UNIVERSITE DE STRASBOURG
FACULTE DE MEDECINE DE STRASBOURG

ANNEE : 2019 N° : 13

THESE

PRESENTEE POUR LE DIPLOME DE

DOCTEUR EN MEDECINE

Diplôme d'Etat

Mention Oncologie option Onco-radiothérapie

PAR

Waïsse Abdullah WAÏSSI

Né le 28/08/1986 à KABOUL

Efficacité et tolérance de l'irradiation conformationnelle avec modulation d'intensité hélicoïdale sous TOMOTHERAPY ® dans le traitement des sarcomes rétropéritonéaux et pelviens.

Président de Thèse : Professeur Georges NOËL

FACULTÉ DE MÉDECINE
(U.F.R. des Sciences Médicales)

Edition OCTOBRE 2018
Année universitaire 2018-2019

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NHC = Nouvel Hôpital Civil HC = Hôpital Civil HP = Hôpital de Hautepierre PTM = Plateau technique de microbiologie

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COLLANGE Olivier PO193	NRPô NCS	• Pôle d'Anesthésie / Réanimations chirurgicales / SAMU-SMUR - Service d'Anesthésiologie-Réanimation Chirurgicale / NHC	48.01	**Anesthésiologie-Réanimation** ; Médecine d'urgence (option Anesthésiologie-Réanimation - Type clinique)
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DUFOUR Patrick (5) (7) P0056	S/nb Cons	• Centre Régional de Lutte contre le cancer Paul Strauss (convention)	47.02	Option : Cancérologie clinique
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FALCOZ Pierre-Emmanuel P0052	NRPô NCS	• Pôle de Pathologie thoracique - Service de Chirurgie Thoracique / Nouvel Hôpital Civil	51.03	Chirurgie thoracique et cardio-vasculaire
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Mme JESEL-MOREL Laurence		• Pôle d'activité médico-chirurgicale Cardio-vasculaire - Service de Cardiologie / Nouvel Hôpital Civil	51.02	Cardiologie
KALTENBACH Georges P0081	RPô CS	• Pôle de Gériatrie - Service de Médecine Interne - Gériatrie / Hôpital de la Robertsau	53.01	Option : gériatrie et biologie du vieillissement
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MASSARD Gilbert P0100	NRPô NCS	• Pôle de Pathologie thoracique - Service de Chirurgie Thoracique / Nouvel Hôpital Civil	51.03	Chirurgie thoracique et cardio-vasculaire
Mme MATHELIN Carole P0101	NRPô NCS	• Pôle de Gynécologie-Obstétrique - Unité de Sénologie - Hôpital Civil	54.03	**Gynécologie-Obstétrique** ; Gynécologie Médicale
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MAZZUCOTELLI Jean-Philippe P0103	RPô CS	• Pôle d'activité médico-chirurgicale Cardio-vasculaire - Service de Chirurgie Cardio-vasculaire / Nouvel Hôpital Civil	51.03	Chirurgie thoracique et cardio-vasculaire
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MEYER Nicolas P0105	NRPô NCS	• Pôle de Santé publique et Santé au travail - Laboratoire de Biostatistiques / Hôpital Civil • Biostatistiques et Informatique / Faculté de médecine / Hôpital Civil	46.04	Biostatistiques, Informatique Médicale et Technologies de Communication (option biologique)
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MONASSIER Laurent P0107	NRPô CS	• Pôle de Pharmacie-pharmacologie • Unité de Pharmacologie clinique / Nouvel Hôpital Civil	48.03	Option : Pharmacologie fondamentale
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MOULIN Bruno P0109	NRPô CS	• Pôle de Spécialités médicales - Ophtalmologie / SMO - Service de Néphrologie - Transplantation / Nouvel Hôpital Civil	52.03	Néphrologie
MUTTER Didier P0111	RPô CS	• Pôle Hépato-digestif de l'Hôpital Civil - Service de Chirurgie Digestive / NHC	52.02	Chirurgie digestive
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PELACCIA Thierry		• Pôle d'Anesthésie / Réanimation chirurgicales / SAMU-SMUR - Service SAMU/SMUR	48.02	Réanimation et anesthésiologie Option : Médecine d'urgences
Mme PERRETTA Silvana P0117	NRPô NCS	• Pôle Hépato-digestif de l'Hôpital Civil - Service d'Urgence, de Chirurgie Générale et Endocrinienne / NHC	52.02	Chirurgie digestive
PESSAUX Patrick P0118	NRPô NCS	• Pôle des Pathologies digestives, hépatiques et de la transplantation - Service d'Urgence, de Chirurgie Générale et Endocrinienne / NHC	53.02	Chirurgie Générale
PETIT Thierry P0119	CDp	• Centre Régional de Lutte Contre le Cancer - Paul Strauss (par convention) - Département de médecine oncologique	47.02	**Cancérologie** ; Radiothérapie Option : Cancérologie Clinique
PIVOT Xavier		• Centre Régional de Lutte Contre le Cancer - Paul Strauss (par convention) - Département de médecine oncologique	47.02	**Cancérologie** ; Radiothérapie Option : Cancérologie Clinique
POTTECHER Julien P0181	NRPô NCS	• Pôle d'Anesthésie / Réanimations chirurgicales / SAMU-SMUR - Service d'Anesthésie et de Réanimation Chirurgicale / Hôpital de Hautepierre	48.01	**Anesthésiologie-réanimation** ; Médecine d'urgence (option clinique)
PRADIGNAC Alain P0123	NRPô NCS	• Pôle de Médecine Interne, Rhumatologie, Nutrition, Endocrinologie, Diabétologie (MIRNED) - Service de Médecine interne et nutrition / HP	44.04	Nutrition
PROUST François P0182	NRPô CS	• Pôle Tête et Cou - Service de Neurochirurgie / Hôpital de Hautepierre	49.02	Neurochirurgie
Mme QUOIX Elisabeth P0124	NRPô CS	• Pôle de Pathologie thoracique - Service de Pneumologie / Nouvel Hôpital Civil	51.01	Pneumologie
Pr RAUL Jean-Sébastien P0125	NRPô CS	• Pôle de Biologie - Service de Médecine Légale, Consultation d'Urgences médico-judiciaires et Laboratoire de Toxicologie / Faculté et NHC • Institut de Médecine Légale / Faculté de Médecine	46.03	Médecine Légale et droit de la santé
REIMUND Jean-Marie P0126	NRPô NCS	• Pôle des Pathologies digestives, hépatiques et de la transplantation - Service d'Hépato-Gastro-Entérologie et d'Assistance Nutritive / HP	52.01	Option : Gastro-entérologie

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Pr RICCI Roméo P0127	NRPô NCS	• Pôle de Biologie - Laboratoire de Biochimie et de Biologie moléculaire / HP	44.01	Biochimie et biologie moléculaire
ROHR Serge P0128	NRPô CS	• Pôle des Pathologies digestives, hépatiques et de la transplantation - Service de Chirurgie générale et Digestive / HP	53.02	Chirurgie générale
Mme ROSSIGNOL -BERNARD Sylvie PO196	NRPô CS	• Pôle médico-chirurgical de Pédiatrie - Service de Pédiatrie I / Hôpital de Hautepierre	54.01	Pédiatrie
ROUL Gérald P0129	NRPô NCS	• Pôle d'activité médico-chirurgicale Cardio-vasculaire - Service de Cardiologie / Nouvel Hôpital Civil	51.02	Cardiologie
Mme ROY Catherine P0140	NRPô CS	• Pôle d'Imagerie - Serv. d'Imagerie B - Imagerie viscérale et cardio-vasculaire / NHC	43.02	Radiologie et imagerie médicale (opt clinique)
SAUDER Philippe P0142	NRPô CS	• Pôle Urgences - Réanimations médicales / Centre antipoison - Service de Réanimation médicale / Nouvel Hôpital Civil	48.02	Réanimation
SAUER Arnaud P0183	NRPô NCS	• Pôle de Spécialités médicales - Ophtalmologie / SMO - Service d'Ophtalmologie / Nouvel Hôpital Civil	55.02	Ophtalmologie
SAULEAU Erik-André P0184	NRPô NCS	• Pôle de Santé publique et Santé au travail - Laboratoire de Biostatistiques / Hôpital Civil • Biostatistiques et Informatique / Faculté de médecine / HC	46.04	Biostatiqtiques, Informatique médicale et Technologies de Communication (option biologique)
SAUSSINE Christian P0143	RPô CS	• Pôle d'Urologie, Morphologie et Dermatologie - Service de Chirurgie Urologique / Nouvel Hôpital Civil	52.04	Urologie
SCHNEIDER Francis P0144	RPô CS	• Pôle Urgences - Réanimations médicales / Centre antipoison - Service de Réanimation médicale / Hôpital de Hautepierre	48.02	Réanimation
Mme SCHRÖDER Carmen P0185	NRPô CS	• Pôle de Psychiatrie et de santé mentale - Service de Psychothérapie pour Enfants et Adolescents / Hôpital Civil	49.04	**Pédopsychiatrie** ; Addictologie
SCHULTZ Philippe P0145	NRPô NCS	• Pôle Tête et Cou - CETD - Serv. d'Oto-rhino-laryngologie et de Chirurgie cervico-faciale / HP	55.01	Oto-rhino-laryngologie
SERFATY Lawrence P0197	NRPô NCS	• Pôle des Pathologies digestives, hépatiques et de la transplantation - Service d'Hépato-Gastro-Entérologie et d'Assistance Nutritive / HP	52.01	Gastro-entérologie ; Hépatologie ; Addictologie Option : **Hépatologie**
SIBILIA Jean P0146	NRPô NCS	• Pôle de Médecine Interne, Rhumatologie, Nutrition, Endocrinologie, Diabétologie (MIRNED) - Service de Rhumatologie / Hôpital Hautepierre	50.01	Rhumatologie
Mme SPEEG-SCHATZ Claude P0147	RPô CS	• Pôle de Spécialités médicales - Ophtalmologie / SMO - Service d'Ophtalmologie / Nouvel Hôpital Civil	55.02	Ophtalmologie
Mme STEIB Annick P0148	RPô NCS	• Pôle d'Anesthésie / Réanimations chirurgicales / SAMU-SMUR - Service d'Anesthésiologie-Réanimation Chirurgicale / NHC	48.01	Anesthésiologie-réanimation (option clinique)
STEIB Jean-Paul P0149	NRPô CS	• Pôle de l'Appareil locomoteur - Service de Chirurgie du rachis / Hôpital Civil	50.02	Chirurgie orthopédique et traumatologique
STEPHAN Dominique P0150	NRPô CS	• Pôle d'activité médico-chirurgicale Cardio-vasculaire - Service des Maladies vasculaires - HTA - Pharmacologie clinique / Nouvel Hôpital Civil	51.04	Option : Médecine vasculaire
THAVEAU Fabien P0152	NRPô NCS	• Pôle d'activité médico-chirurgicale Cardio-vasculaire - Service de Chirurgie vasculaire et de transplantation rénale / NHC	51.04	Option : Chirurgie vasculaire
Mme TRANCHANT Christine P0153	NRPô CS	• Pôle Tête et Cou - CETD - Service de Neurologie / Hôpital de Hautepierre	49.01	Neurologie
VEILLON Francis P0155	NRPô CS	• Pôle d'Imagerie - Service d'Imagerie 1 - Imagerie viscérale, ORL et mammaire / Hôpital Hautepierre	43.02	Radiologie et imagerie médicale (option clinique)
VELTEN Michel P0156	NRPô NCS CS	• Pôle de Santé publique et Santé au travail - Département de Santé Publique / Secteur 3 - Epidémiologie et Economie de la Santé / Hôpital Civil • Laboratoire d'Epidémiologie et de santé publique / HC / Fac de Médecine • Centre de Lutte contre le Cancer Paul Strauss - Serv. Epidémiologie et de biostatistiques	46.01	Epidémiologie, économie de la santé et prévention (option biologique)
VETTER Denis P0157	NRPô NCS	• Pôle de Médecine Interne, Rhumatologie, Nutrition, Endocrinologie, Diabétologie (MIRNED) - Service de Médecine Interne, Diabète et Maladies métaboliques/HC	52.01	Option : Gastro-entérologie
VIDAILHET Pierre P0158	NRPô NCS	• Pôle de Psychiatrie et de santé mentale - Service de Psychiatrie I / Hôpital Civil	49.03	Psychiatrie d'adultes
VIVILLE Stéphane P0159	NRPô NCS	• Pôle de Biologie - Laboratoire de Parasitologie et de Pathologies tropicales / Fac. de Médecine	54.05	Biologie et médecine du développement et de la reproduction (option biologique)
VOGEL Thomas P0160	NRPô CS	• Pôle de Gériatrie - Service de soins de suite et réadaptations gériatriques / Hôpital de la Robertsau	51.01	Option : Gériatrie et biologie du vieillissement
WEBER Jean-Christophe Pierre P0162	NRPô CS	• Pôle de Spécialités médicales - Ophtalmologie / SMO - Service de Médecine Interne / Nouvel Hôpital Civil	53.01	Option : Médecine Interne
WOLF Philippe P0164	NRPô NCS	• Pôle des Pathologies digestives, hépatiques et de la transplantation - Service de Chirurgie Générale et de Transplantations multiorganes / HP - Coordonnateur des activités de prélèvements et transplantations des HU	53.02	Chirurgie générale
Mme WOLFF Valérie		• Pôle Tête et Cou - Service de Neurochirurgie / Hôpital de Hautepierre	49.02	Neurochirurgie

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HC : Hôpital Civil - HP : Hôpital de Hautepierre - NHC : Nouvel Hôpital Civil
* : CS (Chef de service) ou NCS (Non Chef de service hospitalier) Cspi : Chef de service par intérim CSp : Chef de service provisoire (un an)
CU : Chef d'unité fonctionnelle
Pô : Pôle RPô (Responsable de Pôle) ou NRPô (Non Responsable de Pôle)
Cons. : Consultanat hospitalier (poursuite des fonctions hospitalières sans chefferie de service) Dir : Directeur
(1) En surnombre universitaire jusqu'au 31.08.2018
(3) (7) Consultant hospitalier (pour un an) éventuellement renouvelable --> 31.08.2017
(5) En surnombre universitaire jusqu'au 31.08.2019 (8) Consultant hospitalier (pour une 2ème année) --> 31.08.2017
(6) En surnombre universitaire jusqu'au 31.08.2017 (9) Consultant hospitalier (pour une 3ème année) --> 31.08.2017

A4 - PROFESSEUR ASSOCIE DES UNIVERSITES

HABERSETZER François	CS	Pôle Hépato-digestif 4190 Service de Gastro-Entérologie - NHC	52.01	Gastro-Entérologie
CALVEL Laurent	NRPô CS	Pôle Spécialités médicales - Ophtalmologie / SMO Service de Soins palliatifs / NHC	55.02	Ophtalmologie
SALVAT Eric		Centre d'Evaluation et de Traitement de la Douleur		

MO112 B1 - MAITRES DE CONFERENCES DES UNIVERSITES - PRATICIENS HOSPITALIERS (MCU-PH)

NOM et Prénoms	CS*	Services Hospitaliers ou Institut / Localisation	Sous-section du Conseil National des Universités	
AGIN Arnaud M0001		• Pôle d'Imagerie - Service de Biophysique et de Médecine nucléaire/Hôpital de Hautepierre	43.01	Biophysique et Médecine nucléaire
Mme ANTAL Maria Cristina M0003		• Pôle de Biologie - Service de Pathologie / Hautepierre • Faculté de Médecine / Institut d'Histologie	42.02	Histologie, Embryologie et Cytogénétique (option biologique)
Mme ANTONI Delphine M0109		• Centre de lutte contre le cancer Paul Strauss	47.02	Cancérologie ; **Radiothérapie**
ARGEMI Xavier M0112		• Pôle de Spécialités médicales - Ophtalmologie / SMO - Service des Maladies infectieuses et tropicales / Nouvel Hôpital Civil	45.03	Maladies infectieuses ; Maladies tropicales Option : **Maladies infectieuses**
Mme AYME-DIETRICH Estelle		• Pôle de Parmacologie - Unité de Pharmacologie clinique / NHC	48.03	Option: pharmacologie fondamentale
Mme BARNIG Cindy M0110		• Pôle de Pathologie thoracique - Service de Physiologie et d'Explorations Fonctionnelles / NHC	44.02	**Physiologie**
Mme BARTH Heidi M0005 (Dispo → 31.12.2018)		• Pôle de Biologie - Laboratoire de Virologie / Hôpital Civil	45.01	Bactériologie - Virologie (Option biologique)
Mme BIANCALANA Valérie M0008		• Pôle de Biologie - Laboratoire de Diagnostic Génétique / Nouvel Hôpital Civil	47.04	Génétique (option biologique)
BLONDET Cyrille M0091		• Pôle d'Imagerie - Service de Biophysique et de Médecine nucléaire/Hôpital de Hautepierre	43.01	Biophysique et médecine nucléaire
BONNEMAINS Laurent M0099		• Pôle d'activité médico-chirurgicale Cardio-vasculaire - Service de Chirurgie cardio-vasculaire / Nouvel Hôpital Civil	54.01	Pédiatrie
BOUSIGES Olivier M0092		• Pôle de Biologie - Laboratoire de Biochimie et de Biologie moléculaire / HP	44.01	Biochimie et biologie moléculaire
CARAPITO Raphaël M0113		• Pôle de Biologie - Laboratoire d'Immunologie biologique / Nouvel Hôpital Civil	47.03	Immunologie
CAZZATO Roberto		• Pôle d'Imagerie - Service d'Imagerie A interventionnelle / NHC	43.02	Radiologie et imagerie médicale (option clinique)
CERALINE Jocelyn M0012		• Pôle d'Oncologie et d'Hématologie - Service d'Oncologie et d'Hématologie / HP	47.02	**Cancérologie** ; Radiothérapie (option biologique)
CHOQUET Philippe M0014		• Pôle d'Imagerie - Service de Biophysique et de Médecine nucléaire / HP	43.01	Biophysique et médecine nucléaire
COLLONGUES Nicolas M0016		• Pôle Tête et Cou-CETD - Centre d'Investigation Clinique / NHC et HP	49.01	Neurologie
DALI-YOUCEF Ahmed Nassim M0017		• Pôle de Biologie - Laboratoire de Biochimie et Biologie moléculaire / NHC	44.01	Biochimie et biologie moléculaire
Mme de MARTINO Sylvie M0018		• Pôle de Biologie - Laboratoire de Bactériologie / PTM HUS et Faculté de Médecine	45.01	**Bactériologie**-virologie Option bactériologie-virologie biologique
Mme DEPIENNE Christel M0100 (Dispo->15.08.18)	CS	• Pôle de Biologie - Laboratoire de Cytogénétique / HP	47.04	Génétique
DEVYS Didier M0019		• Pôle de Biologie - Laboratoire de Diagnostic génétique / Nouvel Hôpital Civil	47.04	Génétique (option biologique)
DOLLÉ Pascal M0021		• Pôle de Biologie -Laboratoire de Biochimie et biologie moléculaire / NHC	44.01	Biochimie et biologie moléculaire
Mme ENACHE Irina M0024		• Pôle de Pathologie thoracique - Service de Physiologie et d'Explorations fonctionnelles / NHC	44.02	Physiologie
FILISETTI Denis M0025		• Pôle de Biologie - Labo. de Parasitologie et de Mycologie médicale / PTM HUS et Faculté	45.02	Parasitologie et mycologie (option biologique)
FOUCHER Jack M0027		• Institut de Physiologie / Faculté de Médecine • Pôle de Psychiatrie et de santé mentale - Service de Psychiatrie I / Hôpital Civil	44.02	Physiologie (option clinique)
GUERIN Eric M0032		• Pôle de Biologie - Laboratoire de Biochimie et de Biologie moléculaire / HP	44.03	Biologie cellulaire (option biologique)
Mme HARSAN-RASTEI Laura		• Pôle d'Imagerie - Service de Biophysique et de Médecine nucléaire/Hôpital de Hautepierre	43.01	Biophysique et médecine nucléaire
Mme HEIMBURGER Céline		• Pôle d'Imagerie - Service de Biophysique et de Médecine nucléaire/Hôpital de Hautepierre	43.01	Biophysique et médecine nucléaire
Mme HELMS Julie M0114		• Pôle d'Urgences / Réanimations médicales / CAP - Service de Réanimation médicale / Nouvel Hôpital Civil	48.02	Réanimation ; Médecine d'urgence Option : **Réanimation**
HUBELE Fabrice M0033		• Pôle d'Imagerie - Service de Biophysique et de Médecine nucléaire / HP et NHC	43.01	Biophysique et médecine nucléaire
Mme JACAMON-FARRUGIA Audrey M0034		• Pôle de Biologie - Service de Médecine Légale, Consultation d'Urgences médico-judiciaires et Laboratoire de Toxicologie / Faculté et HC • Institut de Médecine Légale / Faculté de Médecine	46.03	Médecine Légale et droit de la santé
JEGU Jérémie M0101		• Pôle de Santé publique et Santé au travail - Service de Santé Publique / Hôpital Civil	46.01	Epidémiologie, Economie de la santé et Prévention (option biologique)

