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EORTC Soft Tissue and Bone Sarcoma Group

EORTC Radiation Oncology Group

A phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with Retroperitoneal sarcoma (RPS)

EORTC protocol 62092-22092

(NCT01344018)

STRASS

Study Coordinator: [redacted]

Study Co-Coordinator: [redacted]

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28/9/16

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Investigator: (if applicable)

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(Date)

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Protocol summary

Title of the Study	**STRASS -** A phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with Retroperitoneal sarcoma (RPS)
Objective(s)	The main objective is to assess whether preoperative radiotherapy, as an adjunct to curative-intent surgery, improves the prognosis of patients with RPS. **Primary objective** To assess whether there is a difference in abdominal recurrence-free survival between RPS patients undergoing curative-intent surgery alone and those undergoing preoperative radiotherapy followed by curative-intent surgery. **Secondary objectives** ♦ To assess whether there is a difference in metastasis-free survival, abdominal recurrence free interval and overall survival between patients undergoing curative-intent surgery alone and those undergoing preoperative radiotherapy followed by curative intent surgery ♦ To assess tumor response in patients undergoing preoperative radiotherapy ♦ To assess the toxicity profile of preoperative radiotherapy given as an "adjuvant" treatment to curative intent surgery in patients with RPS
Methodology	Superiority phase III trial with stopping rules for the tolerance to protocol treatment
Number of patients	The study is designed to provide 90% power to show an increase of 20% in the 5-year abdominal recurrence free survival rate (defined in chapter 7.1.1), from 50% to 70% (which corresponds to a hazard ratio of 0.52) at the 2-sided 5% significance level: 256 patients will be randomized over 39 months.
Diagnosis and main criteria for inclusion	A screening log form will be used in this protocol to collect information about failures of enrollment. (refer to section 6.1). Tumor-related criteria: ♦ Primary soft tissue sarcoma of retroperitoneal space or infra-peritoneal spaces of pelvis ♦ Sarcoma not originated from bone structure, abdominal or gynecological viscera ♦ Unifocal tumor (not multifocal disease) ♦ Absence of extension through the sciatic notch or across the diaphragm ♦ Histologically-proven RPS (local pathologist/ imaging-guided or surgical biopsy), excluding the following histological sub-types: ♦ Gastro-intestinal stromal tumor (GIST) ♦ Rhabdomyosarcomas

	♦ PNET or other small round blue cells sarcoma, osteosarcoma or chondrosarcoma ♦ aggressive fibromatosis ♦ sarcomatoid or metastatic carcinoma ♦ Tumor not previously treated (no previous surgery -excluding diagnosis biopsy-, radiotherapy or systemic therapy) ♦ Tumor both operable and suitable for radiotherapy ♦ This will be based on pretreatment CT scan/MRI and multidisciplinary consultation with surgeon, radiation oncologist and radiologist (anticipated macroscopically complete resection, R0/R1 resection) ♦ Patients for whom surgery is expected to be R2 on the CT-scan before randomization are not eligible ♦ Patients must have American Society of Anesthesiologist (ASA) score ≤ 2 (see Appendix H) ♦ The criteria for non-resectability are: ♦ (i) involvement of superior mesenteric artery ♦ or (ii) involvement of aorta ♦ or (iii) involvement of bone ♦ No metastatic disease ♦ Patient must have radiologically measurable disease (RECIST 1.1), as confirmed by abdomino-pelvic CT (IV and PO contrast) or MRI (with IV contrast) <u>within the 28 days prior to randomization</u> Patient-related criteria: ♦ ≥ 18 years old ♦ WHO performance status ≤ 2 (see Appendix C) ♦ Absence of history of bowel obstruction or mesenteric ischemia or severe chronic inflammatory bowel disease ♦ Normal renal function: ♦ Calculated creatinine clearance ≥ 50ml/min (calculated by Cockcroft-Gault; see Appendix E) ♦ Functional contra-lateral kidney to the side involved by the RPS as assessed by intravenous pyelogram (done during the baseline CT-scan) or differential renal isotope scan ♦ Normal bone marrow and hepatic function: ♦ White Blood cells ≥ 2.5 x10 ^{9} cells/L ♦ Platelets ≥ 80 x10 ^{9} cells/L ♦ Total bilirubin < 2 times the institutional upper limit of normal value (ULN)

	♦ Adequate cardiac function: less or equal to NYHA II (see Appendix D) ♦ Normal 12 lead ECG (without clinically significant abnormalities) ♦ Women of child bearing potential must have a negative pregnancy test within 3 weeks prior to the first day of study treatment ♦ Patients of childbearing / reproductive potential should use adequate birth control measures, as defined by the investigator, during the study treatment period and for at least 1 month after the surgery. A highly effective method of birth control is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly ♦ Female subjects who are breast feeding should discontinue nursing prior to the first day of study treatment and for at least 1 month after the surgery ♦ No co-existing malignancy within the last 5 years except for adequately treated basal cell carcinoma of the skin or carcinoma in situ of the cervix ♦ No relevant prior abdominal or pelvic irradiation precluding per protocol radiotherapy dose for other prior malignancy or other disease ♦ Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before randomization in the trial ♦ Before patient randomization, written informed consent must be given according to ICH/GCP, and national/local regulations ♦ Patients will be eligible for the translational research program if they are eligible for the clinical trial and have given their written informed consent to participate in this program. If patient refuses to take part in the translational research project, patient remains eligible for the clinical trial

Treatment	
Test product, dose and mode of administration	1) Preoperative radiotherapy starting within the 8 weeks following the randomization: 28 daily fractions of 1.8 Gy (5 fractions per week) for a total dose of 50.4 Gy 2) Re-assessment of operability 3) Large en-bloc curative intent surgery within 4-8 weeks following the end of radiotherapy
Duration of treatment	Study treatment will be given as indicated in the protocol unless any of the following events occur: ♦ Disease progression ♦ Occurrence of second malignancy ♦ Unacceptable toxicity based on the investigator's judgment ♦ Patient decision ♦ After preoperative radiotherapy, patients for whom surgery is expected to be R2 on the CT-scan performed two weeks after the end of radiotherapy.
Reference therapy, dose and mode of administration	Large en-bloc curative intent surgery within 4 weeks following randomization.
Criteria for evaluation	
Efficacy	Abdominal recurrence free survival, abdominal failure interval, metastases free survival, overall survival, tumor response to preoperative radiotherapy
Safety	Two scales will be used for assessing adverse events: ♦ CTCAE version 4.0: pre-operative period and follow up ♦ Dindo scale: perioperative period including per- and immediate postoperative periods (refer to chapter 7.2.2)
Statistical methods	Two early safety checks will be performed after 33 and after 66 patients have been treated in each arm with the aim of stopping the experimental arm if an absolute increase of 20% is observed in terms of reoperation rate or if an absolute increase of 12% is observed in terms of non-operable tumors as compared to the control group. The primary analysis and all efficacy endpoints will be performed in the intention-to-treat population. A 2-sided 5% significance level will be applied to all tests and confidence intervals. Abdominal recurrence free survival (primary endpoint), metastatic free survival and overall survival will be described using Kaplan-Meier curves (Ref. 29) in the two treatment arms. The median survival time and its associated non-parametric confidence interval will be calculated. Abdominal failure interval will be described using cumulative incidence

	curves (Ref. 30). All efficacy endpoints will be compared between the randomized groups using the Cox's proportional hazards model (Ref. 31). For the competing risk endpoints (incidence of distant metastases) this will be a cause specific Cox's proportional hazards model. The analysis of the toxicity endpoints will be performed in the safety population. The late toxicity will be investigated in the complete safety population.
Translational research	All patients included in the clinical study will be offered to participate to the associated translational research project defined in section 11.1 and the prospective bio-banking of biological material at the time they are offered participation to the clinical study. The primary aim of the planned translational research is to establish new prognostic factors in patients with retroperitoneal sarcoma, especially liposarcoma.
Quality of Life	The rationale for measuring HRQoL in this study is in measuring long-term impact related to surgical complication on patients' well-being. Quality of Life will be measured by an ad-hoc checklist composed of validated QLQ questions in order to measure fatigue, mobility, digestive troubles, sexual disorders and pain at baseline and years 1 and 5.
PK – PD	Not applicable

1 Background

1.1 Retroperitoneal Sarcoma

Approximately 10-15% of adult soft tissue sarcomas arise in the retroperitoneum (Ref. 1). The mean annual incidence is 2.7 cases per 10^6 persons and does not change significantly over time (Ref. 1). The sex ratio is approximately 1, and the median age at diagnosis is about 55 (Ref. 1, Ref. 2, Ref. 3, Ref. 4).

The most frequent histological subtypes are:

- well-differentiated liposarcomas
- dedifferentiated liposarcomas
- leiomyosarcomas (Ref. 2, Ref. 3, Ref. 4)

Most of the previously so-called “malignant histiocyto-fibroma” or “malignant mesenchymoma” are now classified as dedifferentiated liposarcomas (Ref. 5). About two thirds of retroperitoneal soft tissue sarcomas are intermediate or high-grade tumors (Ref. 2, Ref. 3, Ref. 4).

In this trial, we define as retroperitoneal sarcoma (RPS) all sarcoma arising in soft tissue of the retroperitoneum and the infra-peritoneal pelvic space; excluding sarcoma originating from viscera (intra-abdominal and gynecological) (Ref. 1, Ref. 2, Ref. 3, Ref. 4, Ref. 5).

1.2 Outcome

RPS are marked by a poor outcome, especially over the long term. The 5-year overall survival rate is 50-60%, significantly worse than soft tissue arising from an extremity (Ref. 2, Ref. 3, Ref. 4). The poor outcome of RPS is not explained by the occurrence of metastases, as only about 13% of patients experience distant metastases at 5 years (Ref. 3). The major event leading the poor outcome is local recurrence. The local-recurrence-free survival at 5 years is 52-60% (Ref. 2, Ref. 3, Ref. 4). This is explained by the following phenomena:

- A large median tumor size at diagnosis of 15-18 cm (Ref. 2, Ref. 3, Ref. 4)
- This specific anatomic site implies proximity to and often invasion of contiguous vital structures and organs. This makes complete resection with negative margins difficult (Ref. 2, Ref. 3, Ref. 4)
- Up to 50% of patients are treated by non experienced surgical teams (Ref. 2)

Table 1- Summary of the 4 largest retrospective studies

	Lewis et al. (Ref. 4)	Gronchi et al. (Ref. 3)	Gronchi et al. (Ref. 3)	Bonvalot et al. (Ref. 2)
Period	1982-97	1985-2001	2002-2007	1985-2005
Study	Single-center	Single-center	Single-center	Multicenter
cases	278	136	152	382
Median age (y.o)	58 (16-88)	56 (46-65)	55 (47-67)	57 (14-87)
Median size (cm)	-	15 (10-28)	18 (10-26)	18 (3-60)
Grade				
High	64%	33%	27%	32%
Intermediate	-	29%	39%	34%
Low	36%	38%	34%	29%
Not done	-	-	-	5%
Histology				
Liposarcoma	41%	56%	59%	44%
Leiomyosarcoma	27%	15%	13%	18%
Others	32%	29%	28%	38%
5-y OS	? %	51%	60%	57%
5-y local recurrence free survival	59%	Not done	Not done	Not done
5-y probability of local recurrence	Not done	48%	29%	Not done
5- y abdominal recurrence free survival (*)	Not done	Not done	Not done	51%

(*) including peritoneal sarcomatosis and local relapse

1.3 Current surgical issues

The predictive factors for local recurrence after primary treatment are currently unclear as most of studies merge primary and recurrent RPS (Table 2). The potential predictive factors for local recurrence are high grade (Ref. 2, Ref. 4, Ref. 6), dedifferentiated liposarcoma (Ref. 4), margins of resectability (Ref. 2, Ref. 7), surgery performed in reference centers (Ref. 2) and perioperative radiotherapy (Ref. 2, Ref. 6). Tumor size is not a predictive factor for local relapse (Ref. 2, Ref. 4). For decades, patients have been relatively under-treated with debulking surgery or partial resection. The retrospective studies of Bonvalot et al. and Gronchi et al. suggest that extensive surgery improves outcomes (Ref. 2, Ref. 3). In the study of Bonvalot, “compartmental complete resection” represents the systematic resection of uninvolved contiguous organs in order to obtain a rim of normal tissue surrounding the tumor (like muscles in limb sarcomas), thus ensuring wide margins. This type of surgery was performed since the 90’s by 3 high volume centers participating to the study. Typically, the patient underwent an en bloc tumor resection with

the colon in front, the kidney inside and the psoas (or its aponeurosis) at the back. Compartmental resection led to a 3.29-fold decrease in the local recurrence rate with a 3-year recurrence rate of 10% compared to 50% with standard procedures. In the first study of Gronchi, from 1985 to 2002, the surgery was considered as non optimal in most cases; then the 5-year local-recurrence free survival was 52%. From the beginning of 2002, in a second study, Gronchi et al. have considered all patients for extensive surgery, which comprised liberal en-bloc resection of surrounding tissues and organs when they are located within 1 to 2 cm from the surface tumor, even when not infiltrated (Ref. 3). Therefore, the current surgical approaches implies the resection of one surrounding organ in 30% of cases and 2 or more surrounding organs in 50% of cases (Ref. 3). With this practice their 5-year local-recurrence free survival went up to 71%.

These 2 studies underline that the main factor that contributes to reduce the local relapse rate is the surgeon's expertise.

Nevertheless, despite extensive resections, the result of the surgical procedure cannot be coded according to the classical “R0, R1 and R2 classification”. The determination of “R0” status for RPS is problematic because of the large tumor surface. Complete examination of the tumor specimen is often not feasible. Areas that appear grossly suspicious are typically selected for sampling, along with multiple random sections. Therefore, it is not often possible to claim R0 status. The presence of gross residual disease after resection has been reported as the most significant predictor of tumor-related death (Ref. 2, Ref. 3, Ref. 4, Ref. 8, Ref. 9, Ref. 10).

The perioperative mortality is about 3-4% (Ref. 2, Ref. 4, Ref. 11). **About, 10-12% of patients undergo a re-operation for complications** (Ref. 11). In the French and Italian retrospective study, the most frequent postoperative complications are anastomotic leakage (23/249), infected retroperitoneal collection (10/249), postoperative bleeding (6/249) and wound dehiscence (4/249). **Most of these complications occur within the 60 days following the surgical procedure** (Ref. 11).

Table 2- Potential predictive factors for local recurrence identified by multivariate analysis

	Stoeckle 2001 (Ref. 6)	Singer 2003 (Ref. 10)	Hassan 2004 (Ref. 7)	Bonvalot 2009 (Ref. 2)	Lewis 1998 (Ref. 4)
cases	165	177	97	382	500
Histology	No	-	No	No	Yes (Lipo)
Grade	Yes	No	-	Yes	Yes
Margins	-	-	Yes	Yes	No
Reference center	-	-	-	Yes	-
Radiotherapy	Yes	-	-	Yes	-

1.4 Radiotherapy

Due to the infiltrative nature of RPS, their proximity to vital organs and the difficulty to achieve an en-bloc resection, numerous investigators have addressed the role of pre- and postoperative radiotherapy (Ref. 12, Ref. 13, Ref. 14, Ref. 15, Ref. 16).

Several retrospective studies have suggested that (neo-)adjuvant radiotherapy significantly reduces the risk of local recurrence (Ref. 2, Ref. 3, Ref. 6, Ref. 17, Ref. 18, Ref. 19). In a large multicenter retrospective analysis, the 3-year local recurrence rate was 49% without radiotherapy compared to 34% with radiotherapy (HR=0.64, $p<0.005$) (Ref. 2). Nevertheless, radiotherapy for RPS is complex because of the frequently large field sizes and the proximity of radiosensitive tissues and organs.

Intraoperative radiotherapy (IORT) requires specific equipment, expertise and logistics and therefore its use is restricted to specialist sarcoma centers only (Ref. 20).

Preoperative radiotherapy is preferred to postoperative radiotherapy for the following reasons (Ref. 14):

- The tumor is in situ making delineation and treatment planning more straightforward
- The tumor may displace radiosensitive structures outside the treatment field
- The biologically effective dose of radiation required may be lower before surgery than after surgery due to less hypoxia
- Higher doses can be delivered to tumor field because of fewer surgical adhesions
- The tumor is treated in situ prior to potential contamination of the peritoneal cavity
- Consequently, lower rates of acute and late toxicity may be seen and long term function may be better (Ref. 21)

Jones et al. have reported their experience with preoperative external beam radiotherapy ± postoperative brachytherapy in 41 patients with localized RPS (Ref. 15). The median preoperative dose was 45 Gy (range 42-50 Gy). No patients required hospitalization and none terminated radiotherapy because of acute toxicity, although one patient had to delay radiotherapy because of acute nausea and vomiting. Thirty percent of patients experienced upper gastro-intestinal toxicity grade 2 (RTOG acute toxicity score). Postoperative mortality was 2%. Fifty percent of operated patients received additional postoperative radiotherapy (median dose 25 Gy; range 7.3-30 Gy). 6 out 19 of patients experienced life-threatening toxicity due to postoperative radiotherapy. The 5-year local-recurrence free rate was 60%. The rate of toxic death was 2/41 (5%) (Ref. 15). This study highlights the potential toxicity of additional postoperative radiotherapy delivered after preoperative irradiation and surgery.

