distant recurrence)
- Analysis of recurrence prognostic factors.
- Overall survival at 5 years
- Second cancers

Inclusion criteria

- 18 years or older, ECOG status 0 or 1
- Primary RPS
- confirmed by the local pathologist from a biopsy
- Contra lateral functional kidney
- Resectable
- Suitable for radiotherapy
- No size cut off
- Radiographically measurable disease, as confirmed by abdominal CT or RMI

Exclusion criteria

- Known chemo-sensitive sarcomas (small round cell sarcomas: alveolar/embryonal rhabdomyosarcomas, PNET/extraskeletal Ewing)
- Gynecological sarcomas, GIST
- Multifocal tumor at presentation (sarcomatosis)
- Metastatic disease
- Prior abdominal or pelvic irradiation
- Bowel obstruction at the time of pre treatment evaluation
- Sarcoma arising from bone
- Planned concomitant chemotherapy during radiotherapy



Surgical procedure

- Macroscopically complete resection (R0 or R1) of the tumor mass will be performed with en-bloc organ resection as necessary based on the intraoperative findings.
- Adjacent organs involved with tumor (such as kidney, spleen, part of colon) should be completely resected as indicated by the operative findings.
- The surgeon will have to specify whether resection was wide or marginal in his report.

Radiotherapy (1)

- Target volume definition
- GTV (Gross Target Volume): delineated on each single CT slice with the help of pre-radiotherapy MRI
- CTV (Clinical Target Volume): The margins surrounding the GTV are defined as 0.5 cm
- PTV (Planning Target Volume): Due to organ movements as well as well as set-up uncertainties an additional margin of at least 1.5 cm (laterally and anteriorly and posteriorly) and 2 cm (superior and inferior) is recommended
- No concomitant chemotherapy is allowed.

Statistical considerations

- Alpha 5%
- 2 sided
- Hypothesis: standard arm PFS 50% 5 years
- Preop radiotherapy: PFS 70% 5 years (HR = 1.9)
- Power 90%
- Patients per group= 128
- **Total 256 pts**
- Number events required: 95

Feasibility: 256 pts

- 10 to 15 centers
- 10 pts/year/center
- 100 pts/year
- # 3 Years inclusion

- (May 2009: Feasibility form was sent to EORTC/
FSG/GSG/ISG centers: expected accrual 154 pts /year)

Conclusions

- Radiotherapy could improve the local control of primary RPS
- There is a strong need for randomized study
- EORTC will start a phase III of preoperative radiation plus surgery versus surgery alone
- Participation of centers of the British Sarcoma Group would be appreciated