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JEHL François M0035		• Pôle de Biologie - Institut (Laboratoire) de Bactériologie / PTM HUS et Faculté	45.01	Option : **Bactériologie**-virologie (biologique)
KASTNER Philippe M0089		• Pôle de Biologie - Laboratoire de diagnostic génétique / Nouvel Hôpital Civil	47.04	Génétique (option biologique)
Mme KEMMEL Véronique M0036		• Pôle de Biologie - Laboratoire de Biochimie et de Biologie moléculaire / HP	44.01	Biochimie et biologie moléculaire
Mme LAMOUR Valérie M0040		• Pôle de Biologie - Laboratoire de Biochimie et de Biologie moléculaire / HP	44.01	Biochimie et biologie moléculaire
Mme LANNES Béatrice M0041		• Institut d'Histologie / Faculté de Médecine • Pôle de Biologie - Service de Pathologie / Hôpital de Hautepierre	42.02	Histologie, Embryologie et Cytogénétique (option biologique)
LAVAUX Thomas M0042		• Pôle de Biologie - Laboratoire de Biochimie et de Biologie moléculaire / HP	44.03	Biologie cellulaire
LAVIGNE Thierry M0043	CS	• Pôle de Santé Publique et Santé au travail - Service d'Hygiène hospitalière et de médecine préventive / PTM et HUS - Equipe opérationnelle d'Hygiène	46.01	Epidémiologie, économie de la santé et prévention (option biologique)
Mme LEJAY Anne M0102		• Pôle de Pathologie thoracique - Service de Physiologie et d'Explorations fonctionnelles / NHC	44.02	Physiologie (Biologique)
LENORMAND Cédric M0103		• Pôle de Chirurgie maxillo-faciale, Morphologie et Dermatologie - Service de Dermatologie / Hôpital Civil	50.03	Dermato-Vénéréologie
LEPILLER Quentin M0104 (Dispo → 31.08.2018)		• Pôle de Biologie - Laboratoire de Virologie / PTM HUS et Faculté de Médecine	45.01	**Bactériologie-Virologie** ; Hygiène hospitalière (Biologique)
Mme LETSCHER-BRU Valérie M0045		• Pôle de Biologie - Laboratoire de Parasitologie et de Mycologie médicale / PTM HUS • Institut de Parasitologie / Faculté de Médecine	45.02	Parasitologie et mycologie (option biologique)
LHERMITTE Benoît M0115		• Pôle de Biologie - Service de Pathologie / Hôpital de Hautepierre	42.03	Anatomie et cytologie pathologiques
Mme LONSDORFER-WOLF Evelyne M0090		• Institut de Physiologie Appliquée - Faculté de Médecine • Pôle de Pathologie thoracique - Service de Physiologie et d'Explorations fonctionnelles / NHC	44.02	Physiologie
LUTZ Jean-Christophe M0046		• Pôle de Chirurgie plastique reconstructrice et esthétique, Chirurgie maxillo-faciale, Morphologie et Dermatologie - Serv. de Chirurgie Maxillo-faciale, plastique reconstructrice et esthétique/HC	55.03	Chirurgie maxillo-faciale et stomatologie
MEYER Alain M0093		• Institut de Physiologie / Faculté de Médecine • Pôle de Pathologie thoracique - Service de Physiologie et d'Explorations fonctionnelles / NHC	44.02	Physiologie (option biologique)
MIGUET Laurent M0047		• Pôle de Biologie - Laboratoire d'Hématologie biologique / Hôpital de Hautepierre et NHC	44.03	Biologie cellulaire (type mixte : biologique)
Mme MOUTOU Céline ép. GUNTHNER M0049	CS	• Pôle de Biologie - Laboratoire de Diagnostic préimplantatoire / CMCO Schiltigheim	54.05	Biologie et médecine du développement et de la reproduction (option biologique)
MULLER Jean M0050		• Pôle de Biologie - Laboratoire de Diagnostic génétique / Nouvel Hôpital Civil	47.04	Génétique (option biologique)
NOLL Eric M0111		• Pôle d'Anesthésie Réanimation Chirurgicale SAMU-SMUR - Service Anesthésiologie et de Réanimation Chirurgicale - Hôpital Hautepierre	48.01	**Anesthésiologie-Réanimation** ; Médecine d'urgence
Mme NOURRY Nathalie M0011		• Pôle de Santé publique et Santé au travail - Service de Pathologie professionnelle et de Médecine du travail - HC	46.02	Médecine et Santé au Travail (option clinique)
PENCREAC'H Erwan M0052		• Pôle de Biologie - Laboratoire de Biochimie et biologie moléculaire / Nouvel Hôpital Civil	44.01	Biochimie et biologie moléculaire
PFAFF Alexander M0053		• Pôle de Biologie - Laboratoire de Parasitologie et de Mycologie médicale / PTM HUS	45.02	Parasitologie et mycologie
Mme PITON Amélie M0094		• Pôle de Biologie - Laboratoire de Diagnostic génétique / NHC	47.04	Génétique (option biologique)
PREVOST Gilles M0057		• Pôle de Biologie - Institut (Laboratoire) de Bactériologie / PTM HUS et Faculté	45.01	Option : **Bactériologie**-virologie (biologique)
Mme RADOSAVLJEVIC Mirjana M0058		• Pôle de Biologie - Laboratoire d'Immunologie biologique / Nouvel Hôpital Civil	47.03	Immunologie (option biologique)
Mme REIX Nathalie M0095		• Pôle de Biologie - Labo. d'Explorations fonctionnelles par les isotopes / NHC • Institut de Physique biologique / Faculté de Médecine	43.01	Biophysique et médecine nucléaire
RIEGEL Philippe M0059		• Pôle de Biologie - Institut (Laboratoire) de Bactériologie / PTM HUS et Faculté	45.01	Option : **Bactériologie**-virologie (biologique)
ROGUE Patrick (cf. A2) M0060		• Pôle de Biologie - Laboratoire de Biochimie et biologie moléculaire / NHC	44.01	Biochimie et biologie moléculaire (option biologique)
Mme ROLLAND Delphine		• Pôle de Biologie - Laboratoire d'Hématologie biologique / NHC	44.03	Biologie cellulaire (type mixte : biologique)
ROMAIN Benoît M0061		• Pôle des Pathologies digestives, hépatiques et de la transplantation - Service de Chirurgie générale et Digestive / HP	53.02	Chirurgie générale
Mme RUPPERT Elisabeth M0106		• Pôle Tête et Cou - Service de Neurologie - Unité de Pathologie du Sommeil / Hôpital Civil	49.01	Neurologie

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Mme SABOU Alina M0096		• Pôle de Biologie - Laboratoire de Parasitologie et de Mycologie médicale / PTM HUS • Institut de Parasitologie / Faculté de Médecine	45.02	Parasitologie et mycologie (option biologique)
Mme SAMAMA Brigitte M0062		• Institut d'Histologie / Faculté de Médecine	42.02	Histologie, Embryologie et Cytogénétique (option biologique)
Mme SCHEIDECKER Sophie		• Pôle de Biologie - Laboratoire de Diagnostic génétique / Nouvel Hôpital Civil	47.04	Génétique (option biologique)
Mme SCHNEIDER Anne M0107		• Pôle médico-chirurgical de Pédiatrie - Service de Chirurgie pédiatrique / Hôpital de Hautepierre	54.02	Chirurgie Infantile
SCHRAMM Frédéric M0068		• Pôle de Biologie - Institut (Laboratoire) de Bactériologie / PTM HUS et Faculté	45.01	Option : **Bactériologie**-virologie (biologique)
Mme SOLIS Morgane		• Pôle de Biologie - Laboratoire de Diagnostic Génétique / Nouvel Hôpital Civil	47.04	Génétique (option biologique)
Mme SORDET Christelle M0069		• Pôle de Médecine Interne, Rhumatologie, Nutrition, Endocrinologie, Diabétologie (MIRNED) - Service de Rhumatologie / Hôpital de Hautepierre	50.01	Rhumatologie
TALHA Samy M0070		• Pôle de Pathologie thoracique - Service de Physiologie et explorations fonctionnelles / NHC	44.02	Physiologie (option clinique)
Mme TALON Isabelle M0039		• Pôle médico-chirurgical de Pédiatrie - Service de Chirurgie Infantile / Hôpital Hautepierre	54.02	Chirurgie infantile
TELETIN Marius M0071		• Pôle de Biologie - Service de Biologie de la Reproduction / CMCO Schiltigheim	54.05	Biologie et médecine du développement et de la reproduction (option biologique)
Mme URING-LAMBERT Béatrice M0073		• Institut d'Immunologie / HC • Pôle de Biologie - Laboratoire d'Immunologie biologique / Nouvel Hôpital Civil	47.03	Immunologie (option biologique)
VALLAT Laurent M0074		• Pôle de Biologie - Laboratoire d'Hématologie Biologique - Hôpital de Hautepierre	47.01	**Hématologie** ; Transfusion Option Hématologie Biologique
Mme VILLARD Odile M0076		• Pôle de Biologie - Labo. de Parasitologie et de Mycologie médicale / PTM HUS et Fac	45.02	Parasitologie et mycologie (option biologique)
Mme WOLF Michèle M0010		• Chargé de mission - Administration générale - Direction de la Qualité / Hôpital Civil	48.03	Option : Pharmacologie fondamentale
Mme ZALOSZYC Ariane ép. MARCANTONI M0116		• Pôle Médico-Chirurgical de Pédiatrie - Service de Pédiatrie I / Hôpital de Hautepierre	54.01	Pédiatrie
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LA FACULTÉ A ARRETÉ QUE LES OPINIONS ÉMISES DANS LES DISSERTATIONS QUI LUI SONT PRÉSENTÉES DOIVENT ETRE CONSIDERÉES COMME PROPRES A LEURS AUTEURS ET QU'ELLE N'ENTEND NI LES APPROUVER, NI LES IMPROUVER

SERMENT D'HIPPOCRATE

En présence des maîtres de cette école, de mes chers condisciples, je promets et je jure au nom de l'Etre suprême d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine. Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail.

Admis à l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe.

Ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les moeurs ni à favoriser les crimes.

Respectueux et reconnaissant envers mes maîtres je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis resté fidèle à mes promesses. Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.

« Germaine semblait, ce soir-là, rendre compte de quelque chose d'essentiel dans notre lutte contre le cancer : pour ne pas être distancé par la maladie, il faut sans cesse inventer et réinventer, apprendre et désapprendre des stratégies. Germaine s'était battue contre le cancer sans arrêt, avec intelligence, désespérément, farouchement, follement, brillamment et avec zèle, comme si elle y avait mis toute l'énergie de générations d'hommes et de femmes qui ont combattu le cancer et le feront encore dans l'avenir. »

Extrait de « *l'Empereur de toutes les maladies, une biographie du cancer »*
Siddartha MUKHERJEE

Remerciements :

Au **Professeur Georges NOËL**, qui m'a fait l'honneur d'encadrer et de présider cette première thèse et qui m'a soutenu dans mon projet d'entreprendre un cursus scientifique. Veuillez accepter l'expression de mon plus profond respect.

Au **Docteur Cécile Le PECHOUX,** qui me fait l'honneur de juger cette thèse. Votre engagement dans la prise en charge des sarcomes des tissus mous en radiothérapie est une vraie source d'inspiration pour moi. Veuillez trouver ici l'expression de ma profonde reconnaissance.

Au **Professeur Jean-Emmanuel KURTZ**, pour avoir accepté de juger ce travail. Vous avez été le premier à me faire découvrir le monde si complexe des sarcomes et à me donner envie d'aller plus loin dans sa compréhension. Veuillez trouver l'expression de ma profonde reconnaissance.

Au **Professeur Philippe BACHELLIER**, pour avoir accepté de juger ce travail de thèse. Je vous remercie de l'intérêt que vous accordé à ce travail. Veuillez trouver l'expression de ma profonde reconnaissance.

Au **Docteur Delphine ANTONI**, pour avoir accepté de juger ce travail de thèse. Je te remercie aussi pour ton soutien durant toutes ces années au sein du département de radiothérapie.

Aux médecins oncologues radiothérapeutes du Centre Paul STRAUSS (Drs ANTONI, BAUER, CLAVIER, GANANSIA, GUIHARD, LEPINOY, POP, SALZE, SCHUMACHER, TRUNTZER, VIGNERON) et du CH de Colmar (Dr ATLANI, BOUTENBAT, GUILLERME) pour m'avoir transmis leur savoir et m'avoir donné envie de continuer à exercer ce métier.

Aux Drs ASMANE, BARTHELEMY, BOREL, DUCLOS, GOLDBARG, LITIQUE et SERRA pour leur enseignement de l'oncologie médical.

Au Pr Jean-Pierre BERGERAT, pour m'avoir accueilli dans son département avec beaucoup de bienveillance et m'avoir enseigné l'oncologie médicale au plus proche du lit du malade.

Au Pr NAMER, Pr IMPERIALE, Dr BLONDET et Dr HUBELE de l'équipe de médecine nucléaire des HUS pour m'avoir montré la complexité de l'imagerie métabolique.

A mes co-internes strasbourgeois au contact desquels j'ai appris l'importance du travail d'équipe : Audrey, Thomas, Youssef, Ines, Clara, Sophie, Yvan, Adrien, Chloé-Line, Maxime, Lucas, Sébastien, Céline, Mathias, Nadia, Marion, Mickael, Julie, Clément, Laure D., Laure P., Justine, Frederique, Philippe, Ian…

A l'ensemble du département de radiothérapie du Centre Paul STRAUSS.

Aux Kneckes : Amandine, Felix, Caroline, Cécile, Matthieu, Marina, Moreau, Nico, Seb, Romain, Sophie, William.
A mes amis lyonnais, sans qui l'externat aurait été bien différent : Alexis, Anne, Céline, Diane, Mathieu, Marion, Nico J, Nico R, Noémie, Olivier, Yann.

A Yvan et Adrien. Vous êtes les mecs les plus passionnés et passionnants que j'ai rencontré. J'ai tellement appris à vos côtés durant ces années et c'est pas fini….

A Patricia, Jean-Francois, Bruno, Marion, Emilie pour leur accueil au sein des petits-loups.

A mes oncles tantes, cousins et cousines.
To Aemal. You're a brilliant methodologist and I have learnt so much from you.

A mes Parents, pour leur amour et leur bienveillance. Vous m'avez donné le goût de soigner les autres et ceci depuis mon plus jeune âge.
A mes petits frères, Emran et Bellal. Avoir grandi à vos côtés m'a toujours poussé à faire davantage (même si à la fin c'était toujours vous qui étiez les meilleurs…).
A Marie et Abel.
A Bibi Jan.

A Julie, pour ton amour inconditionnel.

Table des matières

Introduction :

Les sarcomes des tissus mous (STM) sont des tumeurs rares (1% des tumeurs malignes) développées aux dépens des tissus de soutien de l'organisme[1]. La classification OMS 2013 prend en compte leur hétérogénéité histologique et moléculaire pour les regrouper en plus de 50 sous-types, aux pronostics bien distincts [2]. Malgré des avancées majeures en terme de caractérisation génétique et moléculaire, le seul traitement curatif reste la chirurgie d'exérèse complète, monobloc en un temps [3,4].

Selon la localisation (membre ou rétropéritoine), le rôle de la radiothérapie n'est pas démontré avec le même niveau de preuve et la problématique rencontrée est aussi bien différente. Concernant les STM rétropéritonéaux, leur caractère asymptomatique explique leur grande taille au diagnostic, conduisant à des marges de résection chirurgicale le plus souvent microscopiquement positives (R1) [5]. Contrairement aux STM des membres, le pronostic est beaucoup plus sombre (50 à 60% de survie à 5 ans) et principalement lié à des récidives locales [6]. De nombreuses études prospectives non randomisées ou des études rétrospectives semblent montrer une amélioration du taux de contrôle local mais sans impact sur la survie spécifique ou globale [6,7]. Cependant, ce bénéfice se fait au prix d'une toxicité digestive non négligeable allant jusqu'à 50% d'entérite aiguë ou chronique [8].

La radiothérapie conformationnelle avec modulation d'intensité (RCMI) est la principale innovation technologique en radiothérapie de ces deux dernières décennies et ceci a été rendu possible notamment par les avancées de l'imagerie 3D, avec l'intégration des scannographies tridimensionnelles, mais aussi par les progrès de l'informatique permettant l'application d'algorithmes de calcul de plus en plus complexes [9]. Ainsi, il s'agit de mettre en œuvre un traitement de radiothérapie encore plus conformationnel et ainsi de diminuer les doses élevées aux organes critiques tout en maintenant la dose optimale aux volumes cibles. Ainsi, la RCMI a la capacité de produire de hauts gradients de dose nécessaires pour éviter

l'irradiation excessive de structures normales à risque.

Par ailleurs, de nombreuses variations anatomiques peuvent survenir en cours d'irradiation tel que les modifications ou le déplacement du volume cible mais aussi des organes à risques mobile [10]. Les variations morphologiques doivent être prises en compte et ceci grâce à l'intégration des outils de repositionnement 3D associés à l'appareil de traitement, permettant ainsi de réaliser une radiothérapie guidée par l'image (*IGRT : image-guided radiotherapy*) [10].

L'intégration de la RCMI dans la prise en charge des STM du rétropéritoine semble être une idée séduisante et de nombreuses études dosimétriques montrent l'intérêt de la RCMI en terme de diminution des doses aux organes à risques (OAR) tout en garantissant une irradiation hautement conformationnelle du volume cible [11–13]. Cependant peu d'études se sont intéressées d'une part aux résultats cliniques en termes d'efficacité et de tolérance de la RCMI dans le traitement des STM.

Dans ce travail, après avoir fait une revue de la littérature sur la place de la radiothérapie externe dans le traitement des sarcomes du rétropéritoine (Article 1), nous avons évalué tout d'abord l'efficacité et la tolérance de l'irradiation en Tomotherapy® (Article 2). Puis nous avons cherché à mettre en évidence des facteurs dosimétriques liés à la toxicité digestive aiguë (Article 3). Enfin, nous avons quantifié la fonction rénale des patients traités par Tomotherapy® après un traitement chirurgical pour un sarcome du rétropéritoine (Article 4).

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Role of External beam radiotherapy for the treatment of retroperitoneal soft tissue sarcoma : a review of the litterature

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Role of External beam radiotherapy for the treatment of retropertoneal soft tissue sarcoma : a review of the literature.

Abstract :

Retroperitoneal sarcomas (RPS) are rare diseases. The overall 5-year survival rate for these lesions remains low, and surgical management offers the only option for effective treatment and potential for cure. The management of RPS can be very challenging, and the quality of initial treatment strategy appears to be a crucial prognostic factor. En bloc surgery is currently the standard of care and perioperative treatments such as chemotherapy or radiotherapy have not yet been validated. Whereas the curative role of adding radiotherapy to surgery is still controversial, it is increasingly being employed in conjunction to standard surgical treatment. This article reviews the current literature and documents the role of external beam radiotherapy in the management of RPS. We also highlight volumes, doses, and optimal radiotherapy techniques for the treatment of RPS. As the accurate prediction of prognosis in patients with RPS is a challenging issue, we finally emphasize the place of nomograms.