After surgery and radiotherapy, patients are at risk of several late normal tissue complications such as (Ref. 12, Ref. 13):

- small bowel complications (mal-absorption syndrome, adhesions, perforation, fistula)
- neurotoxicity (radiation myelitis, sacral plexopathy)
- kidney damage (reduced glomerular filtration, hypertension)
- liver damage
- secondary malignancies in the irradiated field

In a Phase I trial of preoperative concurrent doxorubicin and radiation therapy, surgical resection, and intraoperative electronbeam radiation therapy for patients with localized RPS, Pisters (Ref. 27) included 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/m^2) followed by a 4-day continuous infusion (4 mg/m^2/d). Preoperative radiotherapy was administered in escalating doses: 18.0, 30.6, 36.0, 41.4, 46.8, or 50.4 Gy in 1.8-Gy fractions. Patients with localized disease underwent surgical resection with IORT (15 Gy). 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 and IORT was feasible and successfully administered to 22 R0 or R1 patients. This study shows that preoperative chemo-radiation, surgical resection, and EB-IORT are feasible and that preoperative external beam radiation can be administered to a total dose of 50.4 Gy with continuous infusion of doxorubicin.

1.5 Rationale

Radiotherapy seems to improve local control in retrospective studies but this potential advantage must be weighted in regards of potential side effects. Preoperative external beam radiotherapy (EBRT) is best tolerated and can be administered to a total dose of 50.4 Gy. Whereas in combined preoperative EBRT and IORT, much of the toxicity may be related to the IORT.

This needs a formal phase III randomized study to evaluate the risk/benefit ratio of this approach with a control arm being surgery alone and investigational arm being pre op radiotherapy.

2 Objectives of the trial

The main objective is to assess whether preoperative radiotherapy, as an adjunct to curative-intent surgery, improves the prognosis of patients with RPS.

2.1 Primary objective

To assess whether there is a difference in abdominal recurrence-free survival between RPS patients undergoing curative-intent surgery alone and those undergoing preoperative radiotherapy followed by curative-intent surgery.

2.2 Secondary objectives

- To assess whether there is a difference in metastasis-free survival, abdominal recurrence free interval and overall survival between patients undergoing curative-intent surgery alone and those undergoing preoperative radiotherapy followed by curative intent surgery
- To assess tumor response in patients undergoing preoperative radiotherapy
- To assess toxicity of preoperative radiotherapy given prior to curative intent surgery in patients with RPS

2.3 End-points

2.3.1 Primary endpoint

The primary endpoint will be "abdominal recurrence free survival" (see chapter 7).

2.3.2 Secondary endpoints

The safety secondary endpoints will be:

- Acute toxicity profile of preoperative radiotherapy
- Perioperative complications
- Late complications

The efficacy secondary endpoints will be:

- Tumor response to preoperative radiotherapy
- Time to abdominal recurrence
- Metastasis-free survival
- Overall survival

3 Patient selection criteria

A screening log form will be used in this protocol to collect information about failures of enrollment. (refer to section 6.1).

3.1 Tumor-related criteria

- Primary soft tissue sarcoma of retroperitoneal space or infra-peritoneal spaces of pelvis
- Sarcoma not originated from bone structure, abdominal or gynecological viscera
- Unifocal tumor (not multifocal disease)
- Absence of extension through the sciatic notch or across the diaphragm
- Histologically-proven RPS (local pathologist/ imaging-guided or surgical biopsy), excluding the following histological sub-types:
  - Gastro-intestinal stromal tumor (GIST)
  - Rhabdomyosarcomas
  - PNET or other small round blue cells sarcoma, osteosarcoma or chondrosarcoma,
  - Aggressive fibromatosis
  - Sarcomatoid or metastatic carcinoma
- Tumor not previously treated (no previous surgery -excluding diagnosis biopsy-, radiotherapy or systemic therapy)
- Tumor both operable and suitable for radiotherapy
  - This will be based on pretreatment CT scan/MRI and multidisciplinary consultation with surgeon, radiation oncologist and radiologist (anticipated macroscopically complete resection, R0/R1 resection)
  - Patients for whom surgery is expected to be R2 on the CT-scan before randomization are not eligible
  - Patients must have American Society of Anesthesiologist (ASA) score ≤ 2 (see Appendix H)
  - The criteria for non-resectability are:
    - (i) involvement of superior mesenteric artery
    - or (ii) involvement of aorta
    - or (iii) involvement of bone
- No metastatic disease
- Patient must have radiologically measurable disease (RECIST 1.1), as confirmed by abdomino-pelvic CT (IV and PO contrast) or MRI (with IV contrast) within the 28 days prior to randomization

3.2 Patient-related criteria

- ≥ 18 years old
- WHO performance status ≤ 2 (see Appendix C)
- Absence of history of bowel obstruction or mesenteric ischemia or severe chronic inflammatory bowel disease
- Normal renal function:
  - Calculated creatinine clearance ≥ 50ml/min (calculated by Cockcroft-Gault; see Appendix E)
  - Functional contra-lateral kidney to the side involved by the RPS as assessed by intravenous pyelogram (done during the baseline CT-scan) or differential renal isotope scan
- Normal bone marrow and hepatic function:
  - White Blood cells ≥ 2.5 x10 ^{9} cells/L
  - Platelets ≥ 80 x10 ^{9} cells/L
  - Total bilirubin < 2 times the institutional upper limit of normal value (ULN)
  - Adequate cardiac function: less or equal to NYHA II (see Appendix D)
- Normal 12 lead ECG (without clinically significant abnormalities)
- Women of child bearing potential must have a negative pregnancy test within 3 weeks prior to the first day of study treatment
- Patients of childbearing / reproductive potential should use adequate birth control measures, as defined by the investigator, during the study treatment period and for at least 1 month after the surgery. A highly effective method of birth control is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly
- Female subjects who are breast feeding should discontinue nursing prior to the first day of study treatment and for at least 1 month after the surgery
- No co-existing malignancy within the last 5 years except for adequately treated basal cell carcinoma of the skin or carcinoma in situ of the cervix
- No relevant prior abdominal or pelvic irradiation precluding per protocol radiotherapy dose for other prior malignancy or other disease
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before randomization in the trial
- Before patient randomization, written informed consent must be given according to ICH/GCP, and national/local regulations
- Patients will be eligible for the translational research program if they are eligible for the clinical trial and have given their written informed consent to participate in this program. If patient refuses to take part in the translational research project, patient remains eligible for the clinical trial

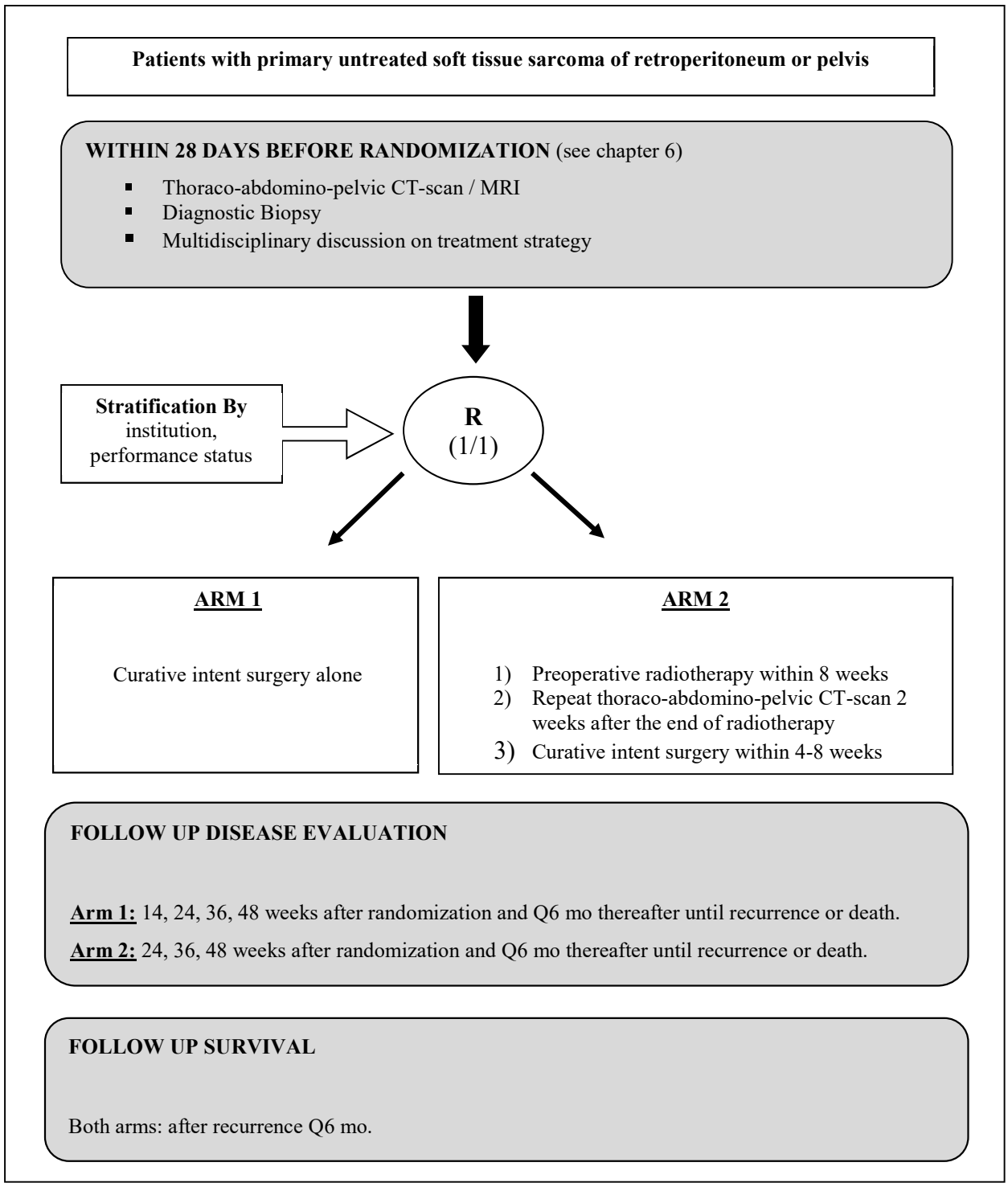
4 Trial Design

This is an open-label randomized phase III superiority trial aiming to demonstrate that preoperative radiotherapy (3D-CRT or IMRT to a dose of 50.4 Gy/28 daily fractions) increases the abdominal recurrence-free survival rate of patients with RPS treated with surgery compared to patients treated with surgery alone.

The study is designed to provide 90% power to show an increase of 20% in the 5-year abdominal recurrence free survival rate (defined in chapter 7.1.1), from 50% to 70% (which corresponds to a hazard ratio of 0.52) at the 2-sided 5% significance level: 256 patients will be randomized over 39 months.

In addition, two early safety checks will be performed in each treatment arm, after 33 and then after 66 patients have been treated with each regimen (see chapter 8) with the aim of stopping any treatment arm that increases the rate of reoperation by 20% or increases the proportion of non-operable tumors by 12% compared to the control group.

Patients will be stratified by institution and performance status.


Patients with primary untreated soft tissue sarcoma of retroperitoneum or pelvis
WITHIN 28 DAYS BEFORE RANDOMIZATION (see chapter 6)
Thoraco-abdomino-pelvic CT-scan / MRI
Diagnostic Biopsy
Multidisciplinary discussion on treatment strategy
Stratification By institution, performance status
R (1/1)
ARM 1
Curative intent surgery alone
ARM 2
1) Preoperative radiotherapy within 8 weeks
2) Repeat thoraco-abdomino-pelvic CT-scan 2 weeks after the end of radiotherapy
3) Curative intent surgery within 4-8 weeks
FOLLOW UP DISEASE EVALUATION
Arm 1: 14, 24, 36, 48 weeks after randomization and Q6 mo thereafter until recurrence or death.
Arm 2: 24, 36, 48 weeks after randomization and Q6 mo thereafter until recurrence or death.
FOLLOW UP SURVIVAL
Both arms: after recurrence Q6 mo.

5 Therapeutic regimens, expected toxicity, dose modifications

5.1 Standard arm: Surgery alone

5.1.1 Operability criteria

Patients for whom surgery is expected to be R2 on the CT-scan before randomization are not eligible.

Surgical procedures have to be done within the defined timelines. Please make sure that the operability criteria are met before surgery:

- Patients must have American Society of Anesthesiologist (ASA) score ≤ 2 (see Appendix H)
- The criteria for non-resectability are:
  - involvement of superior mesenteric artery
  - or involvement of aorta
  - or involvement of bone

5.1.2 Recommended surgical procedure

Surgery will be performed in the investigator's site, following these key recommendations:

- Surgery will be performed as soon as possible (**within 4 weeks following the randomization**)
- Preoperative surgical evaluation will be performed for all patients on cross sectional imaging (both CT scan and MRI are allowed) within 28 days before randomization
- A generous midline laparotomy is preferred, in order to carry out an exploration of the whole abdominal cavity
- Macroscopically complete resection (R0/R1) of the tumor mass will be performed with en-bloc organ resection as necessary, based on preoperative assessment and intraoperative findings
- Ideally, the following organs should be resected when in proximity to the tumor surface: kidney, colon, psoas muscle or its aponevrosis (recommended but not required, systematic resection should be indicated in the operative form)
- The following organs or structures should be resected only if directly infiltrated: duodenum, head of pancreas, liver, stomach, major abdominal vessels and nerves, bone
- Operative report must clearly indicate: whether surgery is macroscopically complete or not, whether per operative rupture was done or not, whether not involved organs were systematically resected or not. The best would be to insert these informations in English at the end of the report: R2 yes/no; Rupture Yes/ No, not involved organs resection yes/ no

The name of the surgeon and data about the type of surgery, extent and morbidity of the surgical intervention will be collected on a "Surgery Form".

If the patient has consented, during the surgical procedure the surgeon has to appropriately collect:

- Tumor tissue
- Abdominal wall fat
- Peripheral blood

5.1.3 Recommendations for perioperative management

We strongly recommend a minimum 24-hour stay in an intensive care unit after the surgical procedure.

5.1.4 Expected toxicity

According to the most recently published literature (Ref. 11) immediate postoperative complications are to be expected in about 18% of patients, including:

- Anastomotic leakage
- Infected postoperative collection
- Postoperative bleeding
- Wound dehiscence
- Limb compartmental syndrome

About 12% of patients will require re-intervention, mainly for:

- Postoperative bleeding
- Retroperitoneal abscess
- Wound dehiscence

Most of these complications occur within the month following surgery. In consequence, patients should be carefully followed until hospital discharge (daily examination during hospital stay) and/or morbidity up to the 60th postoperative day (see chapter 7).

All complications requiring re-operation/percutaneous radiological drainage have to be considered as an SAE.

5.2 Investigational arm- radiotherapy and surgery

5.2.1 Preoperative radiotherapy

Preoperative radiotherapy will be delivered via a 3D-CRT or IMRT technique conducted according to EORTC RTQA guidelines.

The preoperative radiotherapy should be performed in the same center as surgery. "Satellite" centers are not allowed in this trial.

5.2.1.1 Interval between randomization and start of radiotherapy

Radiotherapy should be started within 8 weeks after randomization and will last for about 6 to7 weeks.

5.2.1.2 Patient immobilization and data acquisition

All patients will be irradiated in the supine position, preferably with knee and ankle rests for support of the legs. The arms should be out of the way of the beams; it is highly recommended that they are rested in arm supports above the head. No specific immobilization device is mandatory, but one may be used (e.g. vacuum fix bag).

5.2.1.2.1 Preparation for planning CT-simulation

All patients must undergo a planning CT-simulation for treatment planning.

5.2.1.2.2 Bowel preparation

No specific bowel preparation is required. However if the sarcoma is primarily located within the pelvis, the degree of rectal filling should be assessed. If the patient has a significant amount of air in the rectum (defined as ≥ 5cm rectal wall distention in the transverse plane), the patient should receive laxatives and be rescanned at least 2 days later.

The bowel preparation adopted for the planning CT-simulation scan should be maintained throughout each radiotherapy treatment.

5.2.1.2.3 Bladder preparation

No specific bladder preparation is required. Most patients are more comfortable with empty bladders. In the case of sarcomas above the promontorium the cranial displacement of the small intestine by a full bladder may even be disadvantageous. However, the preferred degree of bladder filling will be left to the discretion of the investigator as this may depend on the exact location and extent of the sarcoma.