1. Introduction :

Soft tissue sarcomas (STS) are rare and heterogeneous malignancies. The annual incidence is not well known. In a prospective population-based study performed between March 2005 and February 2007, *Ducimetière et al.* performed a centralized review of molecular analyses of all suspected cases across a French region and concluded that the observed incidence of sarcomas was higher than expected. The study found a crude incidence rate of 6.4 cases per 100,000. Extrapolating these data to French population, 4000 cases should be diagnosed per year representing 1% of all new yearly cancer (1). The median age at diagnosis of STS is 60 years(1). Approximately 50% of STS occur in the limbs (lower extremity: 75%; upper extremity: 25%) (1). A more rare form of STS occurs in the retroperitoneum, accounting for 15% of all diagnosed STS(2). The recently updated World Health Organization (WHO) classification of soft tissue and bone tumors recognizes 113 histologic subtypes classified into 12 categories (3). The most common subtypes include liposarcoma, undifferentiated-unclassified tumors and leiyomyosarcoma. Comparing to the 2002 WHO classification, major changes concerned liposarcomas. The terms “round cell liposarcoma” and “mixed-type liposarcoma” used in the 2002 classification have been removed (4). Furthermore, over the last decades, several specific genetic alterations have been described, allowing a molecular classification (5,6). Retroperitoneal liposarcomas are classified into well-differentiated, dedifferentiated or myxoid-round cell subtypes (7). In a published series of 177 retroperitoneal liposarcomas, 56% were well-differentiated, 37% dedifferentiated, and 7% myxoid-round cell (8). Approximately 40% of retroperitoneal sarcomas are low grade and the remaining 60% are intermediate or high-grade (9). Low-grade tumors infrequently metastasize, while intermediate and high-grade tumors can metastasize primarily to the lung and liver (10). Surgery is the primary treatment for RPS, but complete resection is often difficult or impossible due to large tumor size and

involvement of adjacent vital structures. Based on large series in the literature, gross tumor resection seems to be difficult, with rates ranged between 54 and 67% (11).

In order to increase local control, the role of radiotherapy has been investigated but remains unclear. Thus, we assessed the role of external beam radiotherapy (EBRT) in the management of RPS by conducting a review of published clinical data.

2. Initial evaluation

2.1. Natural history:

Often, STS are misdiagnosed due to their presentation as a painless enlarged mass (12). A recent large multi-institutional review documented the median size of such masses were 20 cm at diagnosis (13). The incidence of distant metastasis at diagnosis concerns a minority of patients and is approximately 10 % (14,15). For retroperitoneal STS, the most common site of recurrence is locally within the retroperitoneum. Furthermore, myxoid liposarcoma may frequently spread from limbs to the retroperitoneum. Certain histology such as myxofibrosarcoma exhibits higher local recurrences rates and lower distant recurrence comparing to other forms of STS (16).

2.2. Imaging workup:

For STS of the extremity and trunk, magnetic resonance imaging (MRI) is generally preferred to computed tomography (CT) scanning, both for diagnostic characterization and staging purposes to inform clinical management (17). T1-weighted images provide excellent anatomic definition and typically are relied upon for preoperative planning. As the sequence is not fluid sensitive, T2-weighted images evaluate the edema. Specific MRI sequences such as STIR (Short Tau Inversion Recovery) or FAT-SAT (fat saturation) are useful for the evaluation of lipomatous tumors (18). The MRI exam should be performed with and without intravenous gadolinium enhancement. The delineation between tumor tissue and uninvolved tissue is further defined by T1 postgadolinium images (19). In addition to imaging of the mass, further staging

studies of a suspected or diagnosed STS should include a CT scan of the chest to evaluate for pulmonary metastases, especially for patients with high grade tumors. PET scan technology assesses the *in-vivo* metabolic activity via positron-emitting radionuclides, of which Fluorodeoxyglucose-18 (^{18}F-FDG) is the most commonly used. In a recent publication evaluating the diagnostic and prognostic value of PET/CT scans for sarcomas, it was found that the test is highly sensitive and specific in the detection of high-grade bone and STS (20). Furthermore, it was found that the SUVmax of the primary tumor was a strong predictor of survival (21). Although, it has demonstrated potential benefit, the use of FDG-PET in STS is still considered investigational in nature. For diagnosis, a CT scan of the abdomen and pelvis is usually performed, followed by core needle biopsy. Liposarcomas have a characteristic radiological appearance; well-differentiated liposarcomas typically have large areas of abnormal fat, while higher density nodules are usually seen in dedifferentiated liposarcomas. Using CT scan, *Lahat et al.* accurately identified 100% of the well-differentiated liposarcomas (22). In contrast, leiomyosarcomas usually appear as heterogeneous, solid tumors. MRI scans are helpful in delineating the treatment target, particularly for pelvic tumors, but are less commonly performed for lesions above the pelvic brim.

2.3. Biopsy

When a soft tissue mass is suspected to be a sarcoma, the biopsy should be performed with care and consideration of the definitive resection procedure. Core needle biopsy is minimally invasive and more accurate than fine needle aspiration (23). If an incisional biopsy is required, it should be performed in line with the skin incision of the planned resection of the malignant lesion(2). Optimally, the biopsy is performed by the surgeon who will perform the definitive resection (2).

2.4.Management in a multidisciplinary high-volume centre

RPS is a rare and complex disease. Thus, it has been advocated that patients with RPS should be managed in expert high-volume multidisciplinary sarcoma centres. There is emerging evidence that clinical outcomes were improved when patients were treated by a physician with expertise compared to those who were not. *Gutierrez et al.* published the analysis of patients treated for RPS in the Florida Cancer Data System and concluded that overall survival (OS) was improved in patients treated at a high-volume centre (24). Experience of the surgeons at these centres is one of the likely explanatory factors in such a difference. Indeed, the role of surgical expertise is an important part of preserving tumor integrity during surgery, with many studies highlighting that a ruptured tumor is a negative prognostic factor of overall survival (25). Data from the French Association of Surgery demonstrated an association between a high case load per centre and abdominal recurrence‐free survival (26). This is partly attributed to the more radical resections performed but also to the lower tumor rupture rates seen in high-volume centres.

Finally, the determination of histological diagnosis and prognostic factor is essential for defining treatment strategies. *Ray-Coquard et al.* showed in the analysis of three European regional databases that more than 40% of histological diagnoses were modified after a secondary reading in a specialized centre (27).

3. External beam radiotherapy treatment modality

To improve local control, different schedules of radiotherapy (RT) have been developed (pre-operative, intraoperative, and postoperative) (28). In contrary to extremity STS, there are no randomized trials evaluating the benefit of radiotherapy for RPS. The American College of Surgeons Oncology Group phase III trial (ACOSOG Z9031) was launched to determine the effect of adding pre-operative RT to RPS treatment, but closed prematurely due to lack of patient accrual. More recently, the EORTC-STBSG 62092-22092 trial (STRASS), a randomized control trial evaluating patient outcomes between surgery with or without pre-

operative RT is ongoing. Pre-operative RT has several advantages. First, as the tumor is still in place, volume delineation is easier, and secondly preoperative radiotherapy may enhance the rate of complete resections with safe margins. It is interesting to note that in a preoperative setting, the tumor could displace highly radiosensitive organs such as small bowel, away from the area of treatment, minimizing potential side effects. However, the small bowel could still sometimes be in contact with the tumor volume meaning it would potentially receive the maximum dose. In the post-operative setting, the small bowel fills the surgical cavity and thus receivs the full dose of radiation leading to enhanced side effects.

3.1. Target volume and organs at risk contour delineation.

3.1.1. Simulation

Prior to receiving a CT scan, patients should be placed in the supine position with arms resting in supports over their head with their body immobilized with vacuum cushions. To enhance target delineation and to help identify the gastrointestinal tract, intravenous contrast injection or oral contrast ingestion should be performed (29). Slice thickness acquisition should be < 3mm according to recently published international guidelines (30). Tumors and organs located in the upper abdomen may move significantly due to respiration (31). For this reason, 4-dimension CT scan acquisition is mandatory for tumors above the iliac crest (30). Registration of post gadolinium T1-weighted magnetic resonance imaging (MRI) may assist target volume delineation (32).

3.1.2. Delineation of organs at risk (OAR)

The following OARs should be precisely delineated: spinal cord, stomach, intestinal cavity (bowel bag), rectum, liver, kidneys, bladder, uterus, ovaries or testis, and femoral heads. For intestinal cavity delineation, sarcoma experts contoured small bowel and colon as the bowel bag (29). This approach has multiple advantages. First, it is easier and faster to contour

compared to each small bowel loop. Moreover, as the small bowel is a highly moving organ, delineating each bowel segment individually overestimates the volume of the small bowel receiving more than 45 Gy (33). Thus, the EORTC trial (STRASS) recommended delineating the bowel bag as a structure containing all intestinal segments. The other OARs should be contoured according to guidelines (34).

3.1.3. Delineation of target volumes

Accurate delineation of radiation target volumes is a prerequisite for the precise delivery of radiation dose to the region of interest. This is currently one of the main issues in the era of image guided intensity modulated radiotherapy (IG-IMRT).

Different high volume sarcoma centres published their contouring approaches showing a difference between the margins from gross tumor volume (GTV) to clinical target volume (CTV), ranging from 5 to 20 mm (35–38). Only one publication from the MD Anderson Cancer Centre group has described a margin of 45 mm due to volume motion during respiration (39). Therefore, as mentioned above, the importance of using 4D-CT scan for delineation is a key approach to reducing internal margins (31).

Currently the standard guidelines for RPS delineation are based on NRG (NSABP, RTOG, GOG) consensus agreement among experts (29). Twelve international experts' contoured two cases of RPS and the agreement was "almost perfect" according to kappa values ranging between 0.84 and 0.92. CTV was defined as a GTV expansion of 15 mm with edited reduction at bone, bowel bag and air cavity (5mm), renal and hepatic interface (2 mm), and skin surface (3 mm). When a 4D-CT scan was obtained, authors specified that reduction to renal and hepatic interface was 0 mm because 4D-CT scans also take into account organ motion due to respiration (31).

After preoperative radiotherapy, there is still a risk of positive margin after resection. Therefore, "high risk CTV" (HR-CTV) has been defined as the area that is most high risk of a positive

margin after resection (40). The HR-CTV should be contoured with the aid of surgeons, as it includes organs that they would leave *in situ,* including the posterior wall, para- and prevertebral space, and major vessels. In contrary to GTV and CTV, HR-CTV delineation was very moderate among a panel of experts (Kappa values of 0.50 and 0.57) (40).

There are no consensus guidelines for the definition of planned target volume (PTV). The STRASS trial recommends a 9 mm expansion in the anterior and medial directions whereas a 12 mm expansion is recommended in other directions (41). However, daily image-guided radiotherapy (IGRT) could help decrease range uncertainties, leading to a decrease in PTV margins. In a series of RPS patients treated with IG-IMRT, authors from the Princess Margaret Hospital evaluated the temporal and volumetric changes of RPS with weekly cone beam CT. They found that after a slight volume increase, the GTV volume decreased throughout the course of RT. Moreover they showed GTV interfraction displacement of 15 mm in superior/inferior and anterior/posterior directions and 8.6 mm in lateral directions (31). Authors emphasized the benefit of adaptive radiotherapy which allowed for re-planning when necessary.

3.2.Prescription dose

In the ongoing STRASS trial, the prescription dose of is 50-50.4 Gy in 1.8-2 Gy per fraction. Additionally, at least 95% of the PTV should receive 95% of prescription dose. As mentioned above, there has been an interest of the concept of dose escalation to a volume of high risk for positive margins (38,42–44). Dose escalation is feasible with recent techniques of RT such as intensity modulated radiotherapy (IMRT) or protontherapy. When RT is performed postoperatively, dose escalation is limited by late gastro-intestinal (GI) toxicity. Several publications observed significant incidence rates of late GI complications between 50 to 60 Gy (44–47). Therefore, dose prescription with postoperative radiotherapy should not exceed 50 Gy.

3.3.Irradiation technique

Since it was introduced for the treatment of RPS, photon-based RT has evolved from the 3

dimensional conformal radiotherapy (3D-CRT) to IMRT and image guided radiotherapy (IGRT). The goal of these modalities is to improve outcomes, while minimizing acute and late term complications. IMRT is a conformal technique that allows better target coverage while minimizing the dose to neighbouring organs at risks. Many researchers reported the dosimetric superiority of IMRT compared to 3D-CRT in treating patients suffering from RPS (37,48,49). Another advantage of IMRT is that it allows dose escalation to areas of gross disease. Authors from the University of Alabama published their experience using IMRT to treat preoperative RPS. They could deliver 45 Gy in 25 fractions of 1.8 Gy to the entire GTV and a simultaneous integrated boost (SIB) allowing for a total dose of 57.5 Gy in 25 fractions of 2.3 Gy to the posterior retroperitoneal surgical margin, which is at high risk for recurrence. With a two-year local control rate of 80 %, one patient experienced radiation related grade 2 late toxicity and treatment morbidity was acceptable for the remaining patients (50). Another approach from a research group in Belgium tested the preoperative radiation therapy targeting the area of contact between the tumor and the posterior abdominal wall. They delivered a total dose of 50 Gy in 25 fractions of 2 Gy per day with IMRT or conformal radiotherapy. They found low toxicity (2 patients with anorexia CTC grade 3, 1 patient with anorexia CTC grade 1, 2 patients with nausea CTC grade 2, 1 patient with erythema CTC grade 2, 2 patients with gastritis CTC grade 1) and all patients had complete surgical excision except for one (42). The results of the TOMOREP phase II trial, which evaluated the efficacy and toxicity of 54 Gy with the use of helical tomotherapy for preoperative treatment of retroperitoneal liposarcoma, illustrated that it is feasibly and for the most part tolerated well (51).

The use of particle therapies, such as protontherapy and carbon ions, seems to be promising. Proton therapy is currently the most widely used form of charged particles. Because of the absence of exit dose beyond the Bragg peak, protons can spare adjacent organs, thus allowing dose escalation (52). Because radiosensitive organs such as the small bowel or the kidneys are

often close to the target volume, patients with RPS may benefit from the use of charged particles. Comparatively, to the evolution photon-based irradiation from 3D-CRT to IMRT, the delivery of protons evolved from passive scattering to pencil beam scanning offering better treatment conformity (52). *DeLaney et al.* showed in a recent phase 1 trial that protontherapy might be an excellent tool for further dose escalation into the high-risk of relapse volume (43). Patients were treated with 50.4 GyRBE preoperative intensity modulated protontherapy (IMPT) with simultaneous integrated boost dose escalation from 60.2 GyRBE to 63 GyRBE. They showed that dose escalation to 63Gy RBE was feasible without acute limiting dose toxicity. Compared to protons, carbon ions have higher relative biologic effect whilst maintaining comparable physical dose distribution. The research group in Chiba, Japan studied dose escalation with carbon ion radiotherapy in 24 patients with unresectable RPS. The mean dose in the trial was 68.9 GyE (range 52.8-73.6 GyE). At 5 years, the absolute local control and overall survival rates were 69% and 50% respectively. No patients experienced GI toxicity but 21% of the patients had long-term neurological complications (53).

Irrespective of the IMRT technique and protontherapy, IGRT is frequently performed just prior to radiation therapy treatment sessions to verify target position and enable the safe use of conformal high-dose irradiation (54). Adaptive radiotherapy (ART) is an approach to correct for morphological changes in patient's anatomy, such as tumor and normal tissue variations as a result of treatment. *Wong et al.* showed that tumor volume during RT could change and replanning may be mandatory when needed (31).

4. Outcomes

In series, clinical outcomes depend on a large variety of factors, including the proportion of patients treated for recurrent disease, histologic grade, tumor extent, and adjuvant therapy. In addition, the expertise of the surgical team likely influences prognosis. In general, there is a clear trend toward using RT in the preoperative setting to reduce the local recurrence rate (55).

However, given the historical difficulty of enrolling patients with RPS into randomized trials, no benefit have been found in the OS. As local relapse is more prominent than mortality in patients with RPS, this finding is particularly surprising (8,14,56). Published outcomes for patients with RPS receiving RT are depicted in **Table 1**.

In 1993, *Sindelar et al.* reported a randomized prospective trial, comparing postoperative EBRT (dosage: 50–55 Gy) to intraoperative RT (dosage: 20 Gy) and postoperative EBRT (35–40 Gy) in 35 patients treated for RPS (57). At a median follow-up of 8 years, adding intraoperative RT before EBRT decreased local recurrence compared to EBRT alone (40% vs 80%). However, authors did not show differences in overall survival rates and demonstrated a substantial rate of toxicity in both arms (50%– 60%). Although authors demonstrated a benefit in local control, EBRT+/- IORT was not widely adopted. This was mainly due to the toxicity in both arms and the lack of a survival benefit. Furthermore, treating sarcoma patients with IORT is more challenging both technically and from an organisational point of view.

Many retrospective studies have evaluated the role of radiotherapy in decreasing local recurrence. In 2001, *Stoeckle et al.* reported on the French Cancer Centre Federation Sarcoma Group's cohort of patients with non-metastatic RPS (14). In that study, 94 patients (65%) underwent complete resection, and 89 patients (61%) received a median postoperative RT dose of 50 Gy. For patients who underwent a complete excision, those who received adjuvant radiation therapy were 3.4 times less at risk of developing local recurrence compared to patients who did not. The 5-year local control rates were 55% and 23% respectively (P = 0.002). Multivariate analysis of local control revealed that an absence of postoperative RT (P = 0.0002) and Grade 3 histology significantly decreased the probability of local control (P = 0.0047). More recently, in one of the largest series ever reported of surgically managed RPS patients, *Toulmonde et al.* analysed the French Cancer Centre Federation Sarcoma Group's cohort of 586 patients, most of whom received multimodality treatment. Radiotherapy was delivered in

146 patients (29%), mainly with a postoperative schedule (74%). In multivariate analysis, radiotherapy was favourably associated with local control (HR=0.5; CI95% 0.4-0.7; *P*<0.001). In a subgroup analysis, authors showed that patients with dedifferentiated liposarcoma had a better local control when treated with irradiation compared to surgery alone (HR=0.6; CI95% 0.4-0.9; *P*=0.028) (25).

Two retrospective studies analysed the impact of dose scheduling on local control of RPS patients(58,59). The first study looked at 21 patients, between 1965 and 1992, who underwent surgery and received perioperative RT with curative intent at the Fox Chase Cancer Centre and the University of Pennsylvania (Philadelphia). The majority of patients had microscopically or macroscopically positive margins. The dose ranged from 36.0 Gy to 61.2 Gy (median:50.4 Gy) and authors showed that the local control was higher in patients who received greater than 55.2 Gy (58). The second study, from the Princess Margaret Hospital (Toronto, Ontario, Canada), reported outcomes on 104 patients with RPS who were treated between 1975 and 1988 (59). Forty-five patients (43%) underwent macroscopic total resection and 36 of 45 patients (80%) received postoperative RT. The 5-year and 10-year locoregional control rates were 50% and 18% respectively. The median time to local failure was 103 months for patients who received doses greater than 35 Gy but only 60 months for those with lower dose RT. Patients who did not received RT had a median time of 30 months until local failure (59).

Gieschen et al. published on 37 RPS patients who received 45–50.4 Gy preoperatively using EBRT and showed that complete resection was achieved in 78% of the cases (60). More recently, the Scandinavian Sarcoma Group analysed a cohort of 97 patients, 42 of whom received radiotherapy (cite). Among them, a majority underwent postoperative radiotherapy (88%). RT was significantly associated with improved local control resulting in a 5-year LRFS of 77% compared to 39% without RT ($P = 0.001$). Furthermore, 5-year OS was 71% in the RT group compared to 52% with surgery alone ($P = 0.019$) (61). In a recent systematic review of

preoperative irradiation for RPS, *Cheng et al.* reported the results of 15 articles with 464 patients and showed that patients treated with preoperative radiotherapy experienced a median 5-year LC rate and OS of 75% and 58%, respectively (62). As a comparison, a median OS of 33 to 49 months was reported among patients who underwent surgery alone, and the recurrence-free survival rate dropped to only 23% (28). Recently, two studies were published using a propensity score-matched cohort in order to control biases inherent in the use of perioperative irradiation. *Ecker et al.* utilized the US national Cancer Database (NCDB) for patients treated for retroperitoneal liposarcoma by surgery alone or the combination of neo-adjuvant radiotherapy (NRT) and surgery. After identification of the co-variables associated with OS using Cox regression model, authors matched 173 patients treated with surgery alone and 174 patients treated with NRT before surgery by propensity scores and showed an improvement in OS (HR: 1.54; CI 95=1.01-2.36 P = 0.046) (63). *Nussbaum et al.* also used the NCDB in the same timeframe for all RPS treated with preoperative or postoperative radiotherapy and/or surgery. Two case-control propensity scores-matched datasets were created; one for patients who received preoperative irradiation (N=563) compared to those who had surgery alone (N=1126) and another for patients who received postoperative irradiation (N=2196) compared to those who had surgery alone (N=2196). In this research, which was the largest propensity score-matched study on this topic, authors showed that both preoperative radiotherapy (HR: 0.70 CI 95=1.01-2.36 <0.0001) and postoperative radiotherapy (HR: 0.78; CI 95=1.01-2.36 P <0.0001) improved OS when compared to surgery alone (64).

5. Treatment complications

Multiple studies have characterized treatment toxicities related to irradiation (nausea, vomiting, diarrhea, small bowel obstruction neuropathy, hydronephrosis, vaginal fistula) in patients with RPS. In a recent systematic review, *Cheng et al.* reported treatment toxicity within the literature (18.8% Grade 1, 10.2% Grade 2, 16,3% Grade 3, 0.7% Grade 4) (62). Among all toxicities, GI

toxicity is the most widely studied. *Gilbeau et al.* described their experience with 45 patients treated with postoperative RT (40–60 Gy). Three patients experienced grade 3-4 GI toxicity and one patient died from intestinal bleeding (65). In a series of 79 patients treated with irradiation with curative or palliative intent, *Catton et al.* reported acute gastrointestinal toxicity in 27% of the patients (59). *Zlotecki et al.* published their experience with 40 patients treated with pre- or postoperative irradiation. There was significantly more acute grade 1–2 enteritis in postoperative settings compared to preoperative settings (P = 0.0098). Another study from *Pezner et al.* reported acute and late GI toxicity of postoperative irradiation occurring in 33 patients; 26 (79%) patients developed grade 1 to 2 acute GI toxicity and 3 (10%) patients developed grade 3 or 4 (49). Moreover, 5 (15%) of patients developed late GI side effects. When postoperative and preoperative schedules were compared, *Ballo et al.* showed that all patients who developed clinically significant radiation-related toxicities had received postoperative irradiation (45). Patients who receive preoperative RT likely have a modest increased risk of delayed wound healing, depending on the RT dose-fractionation schedule. The acute toxicity of RT is related primarily to irradiating a large volume of the small bowel and is likely to be less pronounced with preoperative RT compared to postoperative RT. This is because the tumor displaces much of the small bowel outside of the field targeted during RT if preoperative RT is employed. Preoperative RT most likely is associated with the lowest risk of small bowel injury, because a smaller volume of bowel is irradiated and there are likely to be fewer adhesions at the time of treatment compared with postoperative RT. If tumors are particularly large, which is the case in most patients, bowel bag dose constraints are exceeded. *Mak et al.* evaluated dose constraints for preoperative irradiation of RPS and showed that V_{30Gy} was predictive of acute GI toxicity (66).

Kidneys are also dose-limiting organs for radiotherapy to upper abdominal cancers. Data evaluating the kidney injury after RPS irradiation is lacking (67). As aggressive surgery with

nephrectomy is part of normal treatment for RPS, it is complicated to evaluate the potential effect of each intervention individually. Recently, a study from Massachusetts General Hospital evaluated the long-term effects of nephrectomy as part of a treatment for RPS in 54 patients. They showed that even if 56% of patients had a worsening of chronic kidney disease, no patient progressed to end stage renal disease (68). When treated with preoperative irradiation, multidisciplinary management with a surgeon is necessary as nephrectomy could be required during surgery. If it is the case, dose constraints to the contralateral kidney should be respected. If a nephrectomy is not necessary, both kidneys should be spared and it is necessary to evaluate renal function carefully prior to RT.

6. Prognostic factors and specific nomogram

Histologic subtype are seemingly important predictors of prognosis. Compared to other histologic subtypes, outcomes are more favourable for well-differentiated LPSs (WDLPS) as it lacks metastatic potential although the risk of Local Recurrence (LR) persists over time after surgical resection. Leïomysarcoma (LMS) is very aggressive and has strong metastatic potential, with a 5-year distant metastasis rate of > 50%, but isolated LRs are rare (13,25). Finally, dedifferentiated LPS could relapse as in both a local or distant manner (13,22,25,69). In a study performed by *Lewis et al.* patients with LPS had a significantly lower local control rate compared with other patients (HR=2.6 CI95=1.5-4.6 P = 0.01). In addition to histologic subtype, tumor size, grade, and completeness of surgical resection influences LR risk (56). A study performed by Stoeckle et al. revealed that incomplete resection (P = 0.0005) and grade 3 histology (P = 0.0017) adversely impacted survival (14). *Gronchi et al.* reported their experience with 167 patients and showed that only histologic grade (P = 0.0183) impacted overall survival. In another study, *Singer et al.* analysed 83 patients who underwent surgery alone or combined with irradiation and/or chemotherapy between 1970 and 1994. Multivariate analysis revealed that intermediate-grade histology (P = 0.009) or high-grade histology (P =

0.008), macroscopic residual disease (P = 0.001) were all associated with decreased overall survival (8).

For clinicians, evaluating patient's prognosis is an important issue and is necessary for adapting the overall course of treatment. In recent years, newer tools for prognosis prediction, such as nomograms, have been applied in many forms of cancer (70). For STS, the group from Memorial Sloan Kettering Cancer Center (MSKCC), New York, United States validated the first nomogram combining 5 prognostic factors to predict 12-year sarcoma specific survival rates (71). The nomogram computes 2 separate predictions: one for patients with low-grade tumors and the other for patients with high-grade tumors. Although, this nomogram underwent various external validations, proving its reliability, the predictions seem to be weaker in patients with RPS (72). Furthermore, prognostic tools specifically for RPS have been proven to have better stratification ability and have predicted prognosis far better than the MSKCC in their respective subsets of patients. Available nomograms for RPS are detailed in Table 3 (10,69,73,74). It is noteworthy that OS was the only outcome in two of four nomograms, whereas disease-free survival and OS were predicted in one nomogram study. Finally, the most recently published nomogram evaluated disease specific death, local recurrence, and distant metastasis endpoints (10). Some of the variability noted in the predicted outcomes of the RPS nomograms were likely due to a combination of a better understanding of this unique site and variation in surgical strategies over the times reflected in the individual studies. All 4 nomograms take into consideration tumor histology as a covariate, but the number of histological categories is different between normograms. Nomograms conducted by *Gronchi et al.* and *Tan et al.* integrated 7 histological subtypes, whereas *Anaya et al.* adopted a more limited 3-subtype classification (WDLPS vs dedifferentiated LPS vs other) and Ardoino et al. used 5 pathology subtypes (10,69,73,74). Tumor size is also considered in all nomograms. When used as a dichotomous variable, tumor size higher than a specified cut-off is consistently

associated with worse prognosis. In contrast, when used as continuous variable, this trend is reversed for tumor sizes > 30 cm (69). One could argue that tumors reaching that size without symptomatology could demonstrate a more indolent behavior. This was confirmed when tumor sized was used as categorical variable with three groups. In the nomogram by *Tan et al.,* greater dimensions were associated with lower risk of distant metastasis compared with intermediate dimensions (10).

Tumor grade is another well-established prognostic factor in patients with RPS (13). Fédération National des Centre de Lutte Contre le Cancer grading was the standard measurement used in two nomograms (14). However, the nomogram by *Tan et al.* distinguishes "low-grade" and "high-grade" LMS and in the nomogram of *Anaya et al.*, grading was not selected as prognostic variable (10,73).

External validation is key component of the prediction capacity of nomograms. However, to date, only the nomograms by *Gronchi et al.* have been externally validated (69,75). Thus, for a patient with primary RPS, nomograms from *Gronchi et al.* are able to predict both OS and DFS (69). The nomograms from *Tan et al.* are able to specifically predict distant metastasis and locale relapse risk. Although, the use of RT was a covariable used for prediction of disease specific survival and distant metastasis, it was not considered as a predictor for local recurrence (10).

7. Conclusions and treatment guidelines

Complete surgical resection of RPS remains the mainstay of treatment as it provides the most significant impact on local control and survival. To date, no randomized control trials have been able to elucidate the efficacy of EBRT and in turn, it is not considered standard practice of care in patients suffering from RPS. Using advanced irradiation techniques such as IG-IMRT or protontherapy could increase the therapeutic ratio by sparing OAR and permitting dose escalation to high-risk target volumes. Until results of the ongoing EORTC randomized trial

(Clinical Trials identifier: NCT01344018) are able to provide further evidence for the role of radiotherapy in the treatment of RPS, patients who receive RT should be selectively chosen based on prognosis. Additionally, treatment plans should be managed in centres having a high expertise in sarcomas and modern techniques of RT. Moreover, closer collaboration between radiation oncologists and surgeons is needed. Finally, the use of recently validated multi-institutional nomograms could help clinicians to make decisions leading to better clinical and functional outcomes for patients.

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Table 1. Published outcomes of patients receiving radiotherapy as a part of RPS treatment

Authors	Number	Median Follow-up (months)	Margin R0/R1 (%)	% EBRT		Local recurrence rate	Survival rates	Negative Prognostic factors
				PRE OP	POST OP			
Stoeckle et al. 2001 (14)	145	47	63% R0	0%	63%	5-yr LC=52%	5-yr OS=46%	High grade Absence of RT
Gilbeau et al. 2002 (65)	45	53	96	0%	100%	5-yr LC= 40%	5-yr OS=60%	Incomplete resection
Youssef et al. 2002 (76)	60	36	45	0%	100%	5-yr LC= 71%	5-Y OS= 56%	Positive surgical margin
Van Dalen et al. 2007 (77)	115	122	55	0%	16%	NR	5-yr OS=39%	Positive surgical margin High Grade

Gieschen et al. 2001 (60)	37	38	84	100% +/- IORT	0%	5-yr LC = 59%	5-yr OS = 50%	Use of IORT
Jones et al. 2002 (78)	55	16	NR	76%	0%	NR	2-yr OS = 88%	NR
Donahue et al. 2010 (79)	55 High Grade	68	82	56%	44%	NR	5-yr DSS = 47%	Non-responders to neo-adjuvant irradiation
Pawlik et al. 2006 (80)	64	40	84	78% +/- BCT	0%	5-yr LRFS = 60%	5-yr OS = 61%	NR
White et al. 2007 (81)	38	57	58	93%	0%	5-yr LRFS = 80%	5-yr OS = 74%	NR
Zlotecki et al. 2005 (46)	40	34	85	37%	63%	5-yr LC = 78% (R0/R1)	5-yr OS = 69% (R0/R1)	Positive surgical margin Tumor Size
Ballo et al. 2007 (45)	83	47	52	60%	40%	10-yr LC = 51%	10-yr DSS= 44%	Positive surgical margin High Grade

								Recurrent tumor
Feng et al. 2007 (82)	85	24	54	65%	25%	5-yr LC= 51%	5-yr DSS= 34%	Positive surgical margin High Grade Male gender
Gronchi et al. 2009 (83)	288	58	89	30.6%		5-yr-LR= 28-48% (Depending on the treatment period)	5-yr OS = 51-60%	Histology Grade RT Period of treatment
Bonvalot et al. 2009 (26)	382	37	93	14%	8%	5-yr LR = 22%	5-yr OS = 64%	Grade
Le Pechoux et al. 2013 (47)	110		98	0	44%	5-yr LRFS = 47-60%	5-yr OS = 71-77%	
Keung et al. 2014 (84)	119 DDLPS	74	80	10%	11%	5-yr LRFS=15%	5-yr OS = 42%	Grade Resection margin Multifocality

								Tumor integrity
Toulmonde et al. 2014 (25)	511	78	76	8%	18%	5-yr LRFS=46%	5-yr OS = 66%	Size Histology Grade Resection margin No. Of resected organs
Gronchi et al. 2015 (85)	377	44	96	18%	13%	5-yr LR=24%	5-yr OS = 64%	Size Grade Resection margin
Smith et al. 2015 (86)	362	26	96	5.5%	2.8%	3-yr LRFS : 98% WDLPS 57% DDLPS 80% LMS	3-yr DSS = 81%	Grade Histology Resection margin
Tan et al. 2016 (10)	632	90	90	4%	4%	5-yr = 39%	5-yrR DSS = 69%	Size Histology Resection margin No. Of resected organs

								RT
Gronchi et al. 2016 (13)	1007	58	95	20%	9%	5-yr LR =26% 10-yr LR =35%	5-yr OS = 67% 10-yr OS = 46%	Size Histology Grade Resection margin multifocality
Ecker et al. 2016 (63)	347 LPS	52	83	50%	0%		5-yr OS = 63%	Neo-adjuvant RT

BCT : Brachytherapy ; DDLPS : Dedifferentiated liposarcoma ; DSS : Disease-specific survival ; EBRT : External beam radiotherapy ; IORT : Intra-operative radiotherapy; LC : Local control; LMS : Leyiomyosarcoma; LPS : Liposarcoma; LR : Local-relapse; LRFS : Local-relapse free survival ; OS : Overall Survival ; RPS: Retroperitoneal sarcoma ; WDLPS : Well-differentiated liposarcoma

Table 2. Published Gastro-intestinal (GI) toxicity of irradiation for RPS

Authors	Number	Radiotherapy timing	Dose	Technique	Acute GI	Late GI	Notes
Zlotecki et al. 2005 (46)	25	preoperative		3DCRT	36% Gr1-2		More peri-operative complications with postoperative RT
	15	postoperative			80% Gr1-2		
Pezner et al. 2011 (87)	33	Postoperative	60 G-yr	3DCRT +/- IORT	80% Gr1-2 10% Gr3-4	15% Gr3-4	
Gilbeau et al. 2002 (65)	45	Postoperative	Median 50.4 Gy	3DCRT+/IORT	Upper GI : 42% Gr2 2% GR3 Lower GI : 30% Gr2 5% Gr4	24% Gr1-2 2% Gr 3 2% Gr4	
Le Pechoux et al. 2013 (47)	110	Postoperative	Median 50 Gy	3DCRT	23% Gr1-2	19 % Gr 1-2 1 Gr3	

Ballo et al. 2007 (45)	50	Preoperative	50	3DCRT+/IORT	0 %	All patients with GI toxicity except one received > 60 Gy
	33	Postoperative	55		15 % GI toxicity	
Bossi et al. 2007 (42)	18	Preoperative	50	IMRT	11% Gr3 (2/18)	

3DCRT : 3D conformal radiotherapy ; IMRT : Intensity modulated radiotherapy; IORT : Intra-operative radiotherapy;

Table 3 : Comparaison between MSKCC general nomogram (Kattan et al.) and four specific RPS nomograms.

Authors	Predicted outcomes	Prognostic factors into the model							Internal/external validation
		Histology (No of categories)	Size	Grade	Surgical resection margin	Age	RT	Other	
Kattan et al. 2002 (71) N (=2163) 1982-2000	DSS (12 -years)	7	<5 cm 5-10 cm >10 cm			yes		Site (6 categories) Depth (superficial, deep)	YES/YES
Anayra et al. 2010 (73) (N=343) 1996-2006	OS (Median, 3 and 5 - years)	3	<15cm >15cm		Complete Vs Incomplete	>65 Vs <65		Multifocality Primary vs localy recurrent	YES/NO
Ardoino et al. 2010 (74) (N=192)	OS (5 and 10 - years)	5	Continuous	FNCLCC	Complete Vs Incomplete	YES			YES/NO

1985-2007								
Gronchi et al. 2013 (69) (N=523) 1999-2009	OS (7 - 7 years)		Continuous	FNCLCC	Complete Vs Incomplete	YES		Multifocality	YES/YES
	DSS (7 - 7 years)		Continuous	FNCLCC				Multifocality	
Tan et al. 2016 (10) (N=632) 1982-2010	3-yr, 5-yr, and 10-yr DSD	7	<10 cm 10-20 cm >20 cm		R0/R1 Vs R2		YES/NO	No of resected organs	YES/NO
	3-yr, 5-yr, and 10-yr LR rate				R0 vs R1	>65 Vs <65		No of resected organs Location Vascular resection	
	3-yr, 5-yr, and 10-yr DR rate						YES/NO	Vascular resection No of resected organs	

DSS : Disease-specific survival ; DR : Distant relapse ; LR : Local relapse ; OS : Overall Survival; RPS: Retroperitoneal sarcoma ; WDLPS : Well-differentiated liposarcoma

Efficacy and safety of perioperative helical tomotherapy of retroperitoneal and pelvic sarcoma

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Résumé :

Actuellement, la place de la radiothérapie dans le traitement des sarcomes rétropéritonéaux reste débattue. De nombreuses études dosimétriques suggèrent que la radiothérapie conformationnelle avec modulation d'intensité hélicoïdale permet d'améliorer la couverture du volume cible tout en épargnant les organes à risque, ceci comparativement avec la radiothérapie 3D. Notre étude a pour but d'évaluer les conséquences cliniques de l'irradiation en Tomotherapy® des sarcomes rétropéritonéaux et pelviens.

Entre Août 2008 et Janvier 2017, 49 patients ont été traités par Tomotherapy® avant ou après une chirurgie d'exérèse. Nous avons évalué le taux de survie sans progression locale (SSPL), de survie sans maladie (SSM), et de survie globale (SG). De même, nous avons évalué la toxicité aiguë et tardive.

Avec un suivi médian de 39 mois, nous avons pu mettre en évidence que le caractère récurrent de la maladie ainsi que le grade étaient des facteurs de SSPL et SSM, alors que le timing de la radiothérapie n'était pas un facteur pronostic. La toxicité était acceptable avec 31% de patients présentant une diarrhée grade 2 et une patiente présentant une diarrhée grade 3.

En conclusion, l'irradiation peri-opératoire des sarcomes rétropéritonéaux en Tomotherapy ® est faisable et permet d'obtenir un taux de contrôle local proche de ceux décrits dans la littérature. La toxicité digestive reste acceptable et moins importante lorsque l'irradiation est pré-opératoire.

Efficacy and safety of perioperative helical tomotherapy of retroperitoneal and pelvic sarcoma

Abstract

Purpose: Currently there is no consensus on the use of adjuvant radiotherapy (RT) in retroperitoneal and abdominal sarcoma. Dosimetric studies suggest enhanced target coverage and improved sparing of non-target normal tissue with Helical Tomotherapy (HT) compared to that of conventional three-dimensional conformal photon therapy (3D-RT). We analyzed clinical outcomes in patients with localized RPS treated with postoperative HT.

Methods and Materials: Between August 2008 and January 2017, 49 patients were treated with perioperative HT for RPS. Local-free progression (LFPS), disease-free progression (DFPS), and overall survivals (OS) were determined from radiation treatment using the Kaplan–Meier method. Toxicity was reported following the Common Terminology Criteria for Adverse Events v4.0.

Results: With a median follow up of 39 months (range: 2-104 months) five patients died, two patients were alive with active disease, and 39 were alive without evidence of progressive disease. The 36-months LFPS, DFPS, and OS were 88.9 %, 73.7 %, and 88.3% respectively. Locally recurrent disease and grade were significantly associated with decreased LFPS and DFPS. The timing of irradiation (pre- vs postoperative) was not a predictive factor of local control. Grade 2 diarrhea occurred in 7 patients (31%), and one patient experienced grade 3 diarrhea requiring intravenous hydration in hospitalization. No Grade 4-5 toxicities were observed.

Conclusions: Perioperative HT for localized RPS was shown to be feasible with good clinical results in terms of medium-term LFS, DFS and OS. There is a relatively moderate rate of acute toxicity with postoperative HT but more than in preoperative series of IMRT. Preoperative radiotherapy should be reasonably preferred when possible.

Keywords: radiotherapy; retroperitoneal sarcoma; IMRT; helicoidal tomotherapy

Introduction:

Soft tissues sarcomas (STS) are infrequent malignant tumors that develop from mesenchymal tissue and account for approximately 1% of all cancers. Retroperitoneal and pelvic sarcomas (RPS) make up approximately 15% of STS (1). Patients are often diagnosed at later stages of the disease with subsequent large tumors infiltrating intra-abdominal organs. Primary therapy for RPS is gross total surgical resection while, if possible, sparing adjacent viscera not invaded by the tumor. Due to the large size of tumors and the anatomic location, microscopically positive margins are frequent, resulting in loco-regional recurrences (2). The long term survival of patients is dependent on the aggressive surgical management, which remains the key treatment of RPS(3). As there are a few fascia in the retroperitoneal space, compartmental resection should involve resection of contiguous organs such as the kidney or adrenal gland, pancreas, spleen, and colon (4). Local failure is the leading cause of RPS patient mortality. Even with gross total resection, the subsequent local recurrence rates ranged from 40-70% and the 5- and 10-year survival rates were 50% and 25%, respectively (5–7).

There exists controversy over the role of radiotherapy (RT) in the treatment of RPS (8). RT is often used as an adjuvant therapy due to the high local recurrence rate although there exists no randomized trial data suggesting that postoperative radiation is superior to stand alone surgery. Those who support RT use for the treatment of RPS argue that treatment is associated with a significant improvement in local control, resulting in a substantial improvement in overall survival (OS), compared with surgery alone (9–11). Nevertheless, combining surgery and RT increases the risk of treatment-related complications due to the irradiation dose to non-target radiosensitive organs such as the bowel, liver, and kidneys.