The bladder preparation adopted for the CT-simulation scan should be maintained throughout each radiotherapy treatment.

5.2.1.2.4 Oral and intravenous contrast agents

To enhance vascular and soft tissue contrast and to facilitate delineation of both target volumes and organs at risk, the use of oral and intravenous contrast agents is highly encouraged. Protocols from the local radiology department can be used for this purpose.

5.2.1.2.5 Planning CT-simulation

The planning CT-simulation scan should fulfill the following criteria:

- Maximum slice thickness 5 mm, preferably less (3mm)
- Cranial slice at or above the level of the tracheal bifurcation
- Caudal slice at or below the level of the lesser trochanter of the femur
- Images will be reconstructed with at least 512 x 512 pixel matrices

Respiratory gating or 4D reconstructions are not mandatory for this trial.

5.2.1.2.6 Co-registration with other imaging modalities

Co-registration with the pre-radiotherapy MRI is highly encouraged but not mandatory for this trial. If a baseline MRI is not available, co-registration can be performed with the pre-radiotherapy contrast-enhanced diagnostic CT. Local matching procedures are to be used for this purpose.

Co-registration with FDG-PET is discouraged because of lack of validation in the setting of sarcomas.

5.2.1.3 Definition and delineation of target volumes

The definition of volumes will be in accordance with ICRU Reports 50, 62 and 83 (Ref. 22, Ref. 23, Ref. 24). Volumes shall be delineated on each planning CT axial slice.

5.2.1.3.1 Gross Tumor Volume

The GTV will include the gross disease as visualized on the planning CT, any co-registration and any applicable diagnostic images.

5.2.1.3.2 Clinical Target Volume

The CTV will include the GTV with a geographic expansion of 5 mm will be used, when the CT slice thickness is 5 mm. It will be 6 mm when the slice thickness is 3 mm. This expansion takes into account subclinical extension.

Note that after three-dimensional generation of margins, an anatomically reasonable correction should be performed at anatomic borders as necessary i.e. in directions where there is fasciae, bone, skin, or air gaps which are not at risk for microscopic disease. In general, the entire anatomic compartment need not be covered. In the rare case of the presence of suspicious edema, include this in the CTV. If the suspicious edema extends outside of the 6 mm margin, expand the CTV to include the edema but do not add additional margin to this. We recommend the vertebral body to be excluded from the CTV. The biopsy tract does not need to be included to skin surface.

5.2.1.3.3 Planning Target Volume

A safety margin will be implemented around the CTV to take into account patient set-up uncertainties and organ motion. PTV will include CTV plus an additional geometrical margin of 9 mm (anteriorly and medially) and 12 mm (superiorly, inferiorly, posteriorly and laterally). In the situation where the PTV is located within 5 mm of the body/external contour, a "PTV_internal" should be defined, which is the PTV collapsed inside the body/external contour by 5 mm. This is the structure to be used for dosimetric evaluation.

5.2.1.3.4 Organs at risk

These are the normal tissue structures whose radiation sensitivity may significantly influence the treatment planning. Every effort should be made to avoid treating genitalia/perineum, lung, femoral heads and delivering full skin dose to areas commonly traumatized.

Every effort should be made to avoid dose maxima in areas where surgical incisions will be placed. This may require reviewing treatment plans with the surgeon.

Mandatory organs at risk (OAR) to be delineated are:

- The spinal cord: osseous borders of the vertebral canal
- Both kidneys
- Liver
- Peritoneal cavity **(includes large and small bowel, but should not include stomach and duodenum)**
- As the bowel is mobile, its location cannot be known on a daily basis with high precision. An efficient, robust, and safe solution to this problem is to define the whole volume where the bowel loops can move inside the peritoneal cavity. This will be contoured as described in Sanguineti et al (Ref. 25). It will be contoured superiorly to the level of the stomach/duodenum, anteriorly to the abdominopelvic wall, posteriorly to the pancreas/IVC/aorta/psoas muscles, laterally to the pelvic wall and inferiorly to the rectum/bladder.Peritoneal Cavity-PTV (which corresponds to peritoneal cavity outside the PTV)

5.2.1.3.5 Facility and Equipment

Institutions must comply with the RTQA requirements and procedures described in the Quality Assurance in Radiotherapy chapter and in the "RTQA Guidelines" which will be sent with the initiation package.

Linear accelerators capable of delivering megavoltage photon beams are required (3D-CRT, IMRT [including tomotherapy]).

For 3D-CRT, energies ≥ 6 MV are allowed.

For IMRT (including tomotherapy), only photon energies of 6 MV to 10 MV are allowed.

Cobalt units, electrons and particle therapy are not allowed.

5.2.1.3.6 Dose Prescription

The prescribed dose will be 50.4 Gy in 28 daily fractions, with five fractions of 1.8 Gy delivered per week over 5 1/2 weeks.

5.2.1.3.7 Treatment Planning

The prescription dose is specified and reported at the ICRU reference point as defined in ICRU Reports 50, 62 and 83 (Ref. 22, Ref. 23, Ref. 24).

5.2.1.3.7.1 General Guidelines

All patients will be treated with an isocentric technique. Volume-based field arrangements determined by conformal planning are left to the discretion of the investigators. Non-coplanar field arrangements are allowed. All fields will be treated every day.

3D-CRT, IMRT (including tomotherapy) are allowed, with the selection of the technique left to the discretion of each center. The technique to be utilized for all patients entered in the trial must be declared prior to site authorization. If a site wishes to upgrade from 3D-CRT to IMRT (including tomotherapy) during the study, all IMRT RTQA procedures should be completed first.

It is highly recommended that treatment plans are computed using modern dose calculation algorithms, such as convolution/superposition, Monte Carlo, collapsed cone or equivalent algorithms. Pencil beam algorithms should not be used for energies above 10 MV. All field entrance and exits should be covered by the CT-simulation scan volume, in order to avoid inadequate dose calculations. The dose matrix to be used must be below 4 mm.

The use of bolus is left to the discretion of the investigator.

5.2.1.3.7.2 Planning Priorities

Missing tissue compensation should be used if required to ensure sufficient dose homogeneity.

The planning priority will be: dose limitations to OAR followed by dose delivery to PTV.

The following PTV dose constraints will be applied to optimize safety and minimize toxicity:

- At least 95% of the PTV should receive 95% of the prescribed dose
- **No more than 10% of the PTV should receive more than 107% of the prescription dose**
- Coverage of the PTV by the 90% isodose (45.4 Gy) will be allowed in the case of close proximity to OARs

Mandatory dose limitations to the following OAR will be incorporated:

- Contralateral kidney: < 2/3 of the kidney volume should receive ≥ 18 Gy
- Spinal cord: ≥ 45 Gy over a maximum length of 2 cm and D2 < 50 Gy
- Peritoneal Cavity-PTV (Peritoneal cavity outside the PTV): < 195 cc to receive ≥ 45 Gy (Ref. 39)
- Liver: mean dose ≤ 26 Gy

5.2.1.3.7.3 Overall Treatment Time (OTT)

The specified dose (50.4 Gy/28 daily fractions) can be delivered in an OTT of 38 days. Equipment maintenance and public holidays can be unavoidable reasons for treatment delays. Therefore:

- an OTT up to and including 42 days will be regarded as adequate
- an OTT up to and including 45 days will be regarded as minor protocol violation and reasons for the delay must be specified
- an OTT > 45 days will be regarded as a major violation and reasons for delay must be specified

In case of treatment interruptions, missing fractions should be added at the end of the course.

5.2.1.3.7.4 Treatment Verification

Daily patient set-up shall be performed using laser alignment to reference marks on the skin of the patient. As a minimum requirement, an off-line set-up correction protocol must be in place that requires imaging at least once per week. It is highly advised to adhere to the adapted "shrinking action level (SAL)" or extended "no action level (eNAL)" off-line protocols as described in the literature. Daily on-line set-up verification and correction is also allowed but not mandatory. A non-daily on-line correction protocol is not allowed. All protocols used shall be based on bony anatomy.

If the total dose used for imaging is expected to exceed 2% of the prescribed dose, this should be taken into account during the treatment planning.

Port films or electronic portal images will be obtained for all fields on the first day of treatment. It is recommended that this procedure be repeated on a weekly basis during treatment. Port films will be compared to localization films and/or digitally reconstructed radiographs and all discrepancies must be corrected. Alternatively, set-up corrections may be done according to local validated correction protocols.

5.2.1.3.7.5 Treatment Modifications or Interruptions

No modifications will be permitted with respect to the treatment volumes, dose prescription, allowable OAR doses or maximum OTT.

5.2.2 Surgery after preoperative radiotherapy

5.2.2.1 Operability criteria

Patients for whom surgery is expected to be R2 on the CT-scan performed two weeks after the end of radiotherapy are not eligible for surgery.

Patients will undergo surgery with an interval of 4 to 8 weeks between the end of radiotherapy and the surgery.

Surgical procedures have to be done within the defined timelines. Patients operated later than 8 weeks after the end of radiotherapy will be considered as a failure. Please make sure that the operability criteria are met before surgery:

- Patients must have American Society of Anesthesiologist (ASA) score ≤ 2 (see Appendix H)
- The criteria for non-resectability are:
  - involvement of superior mesenteric artery
  - or involvement of aorta
  - or involvement of bone

5.2.2.2 Recommended surgical procedure

Surgery will be performed in the investigator's site, following the same key recommendations as in the standard arm:

- Surgery will be performed: after a new thoraco-abdomino-pelvic CT-scan (12 weeks after the randomization) and within 4-8 weeks after the completion of radiotherapy.
- Note: **patients that will not undergo their surgical procedure within 8 weeks after the ending of the radiotherapy because of acute radiotherapy toxicity(ies) will be considered as " non operable tumors" (see chapter 8.2; interim analysis - second interim analysis -)**
- Surgical evaluation will be performed for all patients, on cross sectional imaging (at baseline and after radiotherapy)
- A generous midline laparotomy will be preferred, in order to carry out an exploration of the whole abdominal cavity
- Macroscopically complete resection (R0/R1) of the tumor mass will be performed with en-bloc organ resection as necessary, based on preoperative assessment and intraoperative findings
- The following organs should be resected when in proximity to the tumor surface: kidney, colon, psoas muscle or its aponevrosis (recommended but not required, systematic resection should be indicated in the operative form)
- The following organs or structures should be resected only if directly infiltrated: duodenum, head of pancreas, liver, stomach, major abdominal vessels and nerves, bone

- Operative report must clearly indicate: whether surgery is macroscopically complete or not, whether per operative rupture was done or not, whether not involved organs were systematically resected or not. The best would be to insert this information in English at the end of the report: R2 yes/no; Rupture Yes/ No, not involved organs resection yes/ no

The name of the surgeon and data about extent and morbidity of the surgical intervention will be collected on a "Surgery Form".

If the patient had consented, during the surgical procedure the surgeon has to appropriately collect:

- Tumor tissue
- Abdominal wall fat
- Peripheral blood

5.2.2.3 Recommendations for perioperative management

We strongly recommend a minimum 24-hour stay in an intensive care unit after the surgical procedure.

5.2.2.4 Expected toxicity

According to the most recently published literature (Ref. 11), immediate postoperative complications are to be expected in about 18% of patients, including:

- Anastomotic leakage
- Infected postoperative collection
- Postoperative bleeding
- Wound dehiscence
- Limb compartmental syndrome

About 12% of patients will require re-intervention, mainly for:

- Postoperative bleeding
- Retroperitoneal abscess
- Wound dehiscence

Most of these complications occur within the month following surgery (Ref. 11). In consequence, patients should be carefully followed until hospital discharge (daily examination during hospital stay) and/or every week beyond hospital discharge up to the 60th postoperative day (see chapter 7).

All complications requiring re-operation/percutaneous radiological drainage have to be considered as an SAE.

5.3 Treatment modifications

5.3.1 Surgery

Surgery arm alone: refer to section 5.1.1.

Radiotherapy and surgery arm: refer to section 5.2.2.

5.3.2 Radiotherapy

Preoperative radiotherapy has to be done within the defined timelines. Please respect the dose adaptation and duration of treatment described in chapters 5.2.1.3.7 and 5.2.1.3.7.3.

5.3.3 Withdrawal criteria

Study treatment will be given as indicated in the protocol unless any of the following events occur:

- Disease progression
- Occurrence of second malignancy
- Unacceptable toxicity based on the investigator's judgment
- Patient decision
- After preoperative radiotherapy, patients for whom surgery is expected to be R2 on the CT-scan performed two weeks after the end of radiotherapy

5.4 Concomitant treatment and supportive care management

Supportive care is left to investigator’s discretion.

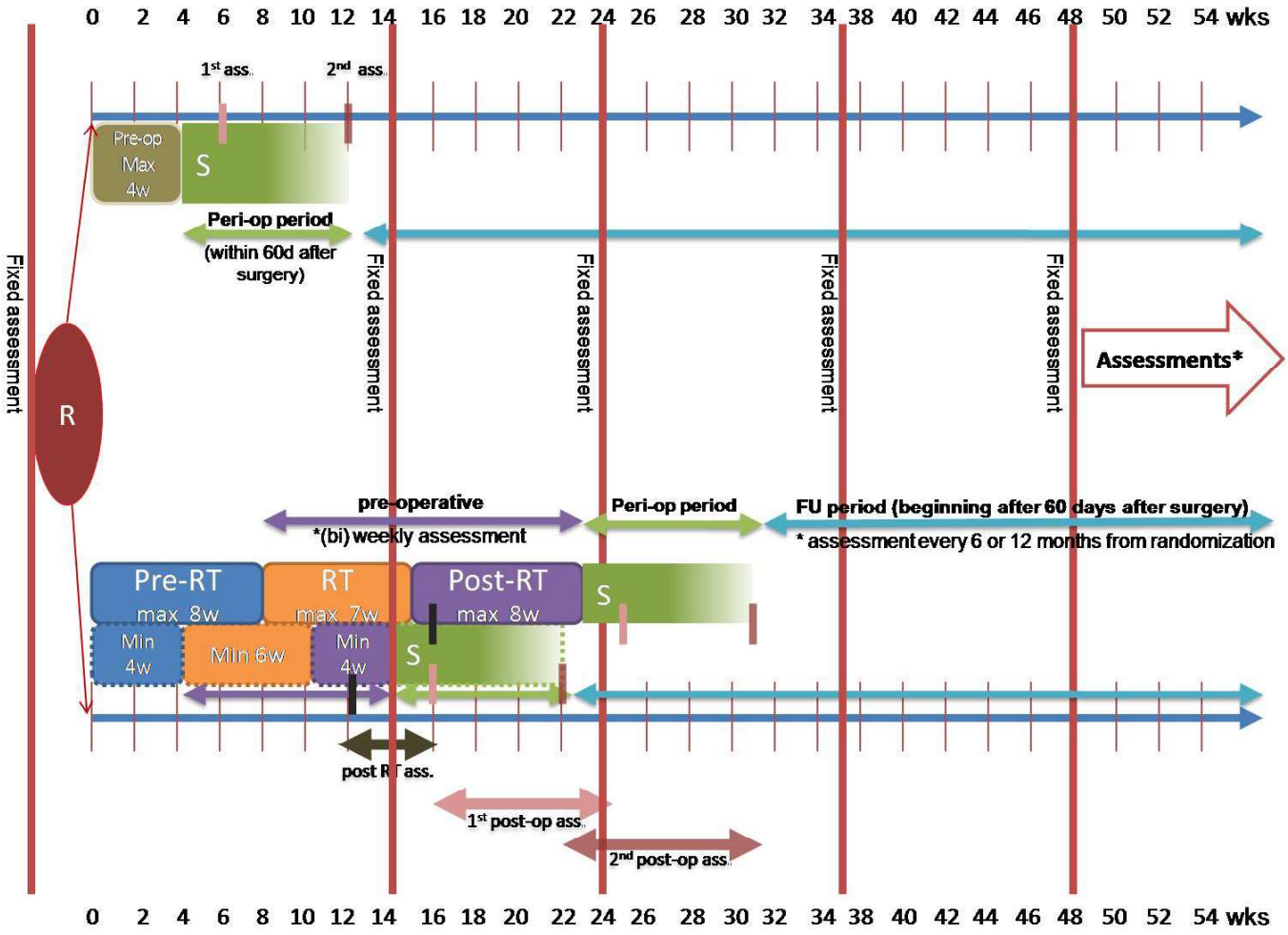
5.4.1 Permitted

- Anticoagulants: warfarin, low molecular weight heparin or aspirin are allowed
- Other concomitant medications: Anti-inflammatory or narcotic analgesics may be offered as needed. Packed red blood cell and platelet transfusions should be administered as clinically indicated
- Patients on this trial may be supported with appropriate hormone replacement therapy in the event that they develop adrenal insufficiency
- All appropriate supportive care (including enteral nutrition)

5.4.2 Not permitted

- **Postoperative Radiotherapy**
- **In case of R2 surgery, postoperative radiotherapy is allowed but the patient will be considered as a failure**
- **In case of R1 surgery, postoperative radiotherapy is not authorized since it is not a standard: benefit of adjuvant radiotherapy is the objective of this trial**
- All systemic anticancer treatment (chemotherapy, molecular targeted therapy …)

6 Clinical evaluation, laboratory tests and follow-up



6.1 Clinical evaluation in both arms, before randomization

A screening log form will be used in this protocol to collect information about failures of enrollment. On this form we will collect:

- Age of the patient (not the date of birth)
- Gender (male or female)
- Reasons for not enrolling the patient like: patient's refusal, screening failure…

These data will be used in fully anonymized way.