Delivering an effective radiation dose to the tumor and minimizing doses to at-risk organ is the major challenge faced by radiation oncologists. Over the past decade, technical advances

have improved tumor targeting and conformal RT delivery. Dosimetric studies suggest enhanced target coverage and improved sparing of normal tissue with intensity-modulated RT (IMRT) compared to that of conventional three-dimensional conformal photon therapy (3D-RT) (12–14). Clinical experience is always a crucial component in the evaluation of any new technology in radiation therapy and helical tomotherapy (HT) is not an exception. In the early implementation stages, the attention was focused on retrospective comparison of treatment plans in search of clinical scenarios where HT was able to offer a significant improvement due to its specific technological design (15). Moreover, image-guided radiation therapy (IGRT) available on HT, thanks to on-board megavoltage computed tomography (MVCT), allows daily patient setup verification and repositioning (16). Thus, we decided to undertake a retrospective evaluation of perioperative HT in RPS patients.

Materials and methods:

Patients:

A retrospective review of patients treated with HT as a component of multimodality treatment of RPS was performed. Between August 2008 and January 2017, 56 RPS patients were treated with HT. Forty-nine (87.5%) had surgery as a part of treatment. The diagnosis of RPS was established by histologic and immunochemical analysis, with or without cytogenetic analysis. Pathologists specializing in sarcoma reviewed centrally all pathologic specimens. The local extent of disease was evaluated by computed tomography (CT), and/or magnetic resonance imaging (MRI), dependent on histologic subtype. Distant metastasis evaluation included a chest CT.

Treatment

Patient cases were discussed in a multidisciplinary meeting. All patients were initially treated with compartmental surgery. All patients underwent computed tomography (CT)-based simulation (General Electric™ OPTIMA 580 RT) in the supine position with vacuum cushions

for immobilization. Serial, non-contrasted CT images were obtained from midthorax to midfemur, and these images were transferred to the treatment-planning system (Tomotherapy planning systems; Accuray Incorporated, Sunnyvale CA) for CT-based treatment planning software program. When patients were treated preoperatively, the gross tumor volume (GTV) was contoured as all gross visible tumor and MRI images were often matched to the planning CT images. The clinical target volume (CTV) was defined as 5-mm expansion and with edited reduction at bone, bowel bag, liver, and contralateral kidney. When patients were treated postoperatively, CTV was defined as ither the tumor bed (exclusively or as boost) or the whole retroperitoneum. A 5-mm isotropic margin was added to obtain the planning target volume (PTV). The median radiation dose was 50.4 Gy (range: 50-70 Gy) in 28 fractions (25-38 fractions), and the median radiation dose for the boost was 12.5 Gy (6-16 Gy). Radiation was delivered once daily via Tomotherapy Hi-art or Tomotherapy HD (Accuray Incorporated, Sunnyvale CA) with 6-MV photons. All patients underwent daily MVCT for setup imaging.

Follow-up and observed outcomes

During radiation treatments, all patients underwent a weekly medical examination and toxicity level was recorded. Follow-up care included a medical history and physical examination, CT scan and/or MRI imaging. The first follow-up visit was planned 6 weeks after completion of radiotherapy and every subsequent 3 months for 1 year. Thereafter, follow-up visits ranged from 4 to 6 months, according to physician discretion.

Statistical analysis

Local failure was scored as an event if a treated lesion increased by 20%, on the basis of the Response Evaluation Criteria In Solid Tumors criteria (RECIST) (18), or if local failure was confirmed pathologically. Metastatic progression was considered if a new lesion appeared in a solid organ. Variables used for local control (LC) and disease-free progression (DFS) analysis included: initial surgery location, resection accuracy, RT fractionation schedule, age at

treatment time, gender, tumor grade, pathology, irradiated volume. Toxicity was graded according to the Common Terminology Criteria for Adverse Events version 4.0.

LC, DFS, and OS survival rates were determined from radiation treatment using the Kaplan–Meier method. Disease-progression-free was defined as the absence of any progression (local, distant, or death). Log-rank analysis was used for group comparisons and the p-values were reported. Statistical difference was considered significant when P values was < 0.05. Clinically pertinent variables, and indicators, which were found to be significant during the univariate analysis, were subsequently analyzed using a multivariate Cox proportional-hazards regression model. We report the Hazard Ratios (HR) and associated 95% confidence intervals (CI). All calculations were performed using *R* software program (ver. 3.0.2 http://cran.r-project. org/).

Results:

Patient's characteristics

Among the 49 patients, 40 (81.6%) were treated for primary disease and 9 (18.4%) for locally recurrent disease. Of the 9 patients with locally recurrent disease, all had previously undergone surgical resection, and only one had previously undergone RT. None of the patients treated for recurrent disease had distant metastasis. Ten patients (20.4 %) received pre-operative radiotherapy and 39 patients (79.6%) received postoperative radiotherapy. The median age at presentation was 61 years (range, 37–79 years), and the median follow-up was 39 months (range, 2 to 106 months). Additional patient tumor and treatment characteristics are listed in Table 1 and 2.

Local control and survival

Median patient follow-up was 39 months (range: 2-106 months) during which five patients died – two of metastasis progression, one of local progression and two without evidence of active disease. Six patients were alive with active metastatic disease, and 38 were alive without evidence of progressive disease. Of the 49 patients, 6 experienced local recurrence (12.2%) in

the retroperitoneum as their initial site of failure and had a new surgical resection.

The 3- and 5-year LC rates were 82.4% (71.1-95.4%) and 73.2% (55.7-96.3%) respectively (Figure 1a). The 3- and 5-year DFS rates were 69.9% (56.6-86.3%), and 57.6% (40.3-82.2%), respectively (Figure 1b). The 3- and 5-year OS rates were 90.9% (82.6-99.9%) and 86.5% (75.6-99.0%), respectively (Figure 1c).

Risk factors of LC and DFS:

We used univariate log-rank analysis to find risk factors associated with LC and DFS (Figure 2-3, Table 3). Locally recurrent disease and tumor grade were both associated with a decrease in LC and DFS.

When we looked at these associations using multivariate analysis, adjusting for a number of clinically relevant risk factors (age, resection margin, pathologic size) only locally recurrent disease at the time of irradiation remained significantly associated with a decreased LC (HR=9.5; 95% CI: 1.8-49.2; P= 0.007) . Both grade 3 (HR=9.7; 95% CI: 1.9-47.8; P= 0.005) and locally recurrent disease at the time of irradiation (HR=5.5; 95% CI: 1.8-19.1; P= 0.003) were associated with decreased DFS.

Toxicity

The compliance to treatment was good, with only one patient that did not adhere to the entire treatment. Eighteen patients (36%) and ten (20%) experienced grade 1 and grade 2 nausea respectively. One patient experienced grade 3 nausea with weight loss and required nutritional complement. All cases of symptomatic nausea were successfully managed with prescribed antiemetic medication. Lower GI toxic effects included Grade 1, 2, and 3 diarrhea in 14 patients (29%), 15 patients (31%), and one patient, respectively. The latter patient required intravenous hydration whilst hospitalized. No patients experienced grade 4 upper or lower acute GI toxicity. The median weight modification during treatment was - 1.3% (range: -11.6%, +4.8%) of initial body mass. Four patients had grade 1 weight loss (between 5-10% of body mass) and one

patient had grade 2 weight loss (>10% of the initial body mass). All patients that experienced weight loss greater than 5% received postoperative irradiation.

At the time of analysis, 43 patients (87.8%) had more than six months of follow-up, and were considered evaluable for late toxicity. Two patients experienced significant late toxicity, which was likely attributed to RT. One patient developed grade 3 small bowel obstruction requiring hospitalization and parenteral nutrition, whilst the other developed a grade 3 jejunum stenosis requiring surgical exploration. No Grade 4-5 toxicities were observed.

Discussion:

Although, the standard treatment of RPS is gross total surgical resection with negative margins, perioperative radiotherapy has demonstrated to delay local recurrence. However, this benefit does not translate to an improvement in OS . This is due to a high likelihood of local recurrence (37-82% at 5 years), resulting from high rates of positive microscopic margins, ranging from 50 to 80% (2, 4, 7, 11). Indeed, adjuvant RT may constitute a valuable treatment option to improve local control.

Despite the publications of many uncontrolled non-randomized trials, the role of radiotherapy is still uncertain, due to important variation in RT schedules such as delivery method (external beam or brachytherapy), timing (preoperative, intraoperative, or postoperative), and technique (3D-RT, IMRT, protontherapy) (18–23). The Scandinavian Sarcoma Group analyzed a cohort of 97 patients; 42 received radiotherapy, which the majority receive postoperatively (88%). RT was significantly associated with improved local control resulting in a 5-year LRFS of 77% compared to 39% without (p=0.001). Furthermore, 5-year OS was 71% in the RT group compared to 52% with surgery alone (p=0.019) (24). In one of the largest series ever reported of surgical managed RPS patients, Toulmonde *et al.* analyzed French Cancer Center Federation Sarcoma Group's cohort of 586 patients, most of them received multimodality treatment. Radiotherapy was delivered to 146 patients (29%), mainly with a postoperative schedule (74%).

In multivariate analysis, radiotherapy was favorably associated with local control (HR=0.5; 0.4-0.7; p=<0.001), especially for patients diagnosed with dedifferentiated liposarcoma (HR=0.6; 0.4-0.9; p=0.028) (25). Because of the heterogeneity of sarcoma subtypes and the small number of patients in our study, we could not show the prognostic value of histology in patients receiving peri-operative radiotherapy. Recently, two studies were published using propensity score-matched cohorts in order to control inherent biases in the use of perioperative irradiation. In the first study, *Ecker et al.* queried the US National Cancer DataBase (NCDB) for patients treated for retroperitoneal liposarcoma by surgery alone or neo-adjuvant radiotherapy (NRT) and surgery. After identification of the co-variables associated with OS using Cox regression model, authors matched 173 patients treated with surgery alone and 174 patients treated with NRT before surgery by propensity scores and showed an improvement in OS (HR: 1.54; *P*=0.046) (26). *Nussbaum et al.* also used the NCDB in the same timeframe for all RPS treated with preoperative or postoperative radiotherapy and/or surgery. Two case-control propensity scores-matched datasets were created; one for patients who received preoperative irradiation (N=563) compared to those who had surgery alone (N=1126) and another one for patients who received postoperative irradiation (N=2196) compared to those who had surgery alone (N=2196). In this study, authors showed that both preoperative radiotherapy (HR: 0.70; *P*<0.0001) and postoperative radiotherapy (HR: 0.78; *P*<0.0001) improved OS when compared to surgery alone (27). With median follow-up of approximately 40 months, 5-year OS rates was 86.5% (75.6-99.0%) in our study. Nevertheless, during the timeframe of all these studies, IMRT was not a common technique and HT had not reached a tipping point yet.

To date, few studies have assessed whether modern techniques of radiotherapy such as IMRT improve outcomes for patients with RPS while minimizing acute and late term complications. IMRT can be delivered in multiple ways such as step and shoot (SAS), sliding window, volumetric modulated arc therapy (VMAT) and HT. In terms of comparisons between 3D-RT

and IMRT plans, all IMRT studies have reported significant improved quality, even if HT seemingly provids better sparing of organs-at-risk (OAR) (12, 28). One could argue that VMAT may reduced treatment time and additionally spares OAR as well (29). Nonetheless, in postoperative situations, these arguments have a limited value because of the size and the complexity of the irradiated volume (30). To the best of our knowledge, this series provides the first clinical analysis evaluating the efficacy and toxicity of perioperative HT in patients with RPS. Koshy *et al*. reported about the dosimetric advantage of static IMRT compared to 3D-RT in treating RPS (14). Tzeng *et al*. used preoperative IMRT to assess dose escalation to the high-risk volume considered as the posterior retroperitoneal surgical margin (57.5 Gy in 25 fractions of 2.3 Gy), while delivering 45 Gy in 25 fractions to the tumor(19). The 2-year LC rate was 80% with an acceptable treatment morbidity rate (19). In another approach, Bossi *et a*l. evaluated a new strategy of preoperative RT for RPS by delivering 50 Gy to a volume limited to the contact area between the liposarcoma and the posterior abdominal wall(13). Among 18 patients, 6 were treated with IMRT and 12 with 3D-RT. The dosimetric comparison showed a better sparing of the ipsilateral and contralateral kidney with IMRT compared to 3D-RT. After a median of follow-up of 27 months, 2 patients presented with a local relapse (12). Further dose escalation with IMRT up to 50 Gy and simultaneous boost up to 56 Gy is currently being tested in an ongoing phase I/II clinical trial. Interim analysis after 27 patients found a 3-year LC rate of 72%. Four patients developed severe acute toxicity and 9 patients presented severe postoperative complication (31). Pezner *et al*. compared SAS and HT dosimetry treatment plans for 7 patients who received adjuvant RT for RPS. In terms of dose distribution, authors showed that the volume of ipsilateral kidney receiving more than 15 Gy was higher in SAS group compared to HT (15).

The main acute side effect reported was diarrhea. More recently, *El Bared et al.* assessed the outcome and toxicities of patients with RSTS treated with preoperative radiotherapy using

IMRT. Among the 21 patients, 6 were treated with HT. With median follow-up of 22 months, the local free-recurrence survival was 41%. However, most of patients (62%) were irradiated for a locally recurrent disease (32).

Finally, combination of surgery and HT resulted in promising 5-year LC, DFS and OS rates. We did not show any difference in outcomes for patient treated with preoperative compared with patients treated with postoperative irradiation. Except for acute side-effects that we routinely assessed, our analysis has some limitations because of the retrospective nature of the study and the small number of patients with relatively short follow-up times, thus limiting the ability to draw definitive conclusions. Nevertheless, it represents a homogenous population of patients treated with aggressive surgery with contiguous organ resection and perioperative radiation therapy using HT. Therefore, this study adds valuable information to the small existing body of evidence for this approach in RPS.

Due to the numerous healthy tissues surrounding the tumor or included in the surgical bed, radiation therapy remains at risk of side-effects and complications, mainly if higher dose is required because of R1 resection. In the current series, patients treated with preoperative irradiation had less acute GI side effects than patients treated with postoperative irradiation. This is mainly due to the displacement of intestinal tract from treatment fields by the tumor and the absence of intestinal flanges after surgery. In our series, the median PTV volume was 2263 cm^3 and fourteen patients were treated on their whole retroperitoneal volume. Despite these characteristics, there was a relatively moderate rate of acute toxicity with postoperative HT but more than in preoperative cases of IMRT. It emphasizes that preoperative radiotherapy should be reasonably preferred as it spared normal neighboring viscera, thus significantly reducing the risk of possible radiation therapy related complications.

To improve tolerance of radiotherapy, options can be discussed such as the use of protons and the preoperative schedule. *Swanson et al.* performed a preoperative, dosimetric study

comparing 3D conformal proton RT (3D-CPT), 3D-RT and IMRT, in 8 patients with retroperitoneal or intra-abdominal sarcomas. Target volume coverage was comparable. The conformity index was better for IMRT than 3D-CPT (p = 0.052). Compared to 3D-CRT, both IMRT (P<0.0001) and 3D-CPT (P=0.0004) conformity indexes were significantly improved. 3D-CPT plans delivered dosages to the lowest bowel, contralateral kidney and liver (28). Recently, *Kelly and al.* compared outcomes of patients treated with surgery alone to patients treated with surgery and peri-operative radiotherapy with advanced modalities such as IMRT or protontherapy. In the peri-operative arm, the majority of patients in the RT arm received preoperative IMRT as a modality of treatment and 22% of patients received IMRT and protons. Authors concluded that adding radiotherapy with modern techniques improved local recurrence-free survival (5-year LRFS 91% in the RT arm vs 63% in the surgery alone arm, p=0.024) without improvement of disease specific survival. The postoperative morbidity was higher in the RT arm but the adverse events mostly fell in the categories of grade 1-2 (33). Finally, *DeLaney et al.* published the results of phase 1 study for preoperative dose escalation onto the high risk of relapse volume for RPS patients, using intensity modulated protontherapy (IMPT). Authors treated eleven patients with increasing IMPT dose levels up to 63 GyE without acute dose limiting toxicities. With a median follow-up of 18 months, all patients who underwent resection after irradiation were free of local relapse (34).

Conclusions:

Although this study demonstrated that perioperative HT for RPS is feasible, the acute GI toxicity remains important, appearing mainly in patients treated with postoperative schedule. Thus, preoperative radiotherapy with advanced techniques such as HT should be preferred. Until results of future randomized trials refines the role of radiotherapy, patients who benefit from radiotherapy should be highly selected and should be managed in centers having a high expertise in sarcoma and modern techniques of radiotherapy.

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		Number (%)
Gender		
	Male	29 (59)
	Female	20 (41)
Age at treatment, median (range)		61 years (37-80)
Presentation		
	Primary	40 (82)
	Recurrent	9 (18)
Tumor location		
	Retroperitoneal	38 (78)
	Pelvic	11 (22)
Histology		
Liposarcoma		37 (76)
	DDLPS	22 (45)
	WDLPS	13 (27)
	Other LPS	2 (4)
Leïomyosarcoma		9 (18)
Other		3 (6)
Grade		
	1	16 (33)
	2	19 (39)
	3	14 (28)
Tumor size in cm, median (range)		13 (3-50)

Table 1: clinical and pathological characteristics of 49 patients who underwent surgery and perioperative helical tomotherapy (HT) for Retroperitoneal Sarcoma (RPS)

		Number (%)
Resection margin		
	R0	18 (37)
	R1	24 (49)
	R2	7 (15)
Contiguous organ resection		
	Yes	34 (69)
	No	15 (31)
Number of organs resected without cholecystectomy		
	1	11 (22)
	2	8 (16)
	3	5 (10)
	>3	10 (20)
Type of organ		
	Nephrectomy	27 (55)
	Hemicolectomy	20 (41)
	Partial pancreatectomy	9 (18)
	Splenectomy	6 (12)
	Vessel resection	7 (14)
	Adnexectomy	6 (12)
	Small bowel resection	5 (10)
	Muscle resection	5 (10)
	Partial hepatectomy	2
	Gastrectomy	1
Radiotherapy schedule		
	Preoperative	10 (20)
	Postoperative	39 (80)
Volume PTV in mL, median (range)		2052 (279-5371)
Dose PTV in Gy, median (range)		50 (50-60)
Dose Boost		12.5 (6-16) Gy
Type of boost		
	Sequential	1
	Simultaneous	7

Table 2: Treatment characteristics of 49 patients who underwent surgery and perioperative helical tomotherapy (HT) for Retroperitoneal and pelvic sarcoma (RPS)

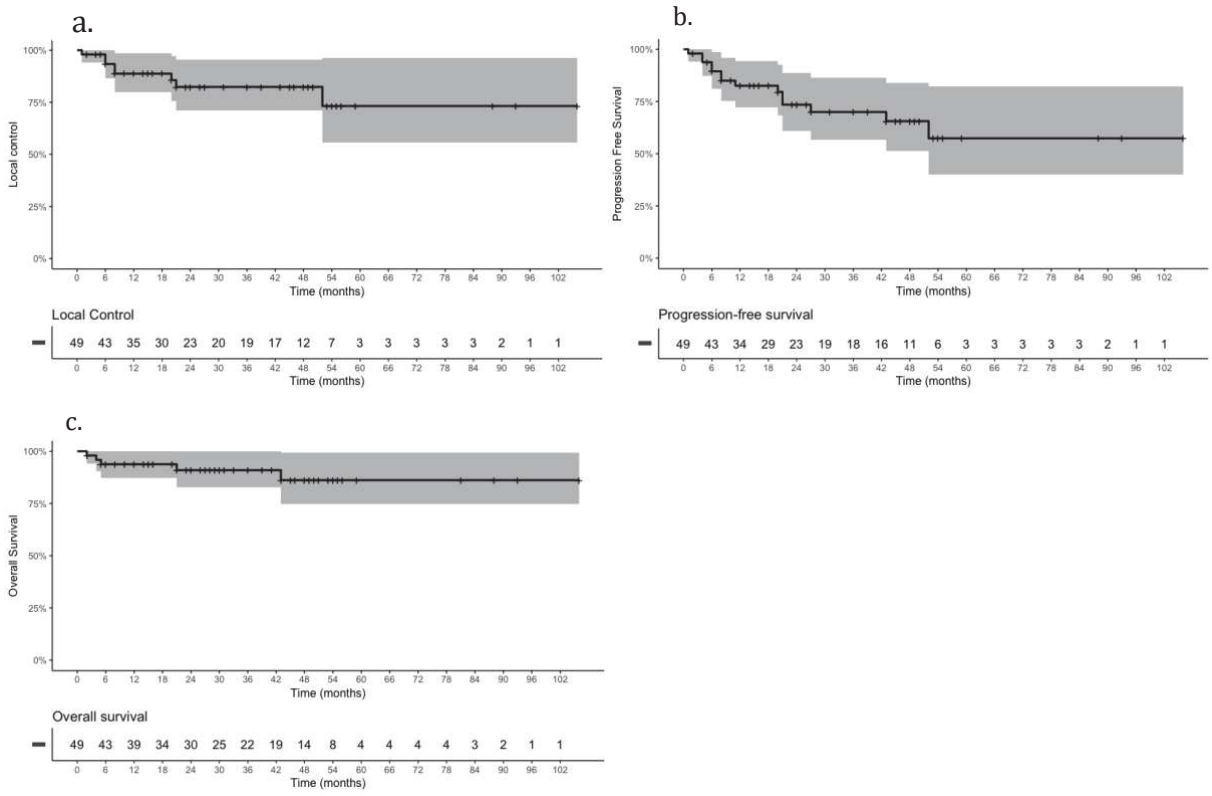

Figure 1: Kaplan-Meier survival curve from time to completion of irradiation for patients with retroperitoneal sarcoma (Grey zone represents the 95% Confidence Interval). 1a. Local control rate; 1b. Progression Free Survival ; 1c. Overall survival ;