6.1.1 The following exams should be done within 28 days before randomization

- Thoraco-abdomino-pelvic CT scan with contrast injection, and in some cases with additional abdomino-pelvic MRI (with IV contrast) within the 28 days prior to randomization

6.1.2 The following exams should be done within 21 days before randomization

- Medical history including associated chronic diseases
- Complete physical exam (performance status)
- Assessment of ASA Score (by anesthesiologist)
- Cancer signs and symptoms
- Assessment of adverse events
- Blood counts (hemoglobin, white blood cells, neutrophils, lymphocytes, platelets)
- Serum chemistry test (bilirubin, creatinine, AST, ALT, alkaline phosphatase, LDH, albumin)
- Renal function:
  - Clearance creatinine will be calculated by Cockcroft and Gault formula (Appendix E)
  - Functional contra-lateral kidney to the side involved by the RPS as assessed by intravenous pyelogram (done during the baseline CT-scan) or differential renal isotope scan
- 12 lead-ECG
- Serum or urine pregnancy test (for women of childbearing potential)
- Multidisciplinary documented discussion (involving at least the surgeon and the radiation oncologist) to confirm that tumor is both potentially resectable (anticipated R0/R1 resection) and suitable for radiotherapy
- Imaging-guided or surgical biopsy to confirm the histological diagnosis may have to be performed
- Translational research: if patient consents, one blood sample of 5 mL to be collected (refer to chapter 11)
- HRQoL checklist (refer to quality of life chapter 10)

6.2 Surgery alone arm

Assessment of adverse events (refer sections 7.2.4).

For the perioperative period (including per- and immediate postoperative periods), the scale used for assessing the severity will be the Dindo scale (Ref. 27).

Translational research: if patient consents, one blood sample of 5 mL to be collected at the time of surgery.

6.2.1 Treatment period

6.2.1.1 The 15th day after the surgical procedure

- Complete physical exam (performance status)
- Cancer signs and symptoms
- Assessment of all adverse events
- Blood counts (hemoglobin, white blood cells, neutrophils, lymphocytes, platelets)
- Serum chemistry test (bilirubin, creatinine, AST, ALT, alkaline phosphatase, LDH, albumin)
  - Clearance creatinine will be calculated by Cockcroft and Gault formula (Appendix E)

6.2.1.2 The 60th day after surgery

- Complete physical exam (performance status)
- Cancer signs and symptoms
- Assessment of all adverse events
- Blood counts (hemoglobin, white blood cells, neutrophils, lymphocytes, platelets)
- Serum chemistry test (bilirubin, creatinine, AST, ALT, alkaline phosphatase, LDH, albumin)
  - Clearance creatinine will be calculated by Cockcroft and Gault formula (Appendix E)

6.2.2 Follow up period

The follow up period starts after the day 60th post surgery.

Assessment of adverse events (refer section 7.2.5).

For follow up period, the scale used for assessing the severity will be CTCAE V.4.0.

6.2.2.1 Week 14 after randomization

- Complete physical exam (performance status)
- Cancer signs and symptoms
- Assessment of all adverse events
- Blood counts (hemoglobin, white blood cells, neutrophils, lymphocytes, platelets)
- Serum chemistry test (bilirubin, creatinine, AST, ALT, alkaline phosphatase, LDH, albumin)
  - Clearance creatinine will be calculated by Cockcroft and Gault formula (Appendix E)
- Thoraco-abdomino-pelvic CT scan with contrast injection, and in some cases MRI (with IV contrast)

6.2.2.2 24 weeks after randomization

- Complete physical exam (performance status)
- Cancer signs and symptoms
- Assessment of all adverse events
- Blood counts (hemoglobin, white blood cells, neutrophils, lymphocytes, platelets)
- Serum chemistry test (bilirubin, creatinine, AST, ALT, alkaline phosphatase, LDH, albumin)
  - Clearance creatinine will be calculated by Cockcroft and Gault formula (Appendix E)
- Thoraco-abdomino-pelvic CT scan with contrast, and on indication (when CT scan is doubtful) MRI (with IV contrast)

6.2.2.3 36 weeks after randomization

- Complete physical exam (performance status)
- Cancer signs and symptoms
- Assessment of all adverse events
- Blood counts (hemoglobin, white blood cells, neutrophils, lymphocytes, platelets)
- Serum chemistry test (bilirubin, creatinine, AST, ALT, alkaline phosphatase, LDH, albumin)

- Clearance creatinine will be calculated by Cockcroft and Gault formula (Appendix E)

- Thoraco-abdomino-pelvic CT scan with contrast, and on indication (when CT scan is doubtful) MRI (with IV contrast)

6.2.2.4 48 weeks after randomization

- Complete physical exam (performance status)
- Cancer signs and symptoms
- Assessment of all adverse events
- Blood counts (hemoglobin, white blood cells, neutrophils, lymphocytes, platelets)
- Serum chemistry test (bilirubin, creatinine, AST, ALT, alkaline phosphatase, LDH, albumin)
  - Clearance creatinine will be calculated by Cockcroft and Gault formula (Appendix E)
- Thoraco-abdomino-pelvic CT scan with contrast, and on indication (when CT scan is doubtful) MRI (with IV contrast)

6.2.2.5 After 48 weeks post randomization

Every 6 months until recurrence or death

The following examinations and tests will be performed:

- Complete physical exam (performance status)
- Cancer signs and symptoms
- Assessment of all adverse events
- Thoraco-abdomino-pelvic CT scan with contrast product injections, and on indication (when CT scan is doubtful) MRI (with IV contrast)

Every 12 months until recurrence or death

The following examinations and tests will be performed:

- Blood counts (hemoglobin, white blood cells, neutrophils, lymphocytes, platelets)
- Serum chemistry test (bilirubin, creatinine, AST, ALT, alkaline phosphatase, LDH, albumin)
  - Clearance creatinine will be calculated by Cockcroft and Gault formula (Appendix E)

At 1 year and 5 years post randomization

- To complete the HRQoL checklist (refer to quality of life chapter 10)

After recurrence

- After recurrence, the patient should be followed every 6 months for survival and further antitumor therapy.

6.3 Preoperative radiotherapy and surgery arm

6.3.1 During preoperative radiotherapy

Assessment of all adverse events (refer section 7.2.3).

For the preoperative period the scale used for assessing the severity will be the **CTCAE V.4.0.**

6.3.1.1 Weekly

- Complete physical exam (performance status)
- Cancer signs and symptoms

6.3.1.2 Every 2 weeks

- Blood counts (hemoglobin, white blood cells, neutrophils, lymphocytes, platelets)
- Serum chemistry test (bilirubin, creatinine, AST, ALT, alkaline phosphatase, LDH, albumin)
  - Clearance creatinine will be calculated by Cockcroft and Gault formula (Appendix E)

6.3.2 2 weeks after the end of radiotherapy

- Complete physical exam (performance status)
- Assessment of ASA Score (by anesthesiologist)
- Cancer signs and symptoms
- Assessment of all adverse events
- Blood counts (hemoglobin, white blood cells, neutrophils, lymphocytes, platelets)
- Serum chemistry test (bilirubin, creatinine, AST, ALT, alkaline phosphatase, LDH, albumin)
  - Clearance creatinine will be calculated by Cockcroft and Gault formula (Appendix E)
- 12 lead-ECG
- Thoraco-abdomino-pelvic CT scan with contrast injection if possible , and in some cases with additional abdomino-pelvic MRI (with IV contrast)
- A second documented multidisciplinary discussion to confirm that tumor is potentially resectable (anticipated R0/R1 resection)

6.3.3 Surgery

6.3.3.1 Perioperative period

Assessment of adverse events (refer section 7.2.4).

For the perioperative period (including per- and immediate postoperative periods), the scale used for assessing the severity will be the Dindo scale.

Translational research: if patient consents, one blood sample of 5 mL to be collected at the time of surgery.

6.3.3.2 The 15th day after the surgical procedure

- Complete physical exam (performance status)
- Cancer signs and symptoms
- Assessment of all adverse events
- Blood counts (hemoglobin, white blood cells, neutrophils, lymphocytes, platelets)
- Serum chemistry test (bilirubin, creatinine, AST, ALT, alkaline phosphatase, LDH, albumin)
  - Clearance creatinine will be calculated by Cockcroft and Gault formula (Appendix E)

6.3.3.3 24 weeks after randomization

- Complete physical exam (performance status)
- Cancer signs and symptoms
- Assessment of all adverse events
- Blood counts (hemoglobin, white blood cells, neutrophils, lymphocytes, platelets)
- Serum chemistry test (bilirubin, creatinine, AST, ALT, alkaline phosphatase, LDH, albumin)
  - Clearance creatinine will be calculated by Cockcroft and Gault formula (Appendix E)
- Thoraco-abdomino-pelvic CT scan with contrast (if possible), and on indication (when CT scan is doubtful) MRI (with IV contrast) - **Please note that this first assessment could be done very early after the surgical procedure in the investigational arm (see schema)**

6.3.3.4 The 60th day after the surgical procedure

- Complete physical exam (performance status)
- Cancer signs and symptoms
- Assessment of all adverse events
- Blood counts (hemoglobin, white blood cells, neutrophils, lymphocytes, platelets)
- Serum chemistry test (bilirubin, creatinine, AST, ALT, alkaline phosphatase, LDH, albumin)
  - Clearance creatinine will be calculated by Cockcroft and Gault formula (Appendix E)

6.3.4 Follow up period

The follow up period starts after the day 60th post surgery.

Assessment of adverse events (refer section 7.2.5).

For follow up period, the scale used for assessing the severity will be **CTCAE V.4.0.**

6.3.4.1 36 weeks after randomization

- Complete physical exam (performance status)
- Cancer signs and symptoms
- Assessment of all adverse events
- Blood counts (hemoglobin, white blood cells, neutrophils, lymphocytes, platelets)
- Serum chemistry test (bilirubin, creatinine, AST, ALT, alkaline phosphatase, LDH, albumin)
  - Clearance creatinine will be calculated by Cockcroft and Gault formula (Appendix E)
- Thoraco-abdomino-pelvic CT scan with contrast (if possible), and on indication (when CT scan is doubtful) MRI (with IV contrast)

6.3.4.2 48 weeks after randomization

- Complete physical exam (performance status)
- Cancer signs and symptoms
- Assessment of all adverse events
- Blood counts (hemoglobin, white blood cells, neutrophils, lymphocytes, platelets)
- Serum chemistry test (bilirubin, creatinine, AST, ALT, alkaline phosphatase, LDH, albumin)
  - Clearance creatinine will be calculated by Cockcroft and Gault formula (Appendix E)
- Thoraco-abdomino-pelvic CT scan with contrast, and on indication (when CT scan is doubtful) MRI (with IV contrast)

6.3.4.3 After 48 weeks post randomization

Every 6 months until recurrence or death

The following examinations and tests will be performed:

- Complete physical exam (performance status)
- Cancer signs and symptoms
- Assessment of all adverse events
- Thoraco-abdomino-pelvic CT scan with contrast product injections, and on indication (when CT scan is doubtful) MRI (with IV contrast)

Every 12 months until recurrence or death

The following examinations and tests will be performed:

- Blood counts (hemoglobin, white blood cells, neutrophils, lymphocytes, platelets)
- Serum chemistry test (bilirubin, creatinine, AST, ALT, alkaline phosphatase, LDH, albumin)
  - Clearance creatinine will be calculated by Cockcroft and Gault formula (Appendix E)

At 1 year and 5 years post randomization

- To complete the HRQoL checklist (refer to quality of life chapter 10)

After recurrence

After recurrence, the patient should be followed every 6 months for survival and further antitumor therapy.

6.4 Summary tables

6.4.1 Surgery alone arm

In grey: Fixed-time assessments based on the date of randomization

	Within 21days before random.	During the perioperative period			Follow-up period						
		At surgery time	Day 15 after surgery	60th day after surgery	14 wks after Random	24 wks, 36 wks & 48 wks after random	48 wks after random until recurrence/death				After recurrence Q 6 mo
							Q 6 mo	Q12 mo	1 year post random	5 years post random	
Medical history	◆										
Biopsy (a)	◆										
Complete physical exam (b)	◆		◆	◆	◆	◆	◆				
ASA assessment	◆										
Cancer signs and symptoms	◆		◆	◆	◆	◆	◆				
Adverse event assessment	◆		◆	◆	◆	◆	◆				
Hematology €.	◆		◆	◆	◆	◆		◆			
Serum chemistry (d)	◆		◆	◆	◆	◆		◆			
12-lead ECG	◆										
IV pyelogram (done during the baseline CT-scan) or differential renal isotope scan	◆										
Serum or urine pregnancy test	◆										
CT scan ± M€(e)	◆ within 28 days				◆	◆	◆				
Multidisciplinary discussion	◆										
TR tissue samples Biopsy (FFPE blocks and/or frozen tissue) Resected specimen (FFPE and frozen tissue)	◆	◆									

TR blood samples (5 mL each)	◆	◆									
HRQoL checklist	◆								◆	◆	
Survival											◆

a -to confirm the histological diagnosis of the tumor a biopsy may have to be performed.
b- including performance status
c - hemoglobin, white blood cells, neutrophils, lymphocytes, platelets
d - bilirubin, creatinine, AST, ALT, alkaline phosphatase, LDH, albumin
e - Thoraco-abdomino-pelvic CT scan with contrast (if iodine injection is possible), and on indication (when CT scan is doubtful) additional abdomino-pelvic MRI (with IV contrast) - The baseline CT-scan will be used to assess the functionality of the contralateral kidney - Because the primary endpoint is local failure, CT-scan must be done until the diagnosis of local failure (see definition in chapter 7.1.1) whatever the diagnosis of metastatic relapse.

6.4.2 Radiotherapy followed by surgery arm

In grey: Fixed-time assessments based on the date of randomization

	Within 21 days before random	Preoperative period			During the perioperative period				Follow-up period					
		Weekly	Q 2 wks	2 wks after the end of radiotherapy	At surgery time	D 15 after surgery	24 wks after random (f)	D 60 after surgery	36 & 48 wks after random	48 wks after random until recurrence/death				After recurrence Q 6 mo
										Q 6 mo	Q 12 mo	1 year post random	5 years post random	
Medical history	◆													
Biopsy (a)	◆													
Complete physical exam (b)	◆	◆		◆		◆	◆	◆	◆	◆				
ASA assessment	◆			◆										
Cancer signs and symptoms	◆	◆		◆		◆	◆	◆	◆	◆				
Adverse event assessment	◆	◆		◆		◆	◆	◆	◆	◆				
Hematology €.	◆		◆	◆		◆	◆	◆	◆		◆			
Serum chemistry (d)	◆		◆	◆		◆	◆	◆	◆		◆			
12-lead ECG	◆			◆										
Serum or urine pregnancy test	◆													
IV pyelogram (done during the baseline CT-scan) or differential renal isotope scan	◆													

	Within 21 days before random	Preoperative period			During the perioperative period				Follow-up period					
		Weekly	Q 2 wks	2 wks after the end of radiotherapy	At surgery time	D 15 after surgery	24 wks after random (f)	D 60 after surgery	36 & 48 wks after random	48 wks after random until recurrence/death				After recurrence Q 6 mo
										Q 6 mo	Q 12 mo	1 year post random	5 years post random	
CT scan ± M€(e)	◆ within 28 days			◆			◆		◆	◆				
Multidisciplinary discussion	◆			◆										
TR tissue samples Biopsy (FFPE blocks and/or frozen tissue) Resected specimen (FFPE and frozen tissue)	◆				◆									
TR blood samples (5 mL each)	◆				◆									
HRQoL checklist	◆											◆	◆	
Survival														◆

a - to confirm the histological diagnosis of the tumor a biopsy may have to be performed.
b - including performance status
c - hemoglobin, white blood cells, neutrophils, lymphocytes, platelets
d - bilirubin, creatinine, AST, ALT, alkaline phosphatase, LDH, albumin
e - Thoraco-abdomino-pelvic CT scan with contrast, and on indication (when CT scan is doubtful) with additional abdomino-pelvic MRI (with IV contrast) - The baseline CT-scan will be used to assess the functionality of the contralateral kidney - Because the primary endpoint is local failure, CT-scan must be done until the diagnosis of local failure (see definition in chapter 7.1.1) whatever the diagnosis of metastatic relapse.
f - Please note that this assessment is a fixed-time one based on the date of randomization - The two other assessments (d15 and d60) refer to the date of the **surgery. As a consequence the order of these 3 assessments could vary according the date of the surgery (d15, weeks 24, d60 or d15, d60 and weeks 24).**

6.4.3 Collection of biological material for translational research

Biological material	At baseline	At the time of surgery
Tissue	Biopsy (FFPE blocks and/or, frozen tissue)	Resected specimen (100 -200 mg) (FFPE and frozen tissue)
Peripheral blood (EDTA tubes)	5 ml	5 ml

7 Criteria of evaluation

7.1 Criteria for efficacy

7.1.1 Abdominal recurrence-free survival

Abdominal failure free survival will be measured from the date of randomization (as reference) to the date of abdominal relapse or death, whichever occurs first. When abdominal recurrence is equivocal (suspicion of recurrence without clear-cut confirmatory image), the next planned CT-scan will be anticipated (2 months instead of 6 months). If the suspicious lesion grows and the diagnosis of recurrence becomes obvious, the date of recurrence will be the first date with suspicion of recurrence.

Abdominal recurrence is defined by one of the following:

- Local relapse (after macroscopically complete resection)
- Macroscopic residual disease after surgery (R2)
- Progressive disease during preoperative radiotherapy and/or tumor becoming non-resectable
- Peritoneal sarcomatosis (presence of peritoneal metastasis)

NB: Liver metastases will be regarded as distant metastatic events, rather than abdominal recurrence. **For patients with distant metastases they will be followed until local failure will be detected**.

Patients without one of these events will be censored at the date of last follow-up.

Please note that the time assessment biases inherent to this trial have been taken into account by the statistical analysis, nevertheless the reference time point will be the date of randomization.

7.1.2 Abdominal failure interval

Abdominal failure interval will be measured from the date of randomization to the date of abdominal relapse or death, whichever occurs first.

Abdominal recurrence is defined in section 7.1.1.

Death in absence of abdominal failure and distant metastases diagnosed before abdominal failure are not considered as events for this endpoint, but will be considered as competing risk.

Patients without one of these events will be censored at the date of last follow-up.

7.1.3 Metastases free survival

Metastases free survival will be measured from the date of randomization to the date of occurrence of distant metastases or death, whichever occurs first. Alive and metastases free patients will be censored at the date of last follow-up.

7.1.4 Overall survival

Overall survival will be measured from the date of randomization to the date of death, whatever the cause. Alive patients will be censored at the date of last follow-up. Causes of death will be recorded and reported as a table.

7.1.5 Tumor response to preoperative radiotherapy

For patients receiving, preoperative radiotherapy, the tumor response will be assessed using RECIST 1.1 by comparison of baseline CT-scan and preoperative CT-Scan.

Objective tumor response, measured according to RECIST 1.1 (Ref. 26), will be used as secondary end-point in this trial. Response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and followed at the end of the radiotherapy. Response is not the primary endpoint, so a confirmatory CT-scan is not mandatory.

Chapters 7.1.5.1, 7.1.5.2 and 7.1.5.3 are general considerations for RECIST 1.1.

7.1.5.1 Measurability of tumor lesions at baseline

7.1.5.1.1 Definitions

- Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology
- Measurable lesions -. *tumor lesions* that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray, and as ≥ 10 mm with CT scan or clinical examination [using calipers]. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component > 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters) by use of a ruler or calipers
- Non-measurable lesions - All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Nodes that have a short axis <10 mm at baseline are considered non-pathological and should not be recorded or followed
- **Target Lesions**. When more than one measurable tumor lesion or malignant lymph node is present at baseline all lesions up to *a maximum of* 3 le*sions total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological nodes must meet the criterion of a *short* axis of ≥ 15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 3 is to be calculated and recorded

- **Non-target Lesions**. All non-measurable lesions (or sites of disease) including pathological nodes (those with short axis ≥ 10 mm but < 15 mm), plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent"

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before randomization.

7.1.5.2 Methods of measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent. While on study, all target lesions recorded at baseline should have their actual measurements recorded on the CRF at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

- **Clinical Lesions**. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.
- **Chest X-ray**. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions > 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- **CT, MRI**. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). While PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).
- **Ultrasound.** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT should be obtained.
- **Endoscopy, Laparoscopy**. The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.
- **Tumor Markers**. Not applicable for this study. **Cytology, Histology**. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

7.1.5.3 Tumor response evaluation

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of all *target* and *non-target* lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures < 10mm (Note: continue to record the measurement even if < 10 mm and considered CR). Tumor markers must have normalized. Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment, for example where the tumor burden appears to have increased by at least 73% in volume (which is the increase in volume when all dimensions of a single lesion increase by 20%). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but on further documentation, the earlier date must be used.

Table 1: Integration of Target, non-Target and New lesions into response assessment:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
Patients with Target lesions ± non target lesions				
CR	CR	No	CR	Tumor nodes < 10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	documented at least once ≥ 4 wks from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Patients with Non target lesions ONLY				
No Target	CR	No	CR	All tumor nodes < 10 mm
No Target	Non-CR/non-PD	No	Non-CR/ non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression [or evidence of unequivocal disease progression] at that time should be reported as "*symptomatic deterioration*". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.				

7.1.5.4 Reporting of tumor response

All patients included in the study must be assessed for response to treatment, even if there is a major protocol treatment deviation or if they are ineligible, or not followed/re-evaluated. Each patient will be assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death or not evaluable.

Early death is defined as any death occurring before the first per protocol time point of tumor re-evaluation.

Patients' response will be classified as "not evaluable" if insufficient data were collected to allow evaluation per these criteria.

7.2 Evaluation of toxicity

7.2.1 Adverse events

All adverse events will be recorded; the investigator will assess whether those events are drug related (reasonable possibility, no reasonable possibility) and this assessment will be recorded in the database for all adverse events.

Only the worst grade per category of event will be recorded per period of treatment.

The collection period will start from randomization until death of all patients.

7.2.2 Scales for toxicity evaluation

For practical reasons, the description of safety/complications will follow the following rules:

7.2.2.1 Preoperative period

The preoperative period will begin from the date of randomization to the date of the surgical procedure. During this period, the expected events will be related mainly to the radiotherapy treatment (acute radiotherapy-related toxicity). As a consequence, events (see list below 7.2.3) will be graded according to the CTCAE Version 4.0.

7.2.2.2 Perioperative period (including per- and immediate postoperative periods)

This perioperative period will begin at the time of anesthesia induction (date of surgery) and will end at the 60th day following the surgical procedure. The perioperative period will begin at the time of anesthesia induction and will end at the time of complete closure of the wound. The immediate postoperative period will begin at the time of complete closure to the wound and will end the 60th day following the surgical procedure. The main expected events will be related to the surgical procedure. Some events could be also the consequence of prior radiotherapy or the combination of both treatments. During this period, we will use the Dindo scale (Ref. 27**).**

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complication. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention.
Grade IV	Life-threatening complication (including CNS complications*) requiring IC/ICU management Single-organ or multi-organ dysfunction (including dialysis)
Grade V	Death of the patient

* Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks

7.2.2.3 Follow-up period

This period will start after the 60th day following the surgical procedure. The main expected toxicities will be related to surgery or radiotherapy (late toxicity). So we will use the CTCAE Version 4.0 for coding and grading these events (see list 7.2.5).

7.2.2.4 Summary

Periods	Preoperative	Perioperative	Follow-up
Guidance for SEVERITY assessment	CTCAE V4.0	Adapted from Dindo et al. (Ref. 27)	CTCAE V4.0
Guidance for causality assessment	Clinical judgment and literature data (related to radiotherapy, related to surgery, related to both treatments and other cause)		

7.2.3 Safety during the preoperative period

This study will use the International Terminology Criteria for Adverse Events (CTCAE), version 4.0 for radiation-related adverse event reporting. A copy of CTCAE can be accessed on the CTEP home page (http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/ctc.htm). A link to this page is provided on the EORTC web site (http://www.eortc.be/; if location is moved to another site, this link will be updated.

Planned safety analysis and tabulations are described in the statistics section.

Toxicity that appears during the preoperative period will be graded as acute radiation related toxicity. The following toxicities are expected:

- General disorders and ASC - Fatigue grade 3
- Gastrointestinal disorders - Constipation grade ≥ 3
- Gastrointestinal disorders - Diarrhea grade ≥ 3
- Gastrointestinal disorders - Nausea grade ≥ 3
- Gastrointestinal disorders - Vomiting grade ≥ 3
- Injury, poisoning and procedural complications - Dermatitis associated with radiation, grade ≥ 3
- Investigations - Creatinine increase grade ≥ 3
- Investigations- Weight loss grade ≥ 3
- Metabolism and nutrition disorders - Anorexia ≥ 3
- Nervous system disorders - Myelitis grade ≥ 2

7.2.4 Safety during the perioperative period

7.2.4.1 "Surgical complications"

During this period, adverse events and side effects either directly or indirectly related to surgery and its sequelae can be attributed to general premedication/anesthesia required to perform surgical procedure or to the surgical procedure itself. Some events could be related to the radiotherapy.

In exceptional cases, premedication or anesthesia may result in a delay or an inability to perform the planned surgical procedure. These instances have also to be recorded in the CRF.

The perioperative period will commence at the time of surgery (at the time of the induction anesthesia) to the complete closure of the wound. The main expected peroperative adverse events are:

- massive hemorrhage
- fistulae

The postoperative period will commence at complete closure of the wound until the 60 days post-surgery. The main expected postoperative adverse events are:

- postoperative hemorrhage/bleeding
- anastomotic insufficiency (with risk of peritonitis, digestive fistula, pancreatic fistula, bile leakage)
- infected postoperative collection and surgical site infection
- intestinal occlusion
- limb compartmental syndrome
- Wound dehiscence

All complications requiring re-operation or per cutaneous drainage have to be considered as SAE.

Description of perioperative care

The description of perioperative care will be based on the following key parameters.

- During the perioperative period:
  - duration of surgery (in minutes: from the incision to the complete closure of the wound) -
  - number of administered Red Blood Cell (RBC) units during surgical procedure
  - number of administered Platelet (PLT) units during surgical procedure
  - number of administered Fresh Frozen Plasma (FFP) units during surgical procedure
- During the immediate postoperative period:
  - duration of hospitalization (from the entry to surgery unit to discharge; including the time spent in secondary care unit)
  - duration of hospitalization in intensive care units (from the entry to the surgery unit to discharge from the intensive care unit). The cause of hospitalization in intensive care units will be recorded i.e.: patient status or local organization.
  - reoperation rate within 60 days after the initial surgery (and reason for this surgical procedure)
  - readmission rate within 60 days after the initial surgery and reason for this admission

7.2.5 Late toxicity

Late toxicity (after the 60th day following the surgical procedure) will be evaluated and graded, if possible, according to the CTCAE version 4.0. Particular attention will be given to the following events (alphabetical order):

- Gastrointestinal disorders - Colonic fistula - Grade ≥ 2
- Gastrointestinal disorders - Colonic stenosis - Grade ≥ 2
- Gastrointestinal disorders - Constipation grade ≥ 3
- Gastrointestinal disorders - Diarrhea - Grade ≥ 3
- Gastrointestinal disorders - Gastro-intestinal fistula - Grade ≥ 2
- Gastrointestinal disorders - Enterovesical fistula - Grade ≥ 2
- Gastrointestinal disorders - Ileal fistula - Grade ≥ 2
- Gastrointestinal disorders - Ileal stenosis - Grade ≥ 2
- Gastrointestinal disorders - Jejunal fistula - Grade ≥ 2
- Gastrointestinal disorders - Jejunal stenosis - Grade ≥ 2
- Gastrointestinal disorders - Rectal fistula - Grade ≥ 2
- Gastrointestinal disorders - Small intestinal stenosis - Grade ≥ 2
- Gastrointestinal disorders - Small intestinal perforation - Grade ≥ 2
- General disorders and ASC - Fatigue grade 3
- Hepatobiliary disorders - Hepatic failure - Grade ≥ 3
- Investigations - Creatinine increase - Grade ≥ 2
- Investigations- Weight loss grade ≥ 3
- Metabolism and nutrition disorders - Anorexia ≥ 3
- Nervous system disorders - Myelitis - Grade ≥ 2

- Nervous system disorders - Peripheral sensory neuropathy - Grade ≥ 3
- Nervous system disorders - Peripheral motor neuropathy - Grade ≥ 3
- Neoplasms benign, malignant and unspecified - Treatment related secondary malignancy - Grade ≥ 3
- Vascular disorders - Hypertension (arterial hypertension) - Grade ≥ 3

7.2.6 Serious adverse events

Serious adverse events are defined by the Good Clinical Practice Guideline.

SERIOUS ADVERSE EVENTS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see chapter on Reporting Serious Adverse Events).

7.2.7 Toxic deaths

Toxic death is defined as death due to toxicity (defined as adverse events at least with reasonable possibility related to study treatment). The cause of death must be reported as "toxicity".

The evaluation of toxic deaths is independent of the evaluation of response (patients can die from toxicity after a complete assessment of the response to study treatment).

7.2.8 Evaluability for safety

All patients who have started the treatment will be included in overall safety analyses.

Patients who have discontinued treatment because of toxicity will always be included in the toxicity analyses.

8 Statistical considerations

8.1 Statistical design

8.1.1 Sample size

The primary endpoint of this trial is "abdominal" recurrence free survival (see chapter 7.1.1 for definition). The trial is designed as a randomized phase III trial. The control arm is curative-intent surgery alone without neo-adjuvant radiotherapy. The experimental group is preoperative radiotherapy plus surgery.

The primary trial objective is to test the null hypothesis (H0) of no difference against the alternative of a difference in abdominal recurrence free survival between the two groups. The number of events and sample size is determined to provide 90% power of rejecting the null hypothesis of no difference against the alternative of a 20% difference in the abdominal recurrence free survival rate at 5 years (from 50% in the control group to 70% in the experimental group or alternatively a shift in median from 5 years in the control group to 9.7 years in the experimental treatment group, HR = 0.52), at a global 2-sided 5% significance level assuming that abdominal recurrence free survival follows an exponential distribution in both groups.

This test requires that 102 events be observed at the time of the final statistical analysis. Events may be a local relapse (after macroscopically complete resection), macroscopic residue after surgery (R2) or progressive disease during the preoperative radiotherapy and/or tumor becoming non-operable or not resected or a "peritoneal sarcomatosis" (presence of peritoneal metastasis).

It is estimated, using EAST® version 5.3 (Cytel Inc) that if 256 patients are randomized during 39 months, 102 events should be observed approximately 41 months after the entry of the last randomized patient in the study under H1.

8.1.2 Randomization and stratifications

Patients will be centrally randomized (for practical details, see chapter on randomization procedure). A minimization technique will be used for random treatment allocation stratifying by institution and performance status (0-1 vs 2).

8.2 Interim analyses

Two early safety checks will be performed in each treatment arm after 33 and then after 66 patients have been treated in each group. This review will be based on monitoring the rate of non-operable tumors and the rate of reoperation (morbidity). If the observed toxicity rate approaches the limits set, the EORTC Data Safety Monitoring Board, a subcommittee of the EORTC IDMC, will be contacted for a recommendation whether the study needs to be amended or stopped. A list of SAEs for the radiotherapy arm will be provided.

The differences between randomized groups used for the stopping rules will be based on the number of patients who are non operable or require reoperation. The stopping rules are defined according to an alpha-spending function of the gamma family (Ref. 28) with gamma parameter = -1 and are the following:

- Morbidity: rate of reoperation >20% difference

The comparisons are done between randomized groups. Assuming that the rate of reoperation in the reference arm is 18%, the probability to observe an absolute increase of 20% in the experimental arm when in fact the rates are identical in both randomized groups is ≤0.0378 (type I) at the first look and ≤0.01 at the second look. The probability of observing a difference >20% when the true difference is 30% is >0.84 (power) at the first look.

- Rate of non-operable tumors >12% difference

The comparisons are done between randomized groups with a one-sided test. Assuming that the event rate in the reference arm is 2%, the probability to observe an absolute increase of 12% in the experimental arm when in fact the rates are identical in both randomized groups is ≤0.0378 (type I) at the first look and ≤0.01 at the second look. The probability of observing a difference >12% when the true difference is 20% is >0.90 (power) at the first look.

8.3 Statistical analysis plan

8.3.1 Primary and secondary endpoints

The endpoints that will be used in the statistical analysis are defined in chapter 7.

The primary endpoint will be "abdominal recurrence free survival".