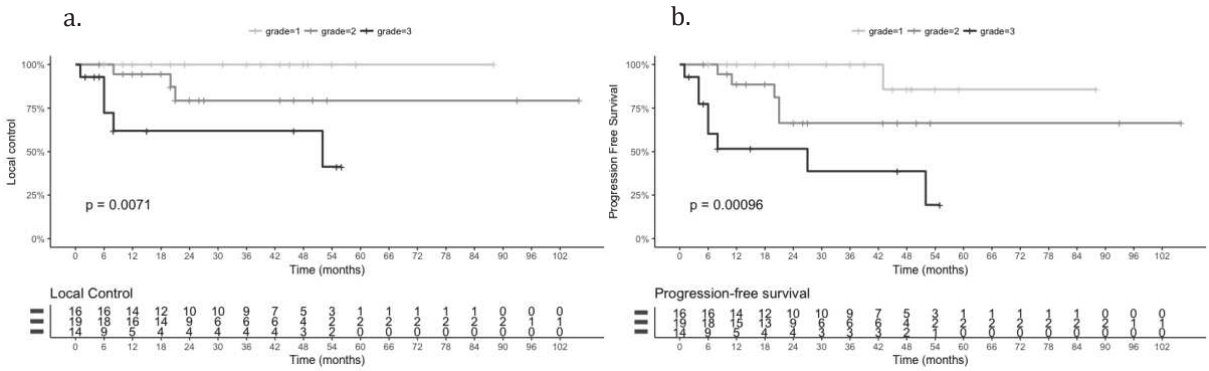

Figure 2: Comparison of Kaplan-Meier survival curve from time to completion of irradiation for patients with retroperitoneal sarcoma according to grade. 2a. Local control; 2b: Progression Free Survival

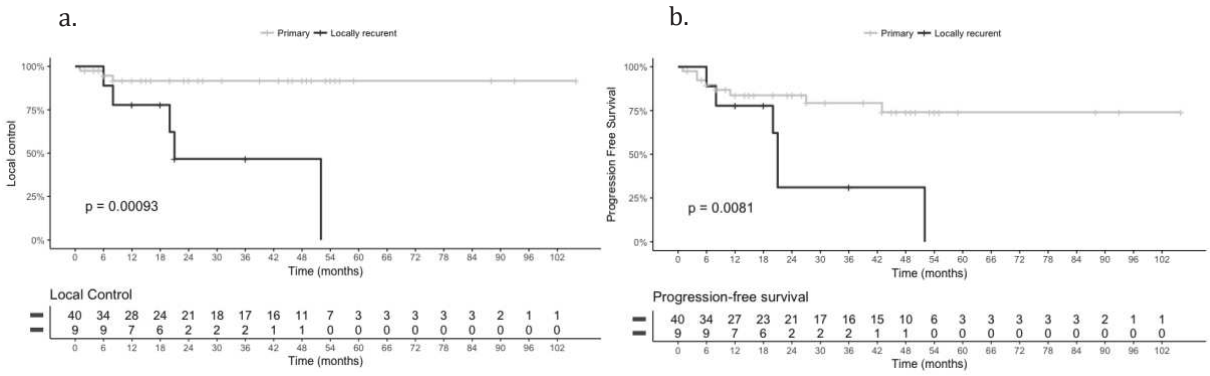

Figure 3: Comparison of Kaplan-Meier survival curve from time to completion of irradiation for patients with retroperitoneal sarcoma according to presentation. 3a. Local control; 3b. Progression Free Survival

Variable		3y-LC	P-value	3y-DFS	P-value
Whole population		82.4%		69.6%	
Locally recurrent					
	Yes	46.7%	0.00093	31.1%	0.0081
	No	91.7%		79,3%	
Grade					
	G1	100%	0.0071	100%	0.00096
	G2	79.3%		66.4%	
	G3	41.3%		38.7%	

Table 3: Results of univariate analysis for local control and disease-free survival

Helical IMRT for Retroperitoneal Soft Tissue Sarcoma: what is the best dosimetric predictor of acute small bowel toxicity?

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Résumé :

La radiothérapie peri-opératoire des sarcomes rétropéritonéaux et pelviens peut être à l'origine d'une mauvaise tolérance digestive, avec principalement des diarrhées à la phase aiguë. Les contraintes dosimétriques précédemment définies dans la littérature ont du mal à s'appliquer compte tenu des volumes d'irradiations importants. Ce travail a pour but d'évaluer les facteurs dosimétriques impliqués dans l'apparition de diarrhée après Tomotherapy®.

Nous avons extrait les histogrammes dose-volume de 56 patients traités par radiothérapie conformationnelle avec modulation d'intensité hélicoïdale pour un sarcome rétropéritonéal ou pelvien. A partir du dossier médical des patients nous avons extrait le grade des diarrhées selon l'échelle CTCAE V4.

Bien que chez 63% des patients, le volume recevant 45 Gy (V_{45Gy}) était supérieur à 195 ml, seulement 31% présentaient une diarrhée de grade ≥ 2. Ainsi, le V_{45Gy} n'était pas corrélé à l'apparition de diarrhée alors le V_{35Gy} était le facteur dosimétrique le plus prédictif de l'apparition de diarrhée de grade ≥ 2 (Se= 90%, Sp=73%, AUC=0.785).

En conclusion, de toutes les variables dosimétriques testées, le V_{35Gy} était le facteur dosimétrique le plus pertinent pour décrire la toxicité digestive aiguë.

Abstract

Background: Because of the absence level 1 evidence, radiotherapy for retroperitoneal sarcoma (RPS) is not the standard of care. Irradiation may be difficult and not well tolerated because of the large volume of irradiated small bowel. Diarrhea is the main acute side effect, induced by the dose to the small-bowel, frequently requiring a treatment modification. Aim of this study was to analyze the differences between the irradiated small-bowel volumes and the occurrence of acute diarrhea during RPS irradiation.

Patients and Methods: 56 patients treated with neo-adjuvant, adjuvant, or definitive radiotherapy with helical tomotherapy (HT) for RPS. Based on the dose-volume histograms, the small-bowel volumes receiving doses of 5 to 50 Gy (V5, V10 ...V50) were calculated and correlated to the occurrence of diarrhea grade ≥ 2.

Results: Whereas 63% of patients had $V_{45Gy} > 195cc$, 15 patients developed grade 2 diarrhea (30%) and only two patients developed grade 3 diarrhea. V_{45Gy} was not correlated to the acute diarrhea. The strongest validity concerning the risk of developing a grade ≥ 2 acute diarrhea was observed at a dose level of 35 Gy (V_{35Gy}) with a small-bowel volume of 650 cc (Se= 90%, Sp=73%, AUC=0.785).

Conclusions: Of all the dosimetric parameters tested, V_{35Gy} was the best predictor of acute small bowel toxicity in patients treated for RPS. This study underscores the need of considering V_{35Gy} in future treatment planning processes.

Introduction :

Among soft tissue sarcomas, retroperitoneal sarcomas (RPS) are approximately 15% (1). Surgical “en bloc” resection of RPS and adjacent infiltrated organs remains to be the initial key treatment of RPS. The major challenge for surgeons is to spare organs that are not invaded by the tumor. There is still a debate concerning the role and the timing of radiotherapy in the management of RPS. To date, randomized controlled trials comparing surgery alone with combined surgery and perioperative RT have failed to clarify the actual role of radiotherapy because of poor accrual (2) but data from uncontrolled non-randomized trials are available (3–7) and trends to show that RT is associated with a significant improvement in local control. However, acute postoperative RT-induced small bowel toxicity ranges from 30% to 80% of patients (7,8). In opposite to post-operative time, in pre-operative radiotherapy time, sarcoma push small bowel away from the target volume, leading to a decrease incidence of acute enteritis (9). Mainly, diarrhea is the symptom of RT induced small-bowel mucositis and appears 1 to 2 weeks after the start of RT. It often requires treatment and sometimes causes a therapy interruption resulting in a reduced efficacy (10) . Emami et al. estimated doses with a 5% or 50% risk at 5 years (TD5/5 and TD50/5, respectively) for late small-bowel toxicities but did not offer estimations to predict acute toxicities (11). Some studies described a statistical significant relationship between irradiated small-bowel volume and treatment induced diarrhea. However, most of these studies included patients with concurrent chemotherapy and/or used 3-dimensional conformal RT as radiotherapy technique (12–14) and most the studies concerned pelvic cancer such as rectal or cervix carcinomas (15). Although many studies were interested of the development of intensity modulated radiotherapy (IMRT) for RPS (16–18), data about which parameters of the dose-volume histogram (DVH) have to be optimized for large abdominal volume such as

RPS are missing. The aim of this study was to report the acute small bowel toxicity and analyze the DVH parameters associated with acute diarrhea following helical IMRT for RPS.

Method and materials:

Patient selection:

A retrospective review of patients treated with HT as a component of multimodality treatment of RPS was performed after that approval was obtained from the appropriate institutional review board. Between August 2008 and January 2017, 56 patients were treated with either pre- or post-operative HT for RPS. The diagnosis of RPS was established by histologic and immunochemical analysis, with or without cytogenetics analysis. Pathologists specializing in sarcoma reviewed centrally all pathologic specimens. The local extent of disease was evaluated by computed tomography (CT), and/or magnetic resonance imaging (MRI) depending on histologic subtype. Distant metastasis evaluation included a chest CT.

Treatment

Patient cases were discussed in a multidisciplinary meeting. All patients underwent computed tomography (CT)-based simulation (General Electric™ OPTIMA 580 RT) in the supine position with vacuum cushions for immobilization if necessary. Serial, non-contrasted CT images were obtained from midthorax to midfemur, and these images were transferred to the treatment-planning system (Tomotherapy planning systems; Accuray Incorporated, Sunnyvale CA) for CT-based treatment planning software program. When patients were treated preoperatively, the gross tumor volume (GTV) was contoured as all gross visible tumor and MRI images were often fused to the planning CT images. The clinical target volume was defined as 5 mm expansion and with edited reduction at bone, bowel bag, liver and contralateral kidney. When patients were treated postoperatively CTV was defined either the tumor bed (exclusively or as boost) or the whole retroperitoneum. A 5 mm isotropic margin was added to obtain the planning target volume (PTV). The median radiation dose

was 50.4 Gy (range: 50-70 Gy) in 28 fractions (25-38 fractions), and the median radiation dose for the boost was 12.5 Gy (6-16 Gy). Treatment plans were optimized using Tomotherapy (Accuray, Sunnyvale, CA) treatment-planning systems. Radiation was administered once daily via Tomotherapy Hi-art or Tomotherapy HD (Accuray Incorporated, Sunnyvale CA) with 6-MV photons. All patients underwent daily MVCT for setup imaging. Characteristics of the treatment are summarized in table 2.

Treatment plan analysis:

To report dosimetric data, all the 56 patient's dosimetric charts were reviewed. Small bowel volume contour, which was assigned as the entire abdominal cavity, was assessed and eventually modified to fit the contour guidelines. The doses that were effectively delivered to new contoured small bowel structure were calculated using Artiview ® (Aquilab, Lille, FRANCE) after importing the tomotherapy data. Then each point of the small bowel DVH curve every 100 mGy was extracted.

Toxicity scoring and statistics:

All patients underwent a weekly medical examination during radiation treatments and toxicity was recorded prospectively in Mosaiq software (Elekta medical system). We choose diarrhea as a measure of acute small bowel toxicity and the degree of diarrhea was classified according to the NCI Common Toxicity Criteria (CTC) scale, version 4.0.

Statistical test used were the $\chi 2$ or the Fischer exact test to compare categorical variables and Mann-Whitney U-test was used to identify significant dosimetric differences between patients that presented diarrhea $\geq$ grade 2 and those who did not. The optimal cut-off value related to acute diarrhea $\geq$ grade 2 as determined using Receiving Operating Curve (ROC) with Youden's index. Univariate and multivariate logistic regression was considered statistically different when P values was < 0.05. All calculations were performed using R software program (ver. 3.0.2 http://cran.r-project. org/).

Results :

Patients characteristics:

Between August 2008 and January 2017, 56 patients were treated with HT for RPS. The median age at presentation was 62 years (range, 30–80 years), and the median follow-up was 41 months (range, 2 to 104 months). Among the 56 patients, 44 (66%) were treated for primary disease and 12 (34%) for locally recurrent disease. Of the 12 patients with locally recurrent disease, all had previously undergone surgical resection. Nine patients received neo-adjuvant and three patients received adjuvant radiotherapy. Small bowel toxic effects included Grade 1 diarrhea in 16 patients (29%), grade 2 diarrhea in 15 patients (27%), and two patients (3.5%) with grade 3 diarrhea required intravenous hydration in hospitalization. No patients experienced grade 4 acute lower GI toxicity. Additional patient and tumor characteristics are listed in Table 1. The mean ± standard deviation time to onset of diarrhea grade ≥ 2 was 25 ± 9 days after the start of radiotherapy.

Analyze of clinical and dosimetric variables:

There were no correlations observed between the incidence of diarrhea grade ≥ 2 and the age, gender and number of resected organs. However, patients with preoperative/definitive radiotherapy had twice less diarrhea ≥ grade 2 (17 %) than patients with postoperative radiotherapy (36%) but this difference did not reach statistical significance (P=0.1). The mean V_{25} and V_{45Gy} for the whole population was respectively 1453 cc and 375 cc (Figure 1). The analysis of irradiated small bowel volume showed that the volume receiving 35 Gy (V_{35Gy}) was a statistically significant predictor for acute diarrhea ≥ grade 2 (P = 0.007). Meanwhile, V_{45Gy} was not found to be associated with higher risks of diarrhea (Figure 2).

In logistic regression model, the best predictor of grade 2-3 diarrhea was V_{35Gy} (P = 0.02). Otherwise, V_{45Gy} was not found to be associated with higher risks of diarrhea.

Dosimetric factors of small bowel toxicity:

There were no significant relationships observed between D_{max} or D_{min} and diarrhea. The analysis of irradiated small bowel volume threshold showed that volume receiving between 20 and 40 Gy (V_{20Gy} and V_{40Gy}) was a statistically ($P<0.05$) significant predictor for acute diarrhea (Table 2). If timing of radiotherapy (Pre/definitive Vs Postoperative) was added to the multivariate model, there was no correlation found for significant parameters of V_{20Gy} ($P=0.08$) and V_{40Gy} ($p = 0.09$). However, parameters V_{25Gy} ($P=0.04$), V_{30Gy} ($P=0.03$) and V_{35Gy} ($P=0.04$) remain significant.

Determination of cut-off doses

ROC analyses were used to identify cut-off values predicting a diarrhea ≥ grade 2. For the irradiated small bowel volumes, which received a dose of 20 to 40 Gy, we observed areas under the curve (AUCs) between 0.71 and 0.78 ($p < 0.05$, Table 3). The highest AUC values were achieved for the V_{30Gy} (AUC=0.76) and the V_{35Gy} (AUC=0.78). The best cut-off point predicting a Grade 2–3 diarrhea calculated for the V_{35Gy} with a threshold-volume of the irradiated small-bowel of 650 mL (sensitivity 90%, specificity 73%, Youden-Index 0.63; Figure 3. Table 3). Nineteen of 29 patients (65%) with $V_{35Gy} > 650$ mL developed a grade 2–3 diarrhea although two of 27 patients (7%) with $V_{35Gy} \leq 650$ mL presented the same side effect ($p = 0.001$). Moreover, an irradiated small-bowel volume of 1061 mL for a dose of 30 Gy could be determined as a second cut-off value (sensitivity 90%, specificity 73%, AUC = 0.76, Youden-Index 0.63).

Discussion:

In RPS, perioperative radiotherapy is not always a standard of care because there is no randomized controlled trial supporting the use of neo-adjuvant or adjuvant radiotherapy. Moreover, the main acute toxicity of this treatment is acute radiation enteritis, mainly manifested as diarrhea that could worsen the quality of life of patients. In attempts to minimize acute and late term complications, IMRT has been investigated. Dosimetric studies

suggest an improvement of non-target normal tissue sparing with IMRT compared to that of conventional three-dimensional conformal photon therapy (3D-RT) (18–20). There are some clinical studies reporting the use of preoperative IMRT for RPS (17,21) but none of them evaluate the relation between quantitative dose-volume of irradiated small bowel and occurrence of diarrhea. In order to be able to minimize enteritis during abdominal irradiation, identification of dosimetric factors associated with it appears a major challenge. This study aims to report on the small bowel acute morbidity following HT without concomitant chemotherapy for 56 RPS treated consecutively from August 2008 to January 2017 and to analyze dosimetric factors. We showed a significant difference between the irradiated small-bowel volumes and the severity of radiation induced diarrhea. The best predictor of acute diarrhea was the area under the DVH curve between 30 Gy and 35 Gy.

In a recent study, *Mouttet-Audouard et al.* (22) analyzed the normal tissue morbidity of a prospective cohort of 61 patients treated with HT and concomitant chemotherapy for cervix cancer. With a median follow up of 40 months, authors reported that AUC data of small bowel DVH between 10 Gy and 40 Gy was significantly associated with late morbidity such as diarrhea. However, in this study, patients had a concomitant chemotherapy and a boost in brachytherapy.

Many other studies analyzed relationship between small bowel DVH and acute toxicity, but are difficult to interpret as a result of notable variation in RT schedules such as timing (preoperative or postoperative), technique (3D-CRT, IMRT), dose fractionation, endpoint (diarrhea or any lower GI toxicity) and concomitant chemotherapy. In our study, we analyzed a homogenous population with same histology (retroperitoneal sarcoma), same technique (helical IMRT), without concomitant chemotherapy. Six patients had a simultaneous integrated boost (SIB) up to 2.5 Gy per fraction. We did not find any difference in acute diarrhea between patients with moderate hypo-fractionation compared to patients with

normofractionation schedules. Indeed, moderate hypo-fractionation has a moderate impact to total dose for normal tissue with high α/β ratio. Because small bowel has different compartments such as epithelial, vascular, or mesenchymal, with a heterogeneous response to radiation, late effect of moderate hypofractionation should be assessed. In our study, 17 patients had preoperative or definitive radiotherapy and 39 patients had a postoperative radiotherapy. Acute diarrhea was lower for patients who had preoperative radiotherapy. Indeed, the tumor acts as a tissue expander, pushing normal organs away from the radiation therapy target and dose escalation to the target is safer with a decreased chance of causing GI complications compared to the postoperative setting (2,23,24).

There are other potential advantages using preoperative setting such as a more precise disease targeting because of better delineation of the Gross Tumor Volume, a decreased risk of intraperitoneal dissemination requiring a prophylactic post-operative irradiation, and a greater biological effect. It emphasizes that preoperative radiotherapy should be reasonably preferred as possible. The quantitative analysis of normal tissue effects in the clinic (QUANTEC) review summarizes the available data to update and refine the normal tissue dose/volume tolerance guidelines for small bowel. If the entire volume of peritoneal space in which the small bowel can move is delineated, the volume receiving >45 Gy should be <195 mL (15). In our cohort, most of the patients had a V_{45Gy} > 195 mL but only a few had acute small bowel toxicity. The intestinal V_{45Gy} was not significantly associated with a higher risk of diarrhea. Nevertheless, in univariate analysis, we found that the high volume receiving doses between 20 and 40 Gy was associated of high risk of diarrhea. Because of large tumours, for most of the case, bowel bag dose constraints are exceeding. *Mak et al.* evaluated dose constraints for preoperative irradiation of RPS and showed that V_{30Gy} was predictive of acute GI toxicity (25). Whereas in the study from *Mak et al.* 39% of patients received IMRT, in our series all patients were treated with external radiotherapy using IMRT with HT. Comparatively to the study from MGH, we decided to include patients with postoperative irradiation in our model and showed that even if patients with

postoperative irradiation had more diarrhea compared to those receiving preoperative radiotherapy, small bowel dosimetric parameters (V_{30Gy}-V_{35Gy}) remained to be significantly associated with diarrhea. Hence, the data in this study highlight the importance of not only considering the high dose regions when reviewing the treatments but also the mean, median or even lower delivered doses.

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		Number (percentage)
Gender		
	Male	32 (57.1 %)
	Female	24 (42.9 %)
Age at treatment in years, median (range)		62 (30-80)
Tumor size in cm, median (range)		13.5 (3-50)
Surgical treatment		
	After irradiation	10 (17.9%)
	Before irradiation	39 (69.6%)
	No surgery	7 (12.5%)
Pathology		
	Liposarcoma	41 (73.2%)
	Leiomyosarcoma	10 (17.9%)
	Other	5 (8.9%)
Grade		
	1	17 (30.4%)
	2	21 (37.5%)
	3	18 (32.1%)
Presentation		
	Primary	44 (78.6%)
	Recurent	12 (21.4%)
Dose PTV in Gy, median (range)		50 (39-64)
Volume PTV in mL, median (range)		2381(279-5371)
Chemotherapy		
	Yes	9 (16.1%)
	No	47 (83.9%)

Table 1 : clinical and treatment characteristics of 56 patients who underwent helical tomotherapy (HT) for Retroperitoneal Sarcoma (RPS)

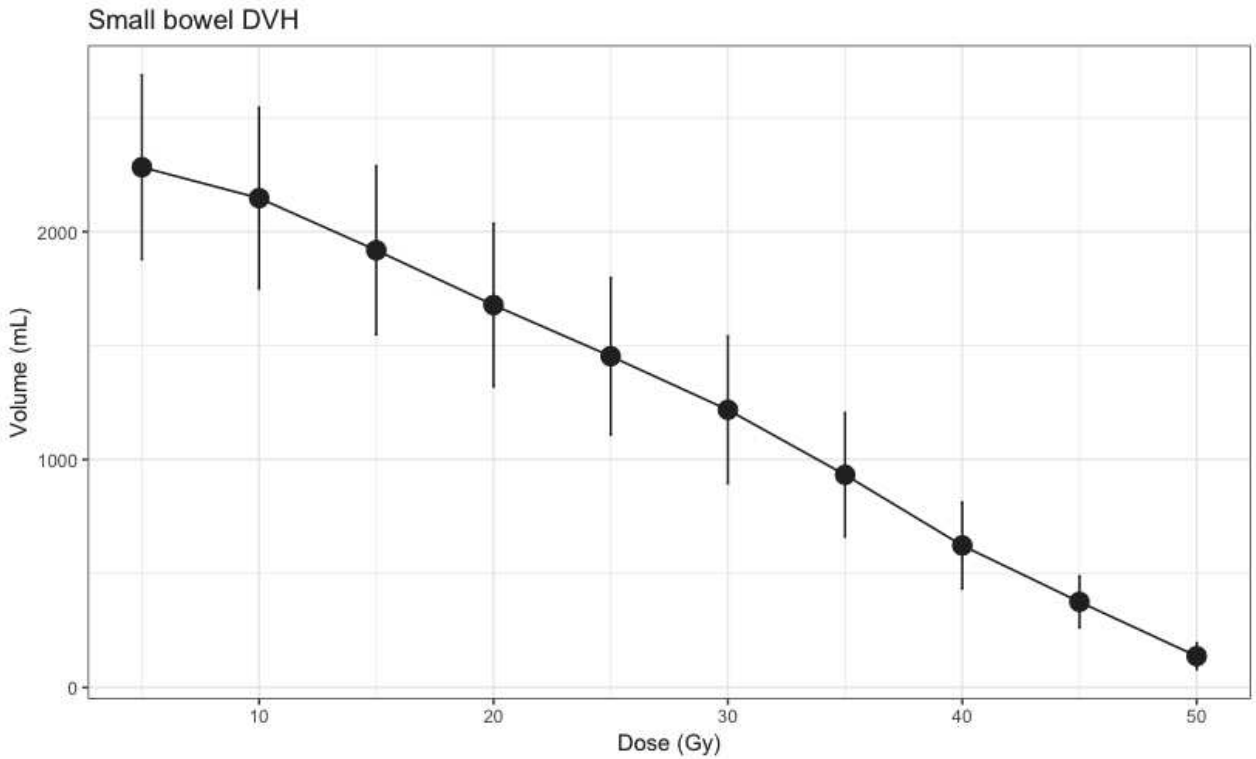

Figure 1 : Averages and 95% confidence interval of the irradiated small bowel volume receiving 5 – 50 Gy (V5-V50 Gy).

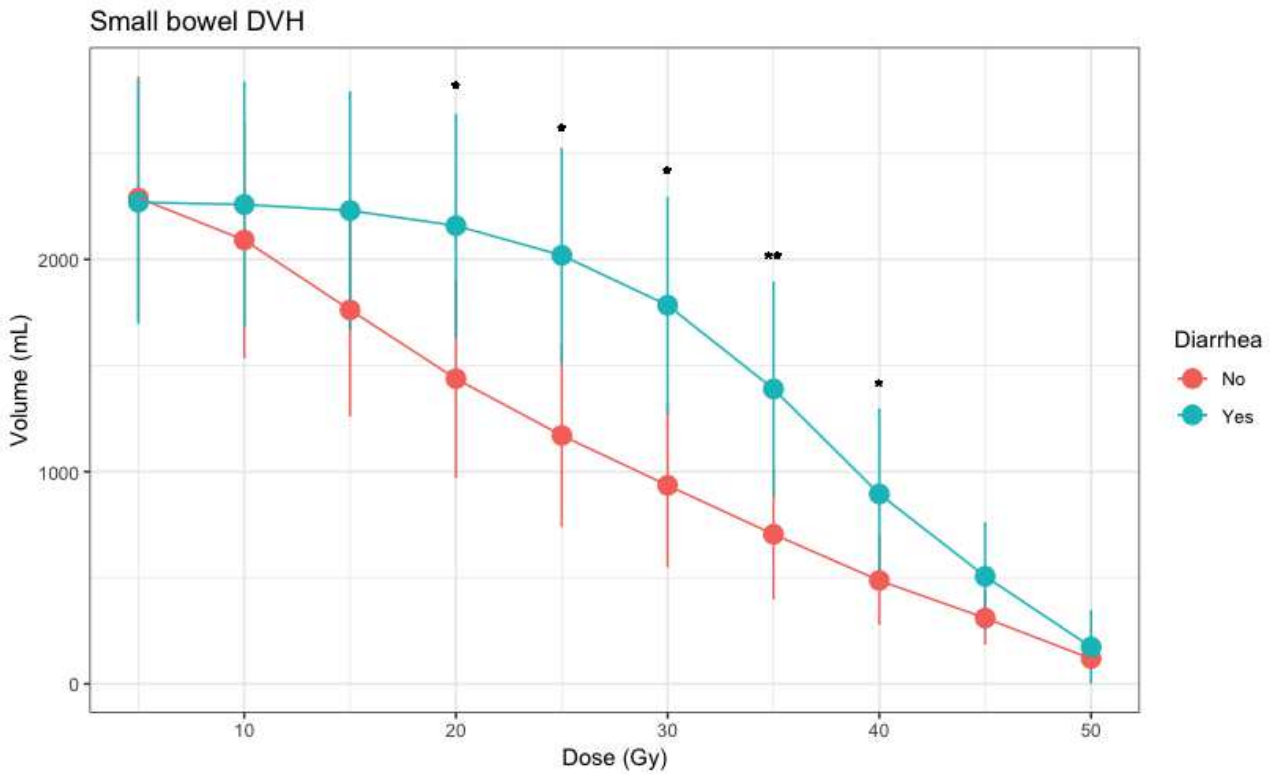

Figure 2 : Comparaison of small bowel DVH between patients with acute diarrhea ≥ Grade 2 (Yes) and patients with diarrhea < grade 2 (No). * : P<0.05; ** P<0.01

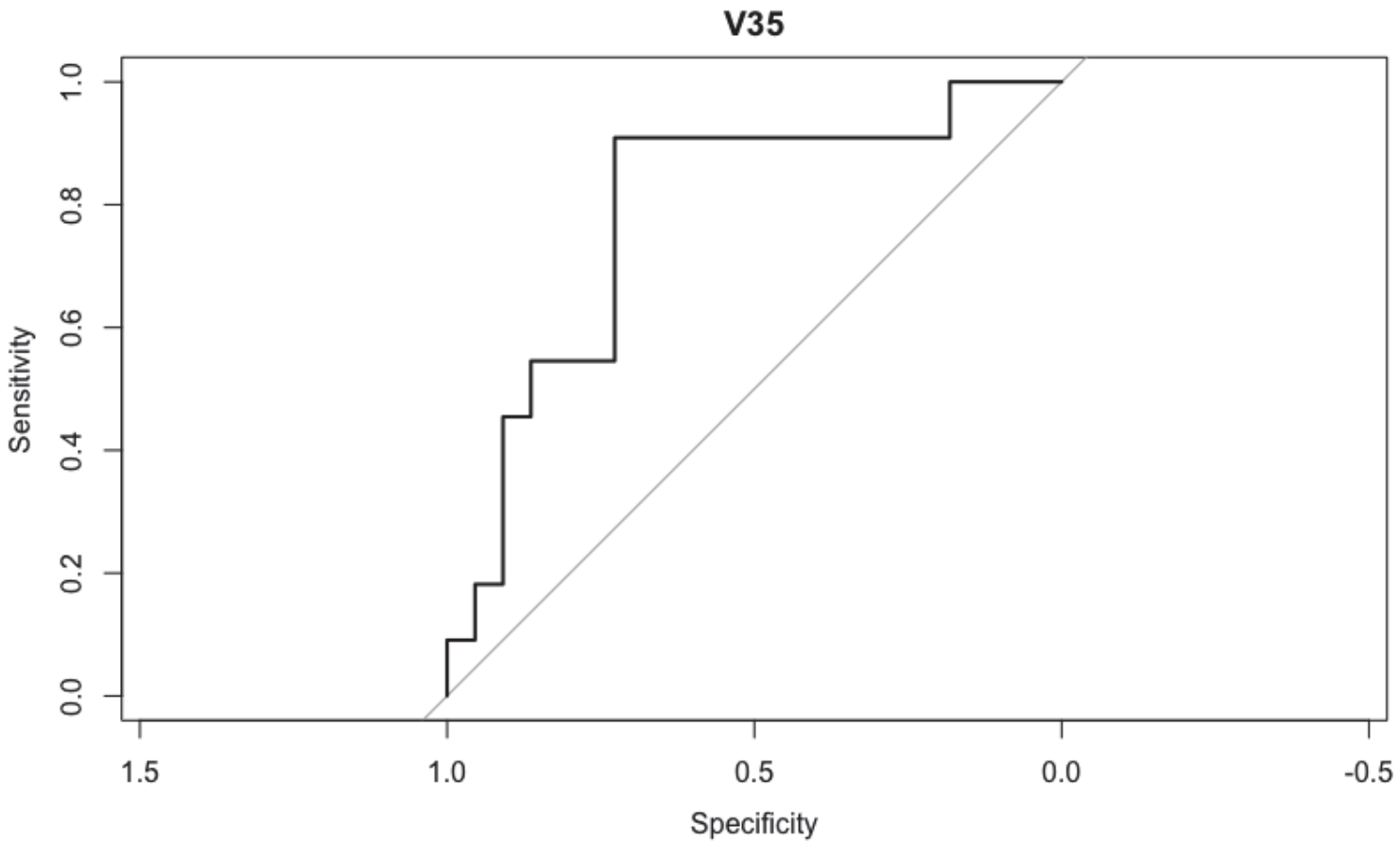

Figure 3 : ROC curve of V35Gy as a predictor of diarrhea ≥ Grade 2.

Dose	Diarrhea ≥Gr2	N	Mean (mL)	Standard deviation (mL)	P Value
	No	39	2290	1280	
V5	Yes	17	2269	847	0.595
	No	39	2092	1247	
V10	Yes	17	2259	854	0.316
	No	39	1762.	1121	
V15	Yes	17	2230	829	0.187
	No	39	1438	1040	
V20	Yes	17	2159	778	**0.043**
	No	39	1171	960	
V25	Yes	17	2019	745	**0.017**
	No	39	935	862	
V30	Yes	17	1784	752	**0.013**
	No	39	705	681	
V35	Yes	17	1390	746	**0.007**
	No	39	487	460	
V40	Yes	17	895	592	**0.02**
	No	39	310	272	
V45	Yes	17	506	372	0.06
	No	39	119	100	
V50	Yes	17	174	250	0.90

Table 2 : Association between bowel bag volume and acute gastrointestinal toxicity.

	AUC	Cut-off (mL)	Se (%)	Sp (%)	Youden index
V20	0.719	1966	82	68	0.49
V25	0.756	1747	81	72	0.54
V30	0.768	1061	90	73	**0.63**
V35	0.785	650	90	73	**0.63**
V40	0.747	407	91	68	0.57

Table 3 : Determination of optimal cut-off values after ROC-analyses.

Quantification of renal function following Helical Tomotherapy after surgery with or without nephrectomy for retroperitoneal sarcoma.

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Résumé :

La chirurgie monobloc est le traitement de référence des sarcomes rétropéritonéaux. L'exérèse des organes adjacents, particulièrement du rein, est une problématique majeure et ceci notamment lorsque les patients bénéficient d'une radiothérapie post opératoire. Peu d'études se sont intéressées aux conséquences fonctionnelles rénales à long terme chez les patients traités par exérèse chirurgicale puis radiothérapie pour un sarcome rétropéritonéal.

Nous avons recueilli les clairances de la créatinine de 27 patients traités pour un sarcome rétropéritonéal avant et après irradiation par Tomotherapy®. Puis nous avons extrait les données cliniques et dosimétriques pour chacun d'entre eux.

Avec un suivi médian de 40 mois, aucun patient n'a présenté d'insuffisance rénale terminale ou n'a eu besoin d'être dialysé. Bien que les patients avec néphrectomie avaient une fonction glomérulaire plus basse que ceux sans néphrectomie, la diminution de la fonction rénale après irradiation n'était pas plus importante quel que soit le statut rénal. De plus, lorsque nous tenions compte de l'évolution du déclin attendu de la fonction rénale en fonction de l'âge, nous n'avons pas mis en évidence de différence entre les résultats attendus et observés.

En conclusion, la radiothérapie conformationnelle avec modulation d'intensité hélicoïdale post-opératoire des sarcomes du rétropéritoine n'impacte pas la fonction rénale, même chez les patients ayant subi une néphrectomie.

Abstract:

Background: Decreasing radiation kidney damage remains to be a major challenge for patients undergoing adjuvant radiotherapy for retroperitoneal sarcomas (RPS), particularly those treated with nephrectomy. Aim of this study was to analyze long term renal function after surgery and radiotherapy for RPS.

Patients and Methods: 27 patients treated with adjuvant radiotherapy with helical tomotherapy (HT) for RPS were reviewed. Dose volume histogram (DVH), Pre- and post-radiotherapy glomerular filtration rate (GFR) were recorded for each patient.

Results: Median pre-radiotherapy GFR for the entire cohort was 81 ml/min and was significantly lower for patients who underwent nephrectomy (P=0.037). With median follow-up of 40 months (5-106), no patient experienced end stage renal disease (ESRD) or required dialysis. The GFR decreased of 10% at last follow-up compared to baseline (72 ml/min ; range : 32-90 ml/min). When accounting for the expected decline seen in GFR as a function of age, we did not show significant difference between expected and observed values.

Conclusions: Post-operative HT after surgical resection of RPS did not impact renal function, even after nephrectomy.

Introduction:

Retroperitoneal sarcoma (RPS) is rare and heterogeneous disease (1, 2). Surgical resection with curative intent remains the cornerstone of treatment for patients with RPS (3). Furthermore, the optimal extent of surgery is still a debate. Aggressive surgery with contiguous organ resection improves local control (4). However, the morbidity of such resection remains important and particularly the long term-effect of chronic kidney disease (CKD) after nephrectomy. Because loco-regional relapse remains frequent after surgery and is an important determinant of survival, adjuvant radiotherapy has been advocated in the management of RPS (5–7). However, radiation treatment is limited by the proximity of viscera such as small bowel or kidneys (8). Thus, combining surgery and RT increases the risk of treatment-related complications due to the dose to non-target radiosensitive organs such as kidneys (9). Delivering an effective radiation dose to the tumor and minimizing dose to organ at risks is the major challenge for radiation oncologists. Recent dosimetric reports suggest improved sparing of normal tissue with intensity-modulated RT (IMRT) compared to three-dimensional conformal photon therapy (3D-CRT) (10–13). Moreover, image-guided radiation therapy (IGRT) available on helical tomotherapy (HT), thanks to on-board megavoltage computed tomography (MVCT) allows daily patient setup verification and repositioning (14). However, clinical experience remains crucial for the evaluation of any new technology in radiation therapy and HT is not an exception. Because at least partial volume irradiation of the kidneys cannot be avoided in postoperative irradiation of RPS, concern exists that even IMRT could lead to renal toxicity. Indeed, many studies investigate the effect of radiotherapy on renal toxicity but a majority of patients had chemotherapy or were treated with 3D-CRT. Moreover, management of RPS could require nephrectomy in more than half of patients (2). Thus, the major challenge for radiation oncologist is to protect the remaining

kidney. Accordingly, we decided to undertake a retrospective evaluation of short and long-term renal effect of postoperative HT in RPS patients.

Method and materials:

Patient selection:

A retrospective review of patients treated with HT as a component of multimodality treatment of RPS was performed after that approval was obtained from the appropriate institutional review board. Between August 2008 and January 2017, 39 patients were treated with post-operative HT for RPS. The diagnosis of RPS was established by histologic and immunochemical analysis, with or without cytogenetics analysis. Pathologists specializing in sarcoma reviewed centrally all pathologic specimens. The local extent of disease was evaluated by computed tomography (CT), and/or magnetic resonance imaging (MRI) depending on histologic subtype. Distant metastasis evaluation included a chest CT.

Treatment

Therapeutic decisions were discussed in a multidisciplinary meeting. All patients underwent computed tomography (CT)-based simulation (General Electric™ OPTIMA 580 RT) in the supine position with vacuum cushions for immobilization if necessary. Serial, non-contrasted CT images were obtained from midthorax to midfemur, and these images were transferred to the treatment-planning system (Tomotherapy planning systems ; Accuray Incorporated, Sunnyvale CA) for CT-based treatment planning software program. The CTV was defined either the tumor bed (exclusively or as boost) or the whole retroperitoneum. A 5 mm isotropic margin was added to obtain the planning target volume (PTV). The median radiation dose was 50.4 Gy (range: 50-70 Gy) in 28 fractions (25-38 fractions), and the median radiation dose for the boost was 12.5 Gy (6-16 Gy). Treatment plans were optimized using Tomotherapy (Accuray, Sunnyvale, CA) treatment-planning systems. Radiation was administered once daily via Tomotherapy Hi-art or Tomotherapy HD (Accuray Incorporated,

Sunnyvale CA) with 6-MV photons. All patients underwent daily MVCT for setup imaging. Characteristics of the treatment are summarized in table 2.

Treatment plan analysis:

To report dosimetric data, all the patient's dosimetric charts were reviewed. The kidneys were contoured individually and were summed to derive a unique volume for dose assessment. The doses that were effectively delivered to kidneys structure were calculated using Artiview ® (Aquilab, Lille, FRANCE) after importing the tomotherapy data. Then each point of the kidneys DVH curve every 100 mGy was exported to an Excel sheet (Microsoft ®). The relative volumes of kidneys receiving a dose (VxGy) were reported in percentage.

Toxicity scoring and statistics:

All patients had documented preoperative, postoperative and pre-irradiation creatinine measurements. First follow-up visit was planned 6 weeks after completion of radiotherapy and every 3 months for 1 year. Thereafter, intervals ranged from 4 to 6 months, according to physician discretion. Moreover, patients had routinely creatinine measurements and estimated glomerular filtration rate (GFR) in ml/min/1.73m^2 was calculated using the chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Moreover, chronic kidney disease (CKD) stage 1-5 was recorded for patient. As GFR decreases as a consequence of age, expected post-irradiation GFR was estimated based on patient age as suggested by Hull et al. Statistical test used were the $\chi 2$ or the Fischer exact test to compare categorical variables and Mann-Whitney U-test for continuous variables. Statistical difference was considered significant when P values was < 0.05. All calculations were performed using R software program (ver. 3.0.2 http://cran.r-project. org/).