The secondary endpoints measuring treatment efficacy are:

- Metastasis-free survival
- Overall survival
- Abdominal failure interval
- Tumor response to preoperative radiotherapy

The secondary endpoints measuring treatment toxicity are:

- Acute toxicity profile in the preoperative period (from the date of randomization to the date of surgical procedure)
- Perioperative complications (from date of surgery today 60 following surgery)
- Late complications (after day 60 following surgery)

8.3.2 Analysis populations

- Intention-to-treat population: all randomized patients will be analyzed in the arm they were allocated by randomization
- Per protocol population: all randomized patients who are eligible and have started their allocated treatment (at least have been operated or received one fraction of irradiation)
- Safety population: all randomized patients who have started their allocated treatment (have at least been operated or received one fraction of irradiation)
  - RT Safety population: patients in the safety population who received at least one fraction of irradiation
  - Surgical safety population: patients in the safety population who have been operated
  - Complete safety population: patients in the safety population who received their allocated treatment (have at least been operated and received one fraction of irradiation in the experimental arm)

A patient will be considered to be eligible if he/she did not have any deviation from the patient entry criteria listed in chapter 3 of the protocol. Potential eligibility problems will be assessed by the Clinical Research Physician at time of medical review.

8.3.3 Statistical methods

The primary analysis of all efficacy endpoints will be performed in the intention-to-treat population.

The analysis of the toxicity endpoints will be performed in the safety population:

- the analysis of acute and late toxicity of radiotherapy will be performed in the RT safety population
- the analysis of the surgical complications (within 60 days after surgery) will be performed in the surgical safety population
- the analysis of late toxicity will also be performed in the complete safety population

The Serious Adverse Events are always reported for all patients who entered the study.

8.3.3.1 Main analysis of the efficacy endpoints (primary and secondary)

A 2-sided 5% significance level will be applied to all tests and 95% confidence intervals will be constructed.

Abdominal recurrence free survival, metastatic free survival and overall survival will be described using Kaplan-Meier curves (Ref. 29) in the two treatment arms. The median survival time and its associated non-parametric confidence interval will be calculated.

For analysis purposes:

Immediate surgery arm: any abdominal recurrence occurring after surgery prior to the week 14 will be counted as occurring at week 14 (+/- 1 week) and any progression occurring after the week 14 will be counted as occurring at week 24.

Deferred surgery arm: any abdominal recurrence occurring prior to surgery will be counted as occurring at week 14 and any abdominal recurrence occurring after surgery and prior to or during the week 24 will be counted as occurring at week 24.

Abdominal failure interval will be described using cumulative incidence curves (Ref. 30). Cumulative event rates at 3 years and at 5 years will be documented, and their confidence interval will be calculated using the normal approximation.

All efficacy endpoints will be compared between the randomized groups using the Cox's proportional hazards model (Ref. 31). For the competing risk endpoints (incidence of distant metastases) this will be a cause specific Cox's proportional hazards model.

8.3.3.2 Analysis for Safety endpoints

8.3.3.2.1 Acute toxicity profile of preoperative radiotherapy

The acute toxicity will be assessed according to the NCI-CTC version 4.0 in the RT safety population. For each item of the CTCAE, the worst grade of acute toxicity will be tabulated. A table will present patients who will not receive radiotherapy and the associated reason. The main items investigated during the preoperative period are defined in chapter 7.2.3.

8.3.3.2.2 Perioperative complications

In this part, we would like to investigate whether the RT increases the complications occurring due to surgery.

A first table will list patients in the ITT population who were not operated and provide the associated reason according to treatment arm.

Other analyses will be performed in the surgical safety population taking into account all events occurring during the perioperative period (as defined in section 7.2.2.2). Adverse events and side effects possibly related to surgery will be assessed according to the Dindo's classification (Ref. 27). For each item, the frequency of the worst grade of the observed toxicity will be tabulated by treatment group.

The main items investigated during the perioperative period are defined in chapter 7.2.4.

8.3.3.2.3 Late toxicity of preoperative radiotherapy (>60 days after the surgery)

The late toxicity occurring more than 60 days after surgery will be tabulated by treatment group.

The cumulative risk for patients to have late treatment side effects (as defined in section 7.2.5) will be estimated using cumulative incidence curves (Ref. 32). Cumulative event rates at 3 years and at 5 years will be estimated, and their 95% confidence interval will be calculated. In these analyses, the time to the occurrence of a specified severe late adverse event is defined as the time counted from randomization to the first reported late (≥60 days after last treatment) adverse event grade ≥3, with censoring at the time of last examination prior to the clinical cut-off date for patients who did not report any such events. Patients without the event of interest who start a new treatment or die will be considered in the analysis as having had a competing risk. Time to event comparisons between the randomized groups will be performed using the Cox's proportional hazards model (Ref. 31). The analysis will be carried out for each side effect separately and for the time to first occurrence of the late side effects regrouped in SOC.

The risks of late treatment toxicity that is present at 3 years (respectively 5 years) after randomization will be estimated from the cumulative incidence curves.

8.3.4 Pre-planned sensitivity or exploratory analyses

The statistical analyses of the efficacy endpoints specified in chapter 7 will be repeated in the per protocol population only if 10% of the patients have been excluded from the per-protocol populations.

Furthermore, the efficacy endpoints will also be analyzed in regression models including important prognostic factors.

8.3.5 Data recoding and display

Frequency tables will be tabulated (by treatment group or otherwise) for all categorical variables by the levels of the variables as they appear on the CRF (with %). Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for the patients fulfilling the condition for the specification (patient id, institution, treatment group, value of the item and text field contents).

Dates relating to events prior to entry will be presented as the delay in days (or weeks, months, or years) between the past event and the date of entry (date of randomization – date of past event + 1) and presented using the median and range. For example, on the randomization checklist, the date of last administration of prior treatment (or the date of first diagnosis of the cancer) will be presented as the time elapsed (in days, weeks, months or years, as appropriate) since the day of the last administration and the date of entry on study (date of randomization – last administration/diagnosis +1).

Other delays (eg. re-treatment delays) are presented as continuous variables using the median and range.

Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for adverse events, the grading scale specified in the protocol will be used). Whenever no specific scale exists, lab data will be categorized based on the normal range: for example, below the lower normal limit (when appropriate), within the normal range, above the upper limit of normal (ULN) and the degree to which it is above the ULN (for example > 2.5 x ULN, > 5 x ULN, > 10 x ULN). For laboratory data, the nadir is generally displayed. The nadir in a given cycle is the lowest laboratory value in that cycle; the overall nadir for a patient is the lowest laboratory value among all cycles.

Other continuous variables (for example age, dose) are presented using the median and range (minimum, maximum).

If appropriate, continuous data may also be presented in categories (for example, age may also be grouped in decades).

8.4 End of study

End of study occurs when all of the following criteria have been satisfied:

1. Thirty days after all patients have stopped protocol treatment
2. The trial is mature for the analysis of the primary endpoint as defined in the protocol
3. The database has been fully cleaned and frozen for this analysis

9 Data Monitoring

Safety data are reviewed within the EORTC Headquarters on a regular basis as part of the Medical Review process. Problems which are identified will be discussed with the Study Coordinators who will take appropriate measures. Safety information will also be included in trial status reports which serve as a basis of discussion during EORTC Group meetings. These reports will be made available to investigators participating in the study.

The EORTC Data Safety Monitoring Board (DSMB), a subcommittee of the EORTC Independent Data Monitoring Committee (IDMC), will review all safety problems identified by the EORTC Headquarters for which an advice is sought. This DSMB has early trials/drug development expertise and will provide a separate review process, having no access to outcome data. The EORTC DSMB will be primarily for phase I and non randomized phase II studies, but will also provide recommendations as an initial step in phase III trials to advise if the study should then go to the full IDMC.

The EORTC IDMC is charged with the interim review (planned or not planned) of randomized phase II and phase III studies. When interim analyses are carried out, the interim monitoring of efficacy and safety data is performed according to the Statistical Considerations chapter in this protocol and EORTC Policy 004 on “Independent Data Monitoring Committees and Interim Analyses”.

The results of the interim analyses are confidential and are discussed by the EORTC IDMC. The IDMC will subsequently recommend to the EORTC Group whether any changes should be made to the study.

No efficacy results will be presented at EORTC Group meetings or elsewhere before the trial is closed to recruitment and the data are mature for the analysis of the primary endpoint, unless recommended otherwise by the EORTC IDMC.

10 Quality of life assessment

10.1 Rationale

Reducing mortality and morbidity is still the most important factor in clinical research. Nevertheless, issues such as reducing side effects, symptom relief and improving patients’ satisfaction have also become relevant parameters in the evaluation of medical strategies. The rationale for measuring HRQoL in this study is in measuring long-term impact related to surgical complication on patients’ well-being.

The following issues were identified to be of interest:

- Fatigue
- Mobility (difficulty to walk, risk of falling with or without fracture)
- Digestive troubles (occlusion)
- Sexual disorders
- Pain

10.2 HRQoL instruments

The EORTC QLQ-C30 is a well-validated 30-item scale that assesses the overall HRQoL of cancer patients (Ref. 40). It is composed of six functional scales (physical, role functioning, emotional functioning, cognitive functioning, social functioning, and global health status/QoL) and nine symptom scales/items (fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, financial impact). However this instrument is aimed at evaluating cancer therapies in general and contains many domains not of particular interest to this study. Therefore only the following domains will be kept:

- Physical functioning
- Role functioning
- Social functioning
- Pain
- Fatigue
- Appetite loss
- Global health status/QoL

In addition, the following domains of interest from existing QLQ modules will be added to complement to scope of the questionnaire:

- Stomach Pain (STO22 module)
  - Have you had discomfort when eating?
  - Have you had pain in your stomach area?
  - Have you had discomfort in your stomach area?
- Sexual interest, Impotence (male), Dyspareunia (female) (CR29 module)
  - To what extent were you interested in sex?
  - Did you have difficulty getting or maintaining an erection?
  - Did you have pain or discomfort during intercourse?

These questions are taken from validated questionnaires in such a way as to preserve their inner scale structure. The respective questionnaires are the STO22 module (Ref. 41) and the CR29 module (Ref. 42).

Although the resulting HRQoL checklist is not a validated instrument, it is an ad-hoc instrument optimized for this specific setting and composed of integral parts of validated HRQoL questionnaires. See Appendix I for the English version of this checklist.

10.3 Study design

10.3.1 Timing of assessment

In both treatment arms, HRQoL should be assessed using the HRQoL checklist as described in 10.2 according to the following schedule: The baseline assessment needs to be collected not earlier than 3 weeks before randomization, but before the start of the protocol treatment. This assessment is preferably done before the randomization but can be performed before, during or shortly after randomization.

Two subsequent assessments will be performed at 1 and 5 years after randomization. Time windows for these assessments will be (+/-) 3 month around the scheduled visit. If a patient progresses or withdraws from the study, QoL should no longer be assessed.

	HRQoL checklist Assessment	Eligible time window
T0	Baseline	From 3 weeks before randomization until start of treatment or patient knowledge of randomized treatment arm
T1	Year 1	Up to 3 months before or after.
T2	Year 5	Up to 3 months before or after.

10.3.2 HRQoL data collection

HRQOL checklists must be filled out at the hospital when the patient comes in for a scheduled visit. The checklists will be handed out to the patients by the investigator or a study nurse prior to seeing the doctor for clinical evaluations. Patients will be asked to fill out the checklists as completely and accurately as possible. Master copies (and appropriate translations) of the checklist will be sent to the institution together with the CRFs. The clinical forms will include a question about whether the HRQoL forms have been filled in and if not, the reason why. Data collection procedures should be followed using the EORTC guidelines in Appendix G.

10.3.3 Missing data

Missing data may hamper assessment of HRQoL in clinical trials. This may be because centers do not collect the checklists at the appropriate time (unit non-response), and because patients may miss questions within the checklists (item non-response). The latter problem occurs less than 2% on average and should not be a problem. The former problem will be minimized by ensuring that participating centers are properly informed and motivated towards HRQoL assessment. Compliance will be calculated as the number of forms correctly received according to the schedule described in the previous section over the number of forms expected. During the study, compliance with completing QoL checklists will be investigated at each time point. The compliance of the HRQoL assessments will also be reviewed twice a year and will be a part of the descriptive report by the EORTC Headquarters for the Group's plenary sessions.

10.4 Statistical considerations

10.4.1 Sample size

The sample size calculation for this study has been performed based on the primary endpoint (see chapter 8). A difference of 10 points on a 100 point scale between the two treatment arms will be considered as clinically significant (Ref. 43). The standard deviation of the global QoL scale is approximately 20 points. With a minimal effect size of 0.5 (i.e. one-half standard deviation), with alpha set at 0.05 and beta at 0.20 (power 0.80), a minimum of 64 patients per treatment arm is required.

It should be noted that at the 5 year time point (T2) about 60% of the patients are expected to have dropped out due to PD or death. So the effective sample size for the 5 year time point will be about 150 patients, discounting patient compliance.

10.4.2 Primary HRQoL endpoint and hypothesis

The primary HRQoL endpoints considered relevant to this trial are listed in the objectives. These correspond to the following scales:

- Fatigue
- Physical function
- Stomach Pain, Appetite Loss
- Sexual Interest, Impotence, Dyspareunia
- Pain

All these scales will be comparatively analyzed between the two treatment arms.

10.4.3 Method for statistical analysis

Summary statistics will be calculated to assess the change from the baseline score to the year 1 (T1) and year 5 (T2) assessment respectively. Absolute change in score will be compared via non-parametric logrank tests. In addition, the changes in scores will be further summarized into categorical responses based on in/decrease of 10 points from baseline. The 10 point change corresponds to a clinical relevant change for the EORTC QLQ-C30 (Ref. 43).

Two-sided tests at 5% significance level will be used. No correction for multiplicity will be made but statistical significance will be contrasted with clinical significance in order to avoid inflation of false positive results.

Missing data will be taken into account via sensitivity analysis where missing scores will be imputed under different assumptions. The sensitivity analyses will only be used to help interpret effects observed during the primary analysis. The results from these analyses should however not take priority over the main analysis.

11 Translational research

11.1 Introduction

This trial provides a unique opportunity to perform a translational research project and to collect biological material (prospective biobanking for future research) in both arms (previously irradiated and non irradiated tissues). Basically the primary aim of the planned translational research is to establish new prognostic factors in patients with RPS, especially liposarcoma. The potential events of interest are:

- MDM2 status explored by fluorescence in situ hybridization, real-time quantitative reverse transcription PCR and immunohistochemistry (Ref. 34, Ref. 35, Ref. 36)
- status of the CCDN1/CDK4/P16INK4a/RB1/E2F pathway explored by fluorescence in situ hybridization, real-time quantitative reverse transcription PCR and immunohistochemistry (Ref. 33)
- HMGCOA status explored by fluorescence hybridization in situ (Ref. 33)
- Carboxypeptidase M expression explored by fluorescence in situ hybridization (Ref. 37)
- C-jun and ASK1 status explored by fluorescence in situ hybridization (Ref. 38)
- Investigation of factors for predicting outcome of radiotherapy and side effects related to

To investigate all these issues, genomic and gene expression profiling will be performed from samples before and after radiotherapy (for patients randomized in the radiotherapy arm). Genomic profiling of

tumor and constitutional DNA will be performed using SNP array, allowing us to test whether there is an association between the genomic profile and response to radiotherapy.

To maximize the development of future research program, we strongly recommend storing fresh frozen large samples of surgically removed tissues.

11.2 Informed consent

Patients will be eligible for the prospective biobanking if they are eligible for the clinical trial and have given their written informed consent to participate to this program.

All patients included in the clinical study will be offered to participate to the associated translational research project defined in section 11.1 and the prospective bio-banking of biological material at the time they are offered participation to the clinical study. Patients will have the possibility to accept or refuse participation to the translational research project and to the prospective bio-banking for future research.

If patient accepts to join, a specific consent form must be signed.

11.3 Human biological material

The Human Biological Material (HBM) will be large samples of surgical specimens and blood samples.

Biological materials	At baseline	At the time of surgery
Tumor tissue	Biopsy (FFPE blocks and/or frozen tissue)	Resected specimen (100-200 mg) (FFPE and frozen tissue)
Peripheral blood (EDTA tubes)	5 ml	5 ml

Store frozen tissue and blood at -80°

11.4 General principles for human biological material collection

Human biological material collection involves the collection and storage of biological material, residual biological material or derivatives in compliance with ethical and technical requirements.

In this study, biological material will be stored at each institution until the identification of a Biobank that will centrally store this material. After identification of the biobank and approvals of the Ethics committees, the biological material will be shipped to this central biobank. From here, the biological material will be used or distributed to the other research laboratories involved in the translational research (TR) projects defined in the future.

The following principles apply to storage of HBM:

- The collected HBM should be documented, i.e. the amount remaining and its location.

The Study Steering Committee (SSC)/Group committee will be responsible for TR project review and prioritization, including the consideration of newly proposed TR projects not specified in the protocol. In the absence of a SSC, responsibilities of the SSC are transferred to the Group and/ or EORTC HQ as applicable.

Final decisions on the use of HBM will be determined by a majority vote of the SSC/Group committee. Additional expertise may be sought through advisory non-SSC/Group committee members.

Access to HBM (see EORTC Biobanking Policy POL020): HBM may be used for another purpose for which it was originally collected, subject to meeting ethical principles/and is covered by informed consent/ethics approval. In the case of secondary use of HBM, (i.e. for new TR projects that are not specified in the clinical study protocol and that were not foreseen at the time of protocol writing) interested parties may apply for the use of HBM and will follow the next steps:

A short description of the new TR projects will be written and submitted to EORTC HQ for coordination with the appropriate SSC/Group committee.

The SSC/Group committee will prioritize the TR projects. Access procedures defined by the SSC/Group committee will build on the following key points:

- Project prioritization
  - should be strongly based on scientific merit
  - should consider the contribution of the different investigators to the trial and TR project
  - will take into consideration if the applicant is an EORTC member or not (whilst maintaining the principle of access to the wider scientific community and commitments owed to study participants and ethical committees)
- Protection of confidentiality must be respected
- An EORTC HQ feasibility check, including recommendations for regulatory and ethical matters and other restrictions on the use of the HBM, will take place. If in the event the HBM collections are still retained at individual clinical sites, the TR project leader and the involved EORTC Group are responsible for collecting and providing information on availability of HBM for the feasibility assessment
- Prioritized TR projects will then be reviewed by the Translational Research Advisory Committee (TRAC)

Once SSC/Group committee prioritization, the EORTC HQ feasibility assessment, and TRAC review are complete and when all applicable competent Ethics Committees approvals are in place and ethical principles are met, the TR project can be activated and HBM release and analysis can commence.

The EORTC Executive Committee will mediate any disagreements of opinion between TRAC, the EORTC HQ feasibility assessment, the SSC/Group committee and the TR project leader(s), as needed.

12 Investigator authorization procedure

Investigators will be authorized to register and/or randomize patients in this trial only once they have returned the following documents to the EORTC Headquarters:

- The updated signed and dated curriculum vitae of the Principal Investigator in English with a GCP training proof.
- The (updated) list of normal ranges for the investigator’s institution signed and dated by the head of the laboratory. Please make sure normal ranges are provided also for those tests required by the protocol but not routinely done at the investigator’s institution.
- The Confirmation of interest by Principal Investigator Form (CIF), stating that the investigator will fully comply with the protocol. This must include an estimate of yearly accrual and a statement on any conflict of interest that may arise due to trial participation.

NB: A signed conflict of interest disclosure form will be required only if a possible conflict is declared on the CIF.

- The Study Agreement between EORTC and investigator's institution.
- A copy of the favorable opinion of the local or national (whichever is applicable) ethics committee mentioning the documents that were reviewed (including the version numbers and version dates of all documents). A list of all members of the ethics committee is also requested.

- A copy of the translated and adapted (according to all national requirements) Patient Information / Informed Consent sheet. Version numbers and dates must be clearly stated on each page.
- The signature log-list of the staff members with a sample of each authorized signature and the indication of the level of delegations. In case patients receive treatment at a satellite institution, i.e. outside the authorized institution, details on the satellite institution, including the CV of the local investigator, normal lab ranges and the approval of an ethics committee will have to be transmitted to the EORTC Headquarters. Please keep in mind that all communication is done ONLY between the primary institution and the EORTC Headquarters.
- The full name, address, phone numbers and e-mail address of the local pharmacist who will be responsible for the trial medication (for any trial where the drug will be provided).
- An accreditation, a certification, an established quality control / external quality assessment or another validation should be provided for the own laboratory.

The center specific list of required documents will be included in the protocol activation package, with proper instructions as required by this protocol, your group and / or the applicable national law.

The new investigator will be added to the "authorization list", and will be allowed to register/randomize patients in the trial as soon as

- All the above mentioned documents are available at the EORTC Headquarters.
- All applicable national legal and regulatory requirements are fulfilled.

Patient randomization from centers not (yet) included on the authorization list will not be accepted.

13 Patient randomization procedure

Patient randomization will only be accepted from authorized investigators (see chapter on "investigator authorization procedure").

Patients should be randomized directly on the **EORTC online randomization system** (ORTA = online randomized trials access), accessible 24 hours a day, 7 days a week, through the internet.

To access the interactive randomization program, the investigator needs a username and a password (which can be requested at http://orta.eortc.be/).

In case of problems investigators can phone the EORTC Headquarters from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday in order to randomize patients via the EORTC call center.

Randomization via the phone is not available on Belgian holidays. A list of these holidays is available on the EORTC web site (http://orta.eortc.be/) and it is updated annually.

Through internet:	http://orta.eortc.be/
In case of problems randomization by phone:	+32 2 774 16 00

A patient can only be randomized after verification of eligibility. Both the eligibility check and randomization must be done before the start of the protocol treatment.

STANDARD INFORMATION REQUESTED:

- institution number
- protocol number
- step number: 1
- name of the responsible investigator
- patient's code (maximum 4 alphanumerics)
- patient's birth date (day/month/year)

PROTOCOL SPECIFIC QUESTIONS:

- all eligibility criteria will be checked one by one
- actual values for the eligibility parameters will be requested when applicable
- stratification factors
- date of written informed consent (day/month/year)
- date foreseen for protocol treatment start

Once eligibility has been verified, treatment will be randomly allocated to the patient, together with a **sequential patient identification number ("seqID")**. This number will allow the identification of the patients in the VISTA/Remote Data Capture system (VISTA/RDC) that will be used to complete the Case Report Forms.

14 Forms and procedures for collecting data

14.1 Case report forms and schedule for completion

Data will be reported on the forms specifically designed by the EORTC Headquarters for this study. Forms should be electronically sent to the EORTC Headquarters through the VISTA/RDC (Remote Data Capture) system with the exception of the SAE form which are paper CRFs.

SERIOUS ADVERSE EVENTS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see chapter on Reporting Serious Adverse Events).

A. Before the treatment starts:

- The patient must be registered/randomized in the trial by INTERNET or in case of problems by phone.

The electronic CRFs to be completed for a patient are available on the VISTA/RDC website one day after the randomization on http://rdc.eortc.be/ or on http://www.eortc.org in the section for investigators.

B. During/after treatment

The list of forms to be completed for this study and their submission schedule are available on the VISTA/RDC website and are also described in the "guidelines for completion of case report forms" that are provided to each participating investigator.

ALL Forms must be electronically approved and sent by the responsible investigator or one of his/her authorized staff members with the exception of the paper SAE form which need to be signed and dated individually by the responsible investigator or one of his/her authorized staff members.

14.2 Data flow

The forms must be completed electronically, with the exception of the SAE form, according to the schedule defined in the guidelines for completion of Case Report Forms.

The list of staff members authorized to enter data (with a sample of their signature) must be identified on the signature log and sent to the EORTC Headquarters by the responsible investigator before the start of the study. To enter the RDC system, the investigator or authorized staff member needs to use the same username and password that are used to access the interactive randomization program (ORTA).

In all cases, it remains the responsibility of the principal investigator to check that data are entered in the database as soon as possible and that the electronic forms are filled out completely and correctly.

The EORTC Headquarters will perform extensive consistency checks on the received data and will issue queries in case of inconsistent data. The queries for the electronic forms will appear in the VISTA/RDC system and must be answered there directly.

The EORTC data manager will subsequently apply the corrections into the database.

When satellite institutions are involved, all contact is made exclusively with the primary institution, for purposes of data collection and all other study related issues.

If an investigator (or an authorized staff member) needs to modify a CRF after the form has been electronically sent to the EORTC Headquarters, he/she should create a request for data correction in the VISTA/RDC system.

15 Reporting of Serious Adverse Events

ICH GCP and the EU Directive 2001/20/EC require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

15.1 Definitions

These definitions reflect the minimal regulatory obligations; specific protocol requirements might apply in addition.

AE: An **Adverse Event** is defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product/protocol treatment and which does not necessarily have to have a causal relationship with this treatment”. An adverse event can therefore be any unfavorable and unintended signs (such as rash or enlarged liver), symptoms (such as nausea or chest pain), an abnormal laboratory finding (including results of blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the protocol treatment.

Severity: The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe, or as described in CTC grades); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as “serious,” which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

SAE: A **Serious Adverse Event** is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that at any dose:

- results in death
- is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient's hospitalization or prolongation of existing inpatients´ hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- results in any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above), e.g. secondary malignancy, AE as a result of an overdose

In this protocol, all complications requiring re-operation/percutaneous radiological drainage have to be considered as an SAE.

Inpatient or in-patient's hospitalization: A patient who is admitted to a hospital or clinic for at least one overnight stay.

15.2 Exceptions

The following situations are not considered to be SAEs and should not be reported on the SAE form:

- Elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment
- A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated
- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an (S)AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, palliative care, rehabilitation, overdose without occurrence of an adverse event)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

By EORTC convention, clinical events related to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, unless the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting.

15.3 Severity assessment

The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v4.0 www.eortc.org\investigators-area\ctc and the Dindo grade.

Periods	Pre-operative	Peri-operative	Follow-up
Guidance for SEVERITY assessment	NCI-CTCAE v4	Adapted from Dindo et al.	NCI-CTCAE v4

15.4 Causality assessment

The investigator is obligated to assess the relationship between protocol treatment and the occurrence of each SAE following definitions in this table:

Relationship to the protocol treatment	Description
Reasonable possibility	There is a reasonable possibility that the protocol treatment caused the event
No reasonable possibility	There is no reasonable possibility that the protocol treatment caused the event

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the protocol treatment will be considered and investigated.

The decision will be recorded on the Serious Adverse Event form, if necessary with the reasoning of the principal investigator.

15.5 Expectedness assessment

The expectedness assessment is the responsibility of the sponsor of the study. The expectedness assessment will be performed against the following documents: study protocol, PIS/IC. If necessary, the EORTC Clinical Physician and/or the EORTC Medical Safety Officer will be consulted.

15.6 Reporting procedure for investigators

This procedure applies to all Serious Adverse Events (SAEs) occurring from the time a subject is randomized until 60 days after protocol surgery and to any SAE that occurs outside of the SAE detection period (after the 60-days period), if it is considered to have a reasonable possibility to be related to the protocol treatment or study participation.

Randomization till 60 days after protocol surgery:	All SAEs
From day 61 after protocol surgery:	Only related SAEs

All reporting must be done by the principle investigator or authorized staff member (i.e. on the signature list) to confirm the accuracy of the report.

All SAE data must be collected on the study-specific SAE form.

All SAEs must be reported immediately and no later than 24 hours from the time the investigator or staff became aware of the event.

All SAE-related information needs to be provided in English.

All additional documents in local language must be accompanied by a translation in English, or the relevant information must be summarized in a follow-up SAE report form.

All SAE-related information must be faxed to:

EORTC Pharmacovigilance Unit:

Fax No. +32 2 772 8027

To enable the EORTC to comply with regulatory reporting requirements, all initial SAE reports should always include the following minimal information: an identifiable patient (SeqID), a suspect medicinal product if applicable, an identifiable reporting source, the description of the medical event and seriousness criteria, as well as the causality assessment by the investigator. Complete information requested on the SAE form of any reported serious adverse event must be returned within 7 calendar days of the initial report. If the completed form is not received within this deadline, the Pharmacovigilance Unit will make a written request to the investigator.

Queries sent out by the EORTC Pharmacovigilance Unit need to be answered within 7 calendar days.

All forms need to be dated and signed by the principle investigator or any authorized staff member (i.e. on the signature list).

15.7 Reporting to investigators and competent authorities

The EORTC Pharmacovigilance Unit will forward all SAE reports within 24 hours of receipt to the appropriate persons within the EORTC Headquarters.

All unexpected events will additionally be forwarded to all participating investigators and Ethics committees.

The EORTC Pharmacovigilance Unit will take in charge the expedited reporting to the Competent Authorities whenever applicable.

The EORTC Pharmacovigilance Unit will provide a six-monthly summary which will be added in the group meeting report and which will be distributed to all participating investigators.

15.8 Pregnancy reporting

Pregnancy occurring during a patient's participation in this trial, although not considered an SAE, must be notified to the EORTC Pharmacovigilance Unit within the same timelines as an SAE (within 24 hours) on a Pregnancy Notification Form. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. This also applies to pregnancies following the administration of the investigational product to the father prior to sexual intercourse.

- Any pregnancy in a female subject or in a female partner of a male subject diagnosed during the treatment period or within 60 days after protocol surgery must be reported to the EORTC Pharmacovigilance Unit
- This must be reported within 24 hours of first becoming aware of the event by fax, to the Pharmacovigilance Unit on a Pregnancy Notification Form/Fax
- If a Serious Adverse Event (SAE) occurs in conjunction with the pregnancy, please also complete an SAE form as explained in the SAE chapter

16 Quality assurance

16.1 Control of data consistency

Data forms will be entered in the EORTC Headquarters database by using the VISTA/RDC (Remote Data Capture) system. Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager. Inconsistent forms will be kept "pending" until resolution of the inconsistencies.

16.2 Audits

The EORTC Quality Assurance and Control Unit (QA&C) regularly conducts audits of institutions participating in EORTC protocols. These audits are performed to provide assurance that the rights, safety and wellbeing of subjects are properly protected, to assess compliance with the protocol, processes and agreements, ICH GCP standards and applicable regulatory requirements, and to assess the quality of data.

The investigator, by accepting to participate in this protocol, agrees that EORTC, any third party (e.g. a CRO) acting on behalf of the EORTC, or any domestic or foreign regulatory agency, may come at any time to audit or inspect their site and all subsites, if applicable.

This audit consists of interviews with the principal investigator and study team, review of documentation and practices, review of facilities, equipment and source data verification.

The investigator will grant direct access to paper and/or electronic documentation pertaining to the clinical study (e.g. CRFs, source documents such as hospital patient charts and investigator study files) to these authorized individuals. All site facilities related to the study conduct could be visited during an audit (e.g. pharmacy, laboratory, archives …). The investigator agrees to co-operate and provide assistance at reasonable times and places with respect to any auditing activity.

If applicable, the company(ies) supplying the study drug(s) may have access to anonymized data but will not have access to source documents.

If a regulatory authority inspection is announced, the investigator must inform the EORTC Headquarters QA&C Unit immediately (contact at: QualityAssuranceandControlUnit@eortc.be).

In this way EORTC can provide support in preparing and/or facilitating the inspection. EORTC representatives/delegates may also attend the inspection.

16.3 External review of histology

16.3.1 Forms

Two electronic "Pathology Review Forms" will be used for this review and will be available on the VISTA/RDC website (http://rdc.eortc.be or http://www.eortc.be)

- Local Pathology Form will be completed by the site
- Pathology Review Form will be completed by the reference pathologist

16.3.2 Shipment of tumor samples

- The local pathologist will send tumor block or 10 unstained slides if block not available and his/her pathology report to reference pathologist. Personal data of the patient must be anonymized and replaced by the EORTC sequential identification number allocated to this patient at the time of randomization
- Copies of informed consent cannot be provided
- For procedures and contact details please refer to Study Procedures Manual

16.3.3 Reference pathologist

- Will complete the Pathology Review Form
- The blocks (if blocks) will be sent back to the sites

16.3.3.1 The list of reference pathologists

- List of pathologists for the EORTC investigators is given in the table hereunder

	The reference pathologist is ⇩		the reference pathologist is ⇩
Italy Spain	[redacted]	Germany Poland Denmark Norway Sweden	[redacted]
U. K.	[redacted]	The Netherlands Belgium	[redacted]
France	[redacted]		

16.4 Other central review procedures

16.4.1 Quality assurance in radiotherapy

All documents pertaining to specific radiotherapy quality assurance (RTQA) procedures will be sent to the centers after receipt of the signed commitment form at the EORTC Headquarters.

The QA procedure consists of completing the following, which must be performed prior to site authorization:

- Level I - Facility Questionnaire (FQ) and submission of Beam Output Audit (BOA)
- Level II - Dummy Run without delineation exercise (DR)
- Level V - Complex Dosimetry Check (CDC) for all centers using IMRT, including tomotherapy.

During the trial, the following RTQA procedures must be performed:

- Level III - Limited prospective Individual Case Review (pICR)
- Level IV - Full retrospective Individual Case Review (rICR)

More information will be found in the separate document "RTQA Guidelines" which will be sent with the initiation package.

16.4.1.1 Prior to authorization

16.4.1.1.1 Facility Questionnaire and External Reference Dosimetry Audit

All EORTC sites seeking authorization must have completed the EORTC Facility Questionnaire (FQ), which is valid for two years. This questionnaire must be completed electronically and submitted online.

The web link is on the webpage of the Radiation Oncology Group (ROG) http://groups.eortc.be/radio/Qualityassurance.htm under "ROG Facility Questionnaire".

All centers at authorization must have a valid (not older than two years) Beam Output Audit (BOA). If a valid BOA has not already been submitted, this should be sent electronically (pdf) to the following address: qart62092@eortc.be.

Further details can be found in the "RTQA Guidelines".

16.4.1.1.2 Dummy Run without delineation exercise (DR)

A Dummy Run without delineation exercise (DR)procedure is mandatory for all centers for their selected irradiation technique prior to authorization. In case centers would like to change their treatment technique (possible once only during the trial and only from 3D-CRT to IMRT [including tomotherapy]), the DR procedure must be repeated with the new technique prior to the change.

Further details can be found in the "RTQA Guidelines".

16.4.1.1.3 Complex Dosimetry Check

Before the use of IMRT or Tomotherapy on this trial, centers should have successfully completed an IMRT complex dosimetry check (CDC) in accordance with RTQA guidelines. In case centers would like to change their treatment technique (possible once only during the trial and only from 3D-CRT to IMRT including tomotherapy), prior to the change, the complex dosimetry check procedure must be performed.

Further details can be found in the "RTQA Guidelines".

16.4.1.1.4 Patient-specific RTQA program

For all patients, complete treatment plans must be submitted for central review in DICOM-RT format. The Individual Case Review (ICR) encompasses the following:

- All patient digital treatment data must be submitted prior to the start of radiotherapy treatment
- The first three cases per center will be verified by the study RTQA team before the end of the first week of radiotherapy
- Subsequently, 1 out of 10 randomly selected cases will be centrally reviewed
- In case that the initial or randomly reviewed cases results in minor or major protocol deviations, supplementary case reviews may take place
- Beyond the prospective RTQA ICR, retrospective evaluation of every patient's treatment plan will be performed

All details about the submission procedure and the supplementary forms are described in the "RTQA Guidelines".

In case of questions or difficulties, please contact the trial RTQA team at the following address: qart62092@eortc.be.

17 Ethical considerations

17.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online athttp://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf).

The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

17.2 Subject identification

The name of the patient will neither be asked for nor recorded at the EORTC Headquarters. A sequential identification number will be automatically allocated to each patient registered in the trial. This number will identify the patient and will be included on all case report forms. In order to avoid identification errors, the patient's code (maximum of 4 alphanumerics) and date of birth will also be reported on the case report forms.

17.3 Informed consent

All patients will be informed about

- the aims of the study
- the possible adverse events
- the procedures and possible hazards to which the patient will be exposed
- the mechanism of treatment allocation
- strict confidentiality of any patient data
- medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician

The template of the patient's informed consent statement is given as a separate document dated and version controlled to this protocol.

An adapted translation of the PIS/PIC will be provided by EORTC Headquarters and it is the responsibility of the Coordinating investigators for this trial (sometimes called National Coordinators) to adapt it to national/local requirements where necessary.

The translated informed consent documents are to be submitted to ethics committees for approval. The competent ethics committee for each institution must approve the informed consent documents before the center can join the study. It is the responsibility of the competent ethics committee to ensure that the translated informed documents comply with ICH-GCP guidelines and all applicable national legislation.

It is emphasized in the patient information sheet that participation is voluntary and that the patient is free to refuse further participation in the protocol whenever he/she wants to. This will not have any impact on the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered and/or randomized at the EORTC Headquarters. The written informed consent form must be signed and personally dated by the patient or by the patient's legally acceptable representative.

All of the above must be done in accordance with the applicable national legislation and local regulatory requirements.

18 Administrative responsibilities

18.1 The study coordinator

The Study Coordinator works closely with the study team to develop the outline and full protocol and discusses the contents of the reports with the study team. The Study coordinator is responsible for publishing the study results. He/she will assist the Clinical Research Physician for answering some clinical questions concerning eligibility, treatment, and contributes to the medical review of the patients.

Study coordinator:

[redacted]

18.2 The EORTC Headquarters

The EORTC Headquarters will be responsible for writing the protocol and PIS/IC, reviewing the protocol, setting up the trial, collecting case report forms, controlling the quality of the reported data, organizing the medical review and generating reports and analyses in cooperation with the Study Coordinator. All methodological questions should be addressed to the EORTC Headquarters.

EORTC HEADQUARTERS

Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Fax: +32 2 7723545

18.3 The EORTC group

All questions concerning ongoing membership in the group should be addressed to the chairman and/or secretary of the group.

For new membership contact Membership Committee at membership@eortc.be

EORTC Soft Tissue and Bone Sarcoma group

Chairman:

[redacted]

Secretary:

[redacted]

19 Trial sponsorship and financing

The Sponsor of the study is the EORTC.

The contact details of the EORTC are:

EORTC Headquarters
Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Phone: +32 2 7741611
Fax: +32 2 7723545
e-mail: eortc@eortc.be

20 Trial insurance

A clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

Clinical trial insurance is only valid in centers authorized by the EORTC Headquarters. For details please refer to the chapter on investigator authorization.

21 Publication policy

All publications must comply with the terms specified in the EORTC Policy 009 “Release of Results and Publication Policy” version 4.1 dated 29 November 2011.

The final publication of the main trial results will be written by the EORTC Study Coordinator on the basis of the final analysis performed at the EORTC Headquarters and published in a major scientific journal.

The final publication of associated translational research studies will be written by the Coordinator of the corresponding translational research study.

Authors of the manuscript(s) will include the Study Coordinators, the investigators who have included more than 5% of the eligible patients in the trial (by order of inclusion), and the statistician and clinical research physician in charge of the trial at the EORTC Headquarters. For publication of translational research results, co-authors will also include scientific collaborators who made substantial contribution to the research.

The title of all manuscripts will include “EORTC”, and all manuscripts will include an appropriate acknowledgment section, mentioning all investigators who have contributed to the trial, the EORTC Headquarters staff involved in the study, as well as supporting bodies (NCI, cancer leagues, supporting company…).

Prior to submission, all publications (papers, abstracts, presentations…) including data pertaining to patients from the present trial will be submitted for review to the EORTC Headquarters, to all co-authors, and to the Trial Steering Committee.

The above rules are applicable to publications involving any individual patient registered/randomized in the trial.

The EORTC study coordinator will represent EORTC on the manuscript(s) study. Further authorship positions attributed to the EORTC according to the publication policy will be attributed to the investigators who have included more than 10% of the eligible patients in the trial (by order of inclusion). One of the pathologists of the pathology review panel will be included in authorship: for studies in which a member of the pathology review panel has reviewed > 25% of cases, that pathologist will qualify for authorship, in other cases the pathology review panel, in consultation with the board of the STBSG, will decide which pathologist will be author on behalf of the pathology review panel.

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Appendix B: Abbreviations

3D-CRT	3 D conformal Radiotherapy
AE	Adverse Event
ALT	Alanine aminotransferase
ASA	American Society of Anesthesiologist
ASC	Anesthesia and Surgical Care
ASK 1	Apoptosis signal-regulating kinase 1
AST	Aspartate aminotransferase
HBM	Human Biological Material (HBM)
CNS	Central nervous system
CDC	Complex Dosimetry e-check
CR	Complete Response
CRF	Case Report form
CRO	Clinical Research Organization
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTV	Clinical Target Volume
CV	Curriculum Vitae
DICOM	Digital Imaging Communication in Medicine
DR	Dummy Run
DSMB	Data and Safty Monitoring Board
EB-IORT	Electron-beam intraoperative radiation
EBRT	External-beam radiotherapy
EBIORT	Electron beam intraoperative radiation therapy
ERDA	External Reference Dosimetry Audit
FDG	Fluorodeoxy-D-glucose
FFP	Fresh Frozen Plasma
FQ	Facility Questionnaire
GFR	Glomerular filtration rate
GIST	Gastro-intestinal stromal tumor
GTV	Gross Tumor Volume
H0	Null Hypothesis

HMGCOA	3-hydroxy-3-methylglutaryl-coenzyme A
HR	Hazard Ratio
IC	Intermediate Care
ICH/GCP	International Conference on Harmonisation /Good Clinical Practice
ICR	Intra Cavitory Radiation
ICRU	International Commission on Radiation Units and measurements
ICU	Intensive Care unit
IDMC	Independent Data Monitoring Committee
IMRT	Intensity-modulated radiotherapy
IORT	Intra-operative radiotherapy
ITT	Intent to treat
IVC	Internal vena cava
MRI	Magnetic Resonance Imaging
MV	Mega Volt
NCI	US National Cancer Institute
NYHA	New York Heart Association
OAR	Organs at Risk
ORTA	Online randomized trials access
OTT	Overall Treatment Time
PCR	Polymerase chain reaction
PD	Progression
PET	Positron Emission Tomography
PIS/IC	Patient Information Sheet/ Inform Consent
PLT	Platelet
PNET	Primitive Neuroectodermal Tumor
PR	Partial Response
PTV	Planning Target Volume
QA	Quality Assurance
RBC	Red Blood Cell
RDC	Remote Data Capture
RECIST	Response Evaluation Criteria In Solid Tumors
RPS	Retroperitoneal sarcoma
RT	Radiation Therapy
RTQA	Radiotherapy quality assurance
SAE	Serious adverse Event

SAL	Shrinking Action level
SD	Stable Disease
seqID	sequential patient identification number
SOC	System Organ Class
SOP	Standard Operation Procedure
STBSG	Soft Tissue and Bone Sarcoma Group
TR	Translational research
ULN	upper limit of normal
VISTA	Visual Information System for Trial Analysis
WHO	World Health Organization

Appendix C: WHO performance status scale

Grade	Performance scale
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

Appendix D: New York Heart Association (NYHA) classification of heart failure

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

(The Criteria Committee of the New York Heart Association: Diseases of the Heart and Blood Vessels; Nomenclature and Criteria for Diagnosis, 6th ed Boston, Little, Brown 1964).

Appendix E: Calculation of the glomerular filtration rate (GFR)

COCKCROFT AND GAULT FORMULA

For the calculation of GFR age is measured in years and weight is measured in kilograms.

If serum creatinine is measured in µmol/l, the following formula applies:

In males: $GFR[ml/min] = \frac{1.23 \times (140 - age) \times weight}{serum\ creatinine}$

In females: $GFR[ml/min] = \frac{1.05 \times (140 - age) \times weight}{serum\ creatinine}$

If serum creatinine is measured in mg/dl, the following formula applies:

In males: $GFR[ml/min] = \frac{(140 - age) \times weight}{72 \times serum\ creatinine}$

In females: $GFR[ml/min] = \frac{0.85 \times (140 - age) \times weight}{72 \times serum\ creatinine}$

Appendix F: Common Terminology Criteria for Adverse Events

In the present study, adverse events and/or adverse drug reactions will be recorded according to the

Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: http://ctep.cancer.gov/reporting/ctc.html.

The EORTC Headquarters web site www.eortc.org\investigators-area\ctc provides a link to the appropriate CTC web site. This link will be updated if the CTC address is changed.

Appendix G: EORTC Quality of Life evaluation: guidelines for administration of checklists

EORTC Quality of Life evaluation: guidelines for administration of checklists

The instructions given below are intended to provide some general guidelines for collecting quality of life (QOL) data in EORTC studies.

1. Who is the responsible person (RP) for QOL data collection?

In each institution, the principal investigator is the responsible for the local organization of QoL data collection. This can be delegated to a physician, data manager, (research) nurse or a psychologist. Such a person should have the full protocol at his/her disposal as well as the questionnaire(s). This person would also be the intermediate contact point in case of any necessary clarification asked by the EORTC Headquarters.

2. Who should fill out the checklist?

In principle it is the patient who has to complete the QOL forms and preferably without help from others. In the case where a patient is too sick to fill out the checklist by him/herself or if the patient is not able to complete the checklist for such reasons as forgetting his/her glasses, another person could read the questions without making any suggestions and report the answers on the forms. It is not allowed for another person to fill in the checklist as if (s)he was the patient (proxy assessment) unless specifically allowed by the protocol.

3. What instructions should be given to the patient?

At entry in a study, the RP should give the patient an explanation of the objective of the study and instructions for completing the checklist.

The patient should be informed that participation in the QOL protocol is voluntary and that the information provided is confidential (identification is only for administrative purposes and includes date of birth and today's date (completion date)).

The following issues should be explained to the patient:

- The schedule of assessments.
- The checklist is a self administered checklist that should be completed by the patient him(her)self. The patient can ask for aid in reading or writing but should not let another person provide the answers.
- The patient should circle the choice that best corresponds to his/her situation.
- There is no right or wrong answer to any of these questions. The answers will not influence any medical decision making.
- All questions should be answered.
- The patient will be given a checklist in the default language(s) of the hospital. If desired, the patient may request another language. The RP will then contact the EORTC Headquarters for the appropriate translation.

The RP should make sure that the patient understands the instructions.

At each subsequent assessment as defined by the protocol, the patient should receive the checklist from the RP or from other appropriate staff if the RP is unavailable.

4. Where should the patient complete the checklist?

The patient should complete the checklist at the clinic, and, ideally in a quiet, private room. If this is not possible, the waiting room is an acceptable alternative. In general it does not take long to complete the checklist, but patients should be given the time they need to answer all questions.

5. When should they complete the checklist?

The timing of the planned QoL assessments is detailed in the protocol. When a QOL assessment is planned, the checklist should be given to the patient preferably before the meeting with the physician, ensuring that the patient has enough time to complete the checklist. If the patient is to receive a therapy, the checklist should be filled out before administration of the treatment (unless indicated otherwise in the protocol). The checklist should not be taken home and/or mailed (unless indicated otherwise in the protocol).

6. Review of the completed checklist

After the patient has completed the checklist, the person handling the checklist should:

- Complete the "Hospital Staff" specific data box.
- Check that the completion date is correctly filled in by the patient.
- Screen the checklist for omissions.

If this is the case:

- Please ask the patient the reason for omissions. It may be that patient forgot to flip a page or did not understand a question. The patient should not be forced to provide an answer if (s)he does not wish to do so.
- Additional explanation may be provided, but the questions should not be rephrased.

7. Missing forms

If for some reason the patient is unable or does not wish to complete a quality of life checklist the reason and the date of visit should be documented on the corresponding CRF (case report form).

8. Mailing to EORTC Headquarters

A copy of the checklists should be sent to EORTC Headquarters as soon as possible, while the original source document should be kept on site. As it is impossible to retrospectively collect missing quality of life data, please make sure the patient completes the checklist at the time-point when he/she is supposed to complete it.

Thank you very much for your cooperation. If you have any remarks about this leaflet or if you need further information, please contact:

Quality of Life Department - EORTC Headquarters:

Phone: 32 2 774 16 61/16 06

Fax: 32 2 772 35 45

E-mail: qualityoflife@eortc.be

Appendix H: American Society of Anesthesiologists score

The ASA Score is a system for assessing the risk for postoperative morbidity/mortality. In 1963 the American Society of Anesthesiologists (ASA) adopted the five-category physical status classification system; a sixth category was later added:

Score	
1	A normal healthy patient.
2	A patient with mild systemic disease.
3	A patient with severe systemic disease.
4	A patient with severe systemic disease that is a constant threat to life
5	A moribund patient who is not expected to survive without the operation
6	A declared brain-dead patient whose organs are being removed for donor purposes

Reference:

Owens WD, Felts JA, Spitznagel EL (1978). "ASA physical status classification: A study of consistency of ratings". Anaesthesia 49: 239–43

Link: http://www.ncbi.nlm.nih.gov/pubmed/697077

Appendix I: EORTC QlQ-C30 (version 3)

EORTC QLQ-C30 (version 3)

FOR THE PATIENT
TO BE COMPLETED BY HOSPITAL STAFF (EN)
Protocol: **62092** Form 930, page 1 of 2
Date completed by patient (DD/MM/YY) |_|_|/|_|_|/|_|_|_|_|
Inst |_|_|_|_| Seq id |_|_|_|_| Patient Code |_|_|_|_|

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|

Today's date (Day, Month, Year): 23 |_|_|_|_|_|_|_|_|

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Have you had pain?	1	2	3	4
9. Did you need to rest?	1	2	3	4
10. Have you felt weak?	1	2	3	4
11. Have you lacked appetite?	1	2	3	4
12. Were you tired?	1	2	3	4
13. Did pain interfere with your daily activities?	1	2	3	4
14. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4

15. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4

Please go on to the next page

FOR THE PATIENT
TO BE COMPLETED BY HOSPITAL STAFF (EN)
Protocol°: **62092** Form 930, page 2 of 2
Date completed by patient (DD/MM/YY) |_|_|/|_|_|/|_|_|_|_|
Inst |_|_|_|_| Seq id |_|_|_|_| Patient Code |_|_|_|_|

For the following questions please circle the number between 1 and 7 that best applies to you

16. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

17. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
18. Have you had discomfort when eating?	1	2	3	4
19. Have you had pain in your stomach area?	1	2	3	4
20. Have you had discomfort in your stomach area?	1	2	3	4

During the past 4 weeks:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
For men only:				
21. To what extent were you interested in sex?	1	2	3	4
22. Did you have difficulty getting or maintaining an erection?	1	2	3	4

For women only:				
21. To what extent were you interested in sex?	1	2	3	4
22. Did you have pain or discomfort during intercourse?	1	2	3	4