Results

Thirty-nine patients, identified from our database, underwent surgery and adjuvant radiotherapy as a part of the treatment of their abdominal sarcoma. Of these 39 patients, 8

patients were excluded due to the pelvic localization of their sarcoma and 4 were excluded because they had adjuvant chemotherapy. The remaining cohort of 27 patients comprised our study group. The median age was 61 years (range, 37–79) and ten patients (37%) were female. The median dose was 50 Gy (range: 50-60 Gy). Five patients had a simultaneous integrated boost (SIB) of 2.5 Gy per fraction to the macroscopic disease or high risk of relapse zone. The median PTV volume was 2381 cc (range, 279-5371 cc). No patient had pre-irradiation medical renal disease. Additional information on patient characteristics is given in Table 1. Dose volume histogram for each patient is presented in supplementary file 1.

The median pre-irradiation GFR was 81 ml/min (40-99 ml/min). Figure 1 showed that patients treated with nephrectomy had significantly lower GFR before irradiation compared to those without nephrectomy (P=0.037). With median follow-up of 40 months (5-106), no patient experienced end stage renal disease (ESRD) or required dialysis. Figure 2 displays the GFR values from the start of therapy to the longest available follow-up examination. Almost all patients had a decreased or stable calculated GFR value at the longest available follow-up point. At last follow-up, GFR approximately decreased of 10% compared to GFR before irradiation and the mean GFR at last follow-up was 72 ml/min (range: 32-90 ml/min) for the whole population. In the subset of patients with nephrectomy, the mean GFR at last follow–up was 64 ml/min (range : 32-90), a decrease of 10 % from baseline values (70 ml/min ; range 40-98 ml/min). Patients without nephrectomy also experienced a decrease of 10% at last follow-up (76 ml/min ; range : 68-90 ml/min) compared to pre-irradiation values (85 ml/min ; range 70-99) (Figure 3). The worst outcome was a reduction of 36 % and paradoxically concerned a patient without nephrectomy. Of the four patients with pre-irradiation GFR $\geq$ 90 ml/min, two maintained GFR $\geq$ 90 ml/min and two progressed to CKD stage 2 at last follow-up. Of the four patients with CKD stage 3 (GFR between 30-60 ml/min), none experienced evolution to CKD stage 4. Finally, of the 19 patients with baseline GFR between 60-90

ml/min, two progressed to CKD stage 3 and the remaining 17 patients experienced no change in CKD change (Figure 4). When accounting for the expected decline seen in GFR as a function of age, we did not show significant difference between expected and observed values for the whole population (73 ml/min vs 69 ml/min; P=0.35), neither for nephrectomy group (66 ml/min vs 63 ml/min; P=0.63), nor for patients without nephrectomy (82 ml/min vs 76 ml/min; P=0.26) (figure 5).

Dosimetric analysis showed a significantly lower mean dose to kidney for patients with nephrectomy than for patients without nephrectomy (9.5 Gy ss 16.2 Gy ; P<0.001). Moreover, all Vx parameters known to be significantly associated with kidney function impairment (V_{12Gy}, V_{20Gy}, V_{23Gy}, V_{28Gy}) were significantly lower in nephrectomy group compared to patients without nephrectomy (Figure 5). Furthermore, for patients who did not undergo nephrectomy, we noticed that ipsilateral kidney received significantly higher doses compared to contralateral (figure 5). However, using linear regression model, we could not show that GFR change was correlated with any dosimetric data (supplementary file 2).

Discussion:

The median decrease in GFR value was 10% of the pre-irradiation. In our study, with a median follow up of 40 months, none of the patients experienced ESRD or required dialysis. Moreover, patients with nephrectomy as a part of en-bloc resection did not experienced significantly GFR change compared to patients without nephrectomy.

Recently, a study from Massachusetts General Hospital (MGH) evaluates in 54 patients the long-term effects of nephrectomy as a part of treatment for RPS. They showed that even if 56% of patients had a worsening of chronic kidney disease, no patient progressed to end stage renal disease. In their series, 70 % of patients received radiotherapy, and mainly in preoperative setting. In the case of preoperative radiotherapy, surgeons and radiation oncologist may anticipate nephrectomy and radiation oncologist is less concerned about the

dose received to the kidney. In a postoperative setting, dose constraint to the kidney should carefully be respected and particularly for patients who have nephrectomy as part of en-bloc resection. Another difference between our series and MGH cohort is that we excluded patients who received chemotherapy as a part of adjuvant treatment, to avoid long-term interference between those treatments, whereas in the series from MGH, 25% of patients received chemotherapy. Thus, to the best of our knowledge, our study represents the first study assessing the renal long-term effect of postoperative IMRT with HT in a homogeneous group of patients treated for RPS.

The effect of RT on renal function was reviewed by *Emami et al.*, who made assumptions concerning the doses tolerated by the kidneys according to retrospective patient data (15). Their conclusion was that the 5% risk-dose of nephritis at 5 years is 23 Gy and the 50% risk-dose at 5 years is 28 Gy for irradiation of the whole kidney. On the basis of these data, constraints on the absorbed doses by the kidneys were defined. Because the kidney is an organ with a parallel functional structure, the assessment of the effects of partial volume irradiation is difficult.

The most recent recommendation about dose constraint to the kidney is based on QUANTEC publication (16). Authors suggested dose volume constraints for estimated risks of <5%: mean dose to kidneys <18 Gy, V_{28Gy}<20%, V_{23Gy}<30%, V_{20Gy}<32%, V_{12Gy}<55%. These recommendations are based onto 3 publications (N=80) and chemotherapeutic agents were associated in 2 of these studies (17–19). More recently, *Diavolitsis et al.* published their experience of upper abdominal irradiation of 125 patients between 1996 and 2006 (20). Twenty-three patients received a platinum agent at some point of their therapy. With a median follow-up of 2.4 years (range: 1-7.6 years), authors found a significant correlation between the decrease of creatinine clearance and mean dose to the kidney (P=0.002), V_{5Gy} (P=0.002), V_{10Gy} (P=0.024), V_{20Gy} (P=0.012) and volume of kidney receiving more than 20 Gy (P=0.002)

(20). In our series, we could not find a correlation between GFR decline and dosimetric parameters. One explanation would be that in our series, dose constraints to kidneys were carefully respected. Indeed, the median of the mean dose to kidney was 14.2 Gy (range: 1.3-18.7 Gy) in our series compared to 16.16 Gy (range: 0.18-98.72 Gy) for *Diavolitsis et al.*(20), and authors reported median 32% (range : 0-58.36 %) of kidneys receiving 20 Gy, compared to 13.6% (range : 0-32.2%) in our series. Thus, only four of the 27 patients experienced change in CKD stage. Furthermore, authors emphasize that no patient experienced severe clinical problems related to creatinine clearance modifications(20). As our series, all these studies showed modifications of creatinine clearance during time but none of them reported any clinical change such as induction of ESRD or dialysis.

Creatinine clearance may be estimated with different equations based on serum creatinine levels. First, the Cockroft-Gault formula uses Age, body mass and gender to estimate creatinine clearance. The Modification of Diet in Renal Disease (MDRD) formula is four parameters based equation using age, gender, ethnicity, and serum creatinine. As, it is not adjusted for body mass and it has been developed in patients with CKD, it underestimates GFR in patients with GFR > 60 ml/min and for overweighted patients. As the majority of our patients had creatinine clearance > 60 ml/min, we choose to use CKD-EPI formula which is more accurate for patients with creatinine clearance > 60 ml/min before treatment. *Hull et al.* also choose the CKD-EPI to evaluate the long-term effect of nephrectomy for RPS patients.

This retrospective study has several limitations. First, in order to have a homogenous cohort of patients, we restricted our population to patients receiving postoperative IMRT and without history of adjuvant chemotherapy. Thus, given its small ample size, our study may not be powered to detect clinical change affecting patients. Another limitation is that some of the patients in this series had a nephrectomy as part of surgery leading to a potential bias. Studies in patients with renal cell carcinoma showed that GFR could decrease to 18% after

nephrectomy, but progression to ESRD is rare. The recent analysis of MGH patients showed that factors contributing to a decrease in renal function after nephrectomy for RPS patients are a greater age and pre-surgery GFR. In our series, although patients with nephrectomy had significantly lower eGFR before irradiation, we did not show differences between patients who underwent nephrectomy and those who did not, perhaps a consequence of our small sample size. Another reason is probably that for patients who underwent nephrectomy, dose constraint to the remaining kidney was cautiously and strictly respected. Indeed, the mean dose and percentage of kidney volume receiving 12 to 28 Gy to remaining kidney for patient who underwent nephrectomy was significantly inferior compared to patients who did not. A third limitation of our study relates to the fact that it is retrospective. However, the impact of this factor is likely because serum creatinine was regularly measured and all patients had the relative same follow-up schedule.

In summary, although patients treated with post-operative radiotherapy for retroperitoneal sarcomas are at risk for developing kidney dysfunction, helical intensity-modulated radiotherapy could safely protect kidneys. This is more challenging for patients experiencing nephrectomy as a part of en-bloc resection and in this subset of patients, our analysis did not show detrimental GFR variation.

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Table 1 : Clinical and treatment characteristics of 27 patients who underwent surgery and postoperative helical tomotherapy (HT) for Retroperitoneal Sarcoma (RPS)

	Number (percentage)
Gender	
Male	17 (63)
Female	10 (37)
Age at treatment in years, median (range)	62 (40-80)
Comorbidities	
Hypertension	7 (26)
Diabetes	3 (11)
Tabacco use	4 (15)
Tumor size in cm, median (range)	16 (4-50)
Surgical treatment	
Margin status, R0/R1/R2	12 (44)/11 (41)/4 (15)
Nephrectomy	16 (59)
Histology	
Liposarcoma	21 (78)
Leiomyosarcoma	5 (19)
Other	2 (7)
Grade	
1	8 (30)
2	12 (44)
3	7 (26)
Presentation	
Primary	19 (70)
Recurent	8 (30)
Dose PTV in Gy, median (range)	50 (50-60)
Volume PTV in cc, median (range)	2381(279-5371)

Figure 1: Boxplot representing pre-irradiation glomerular filtration rate (GFR) according to nephrectomy status.

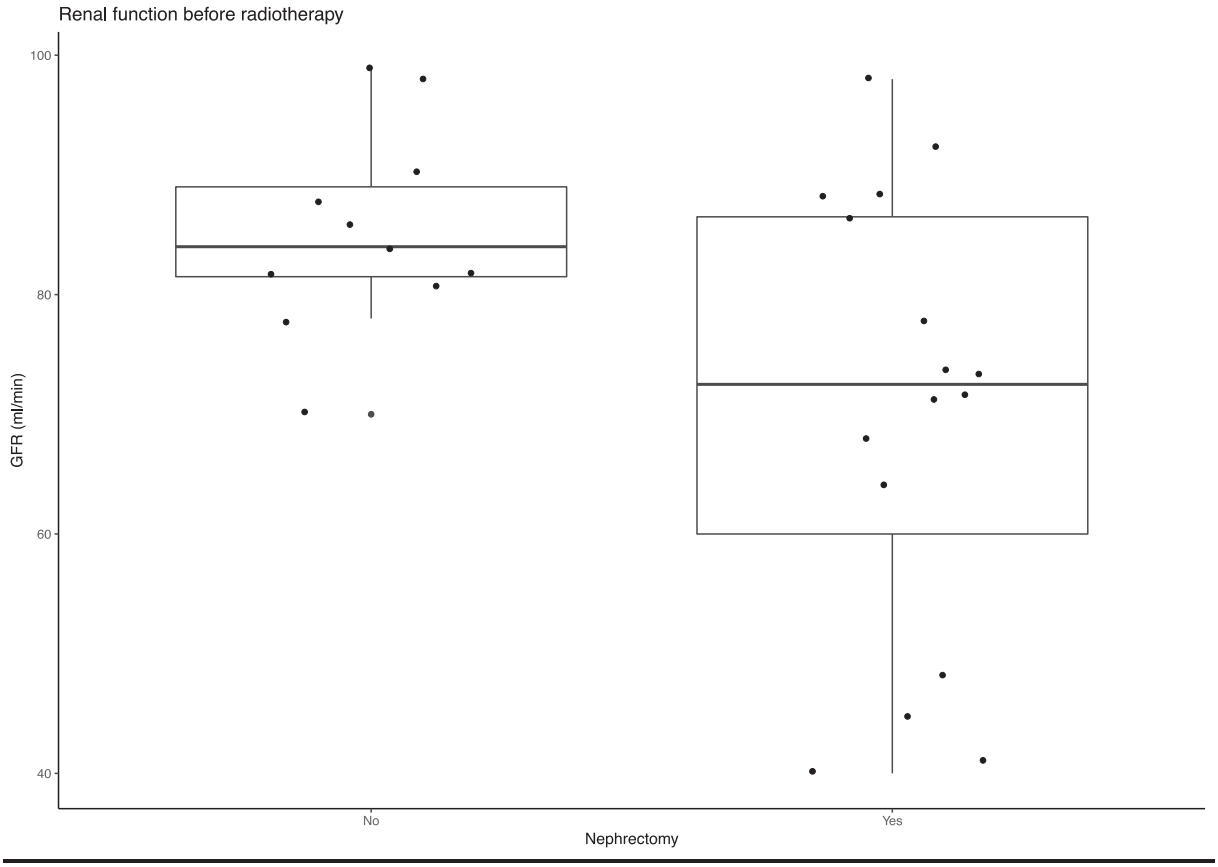


Figure 2: Evolution of glomerular filtration rate after radiotherapy according to nephrectomy status. Dashed lines represents GFR transition thresholds between different CKD stages.

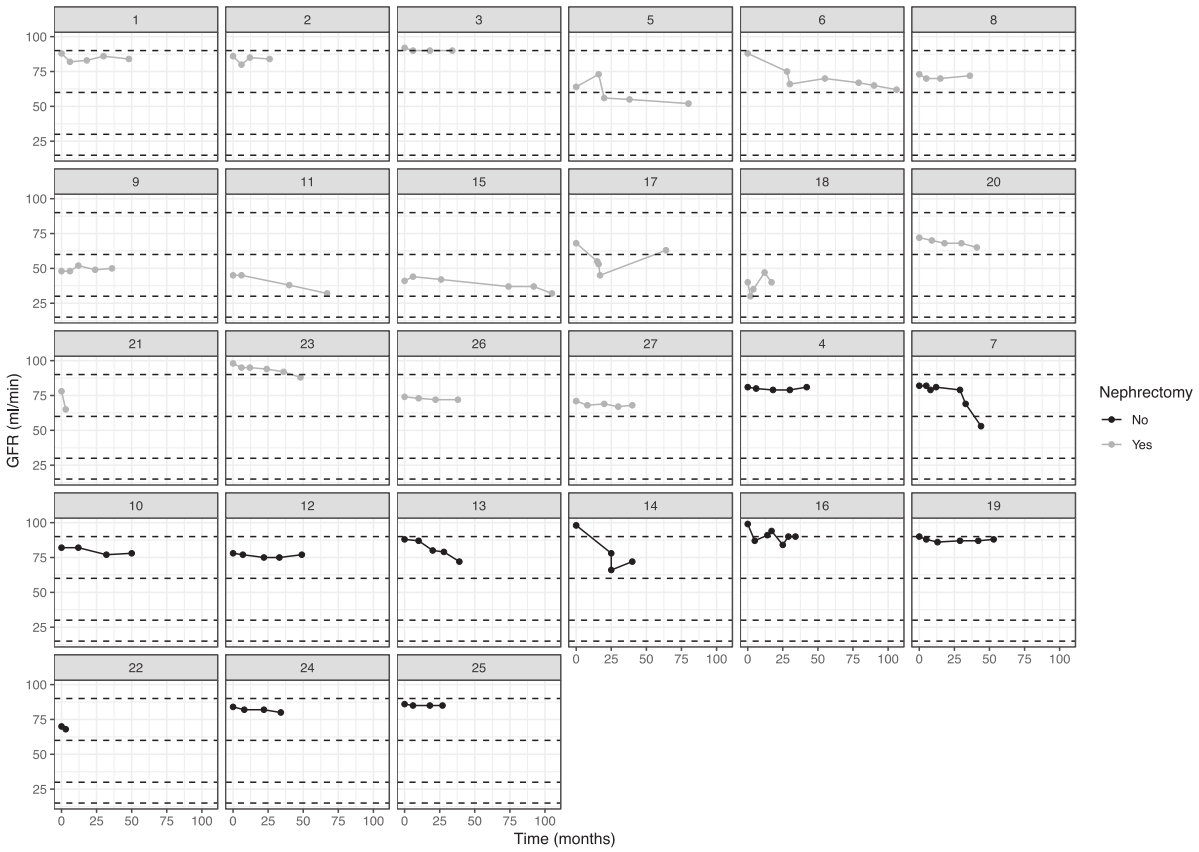


Figure 3: Boxplot representing glomerular filtration rate (GFR) before irradiation and at last follow-up date according to nephrectomy status.

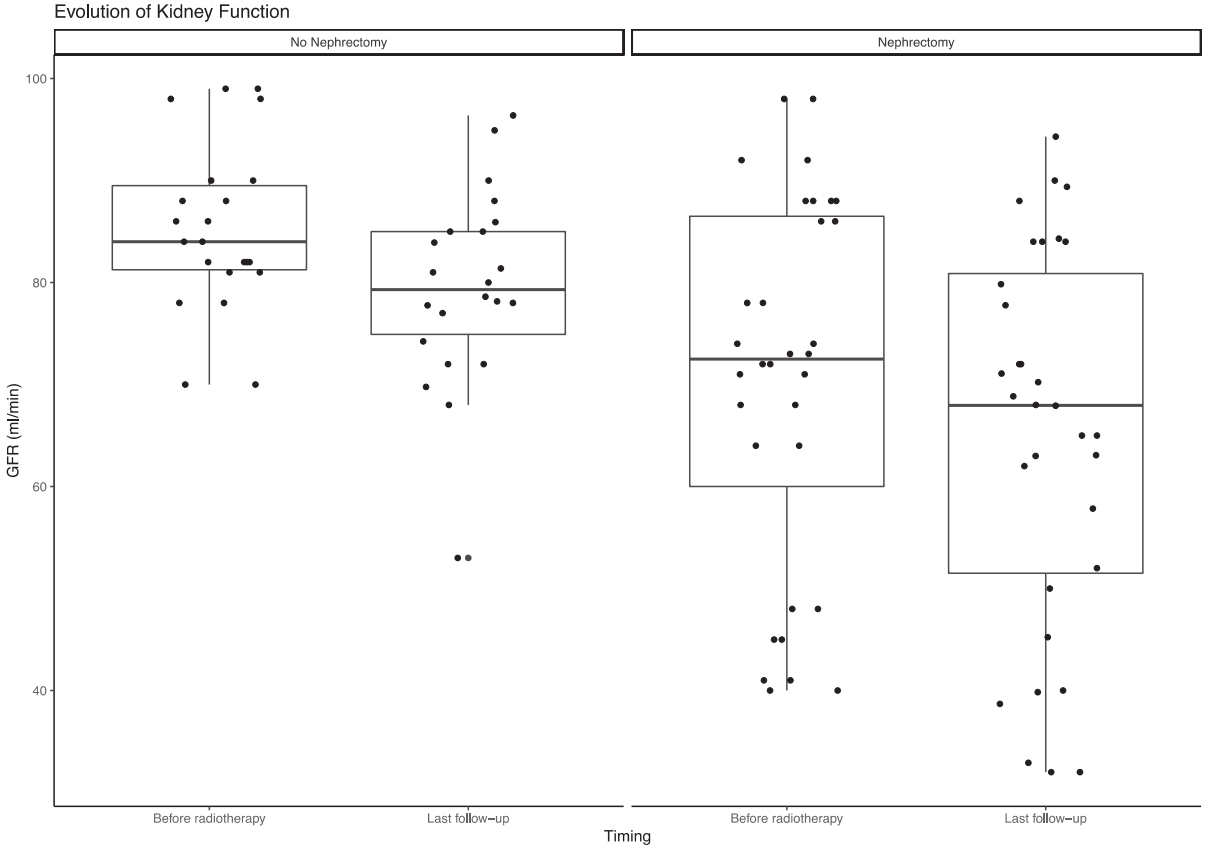


Figure 4: Box plot showing expected and observed glomerular filtration rates (GFR) at last follow-up.

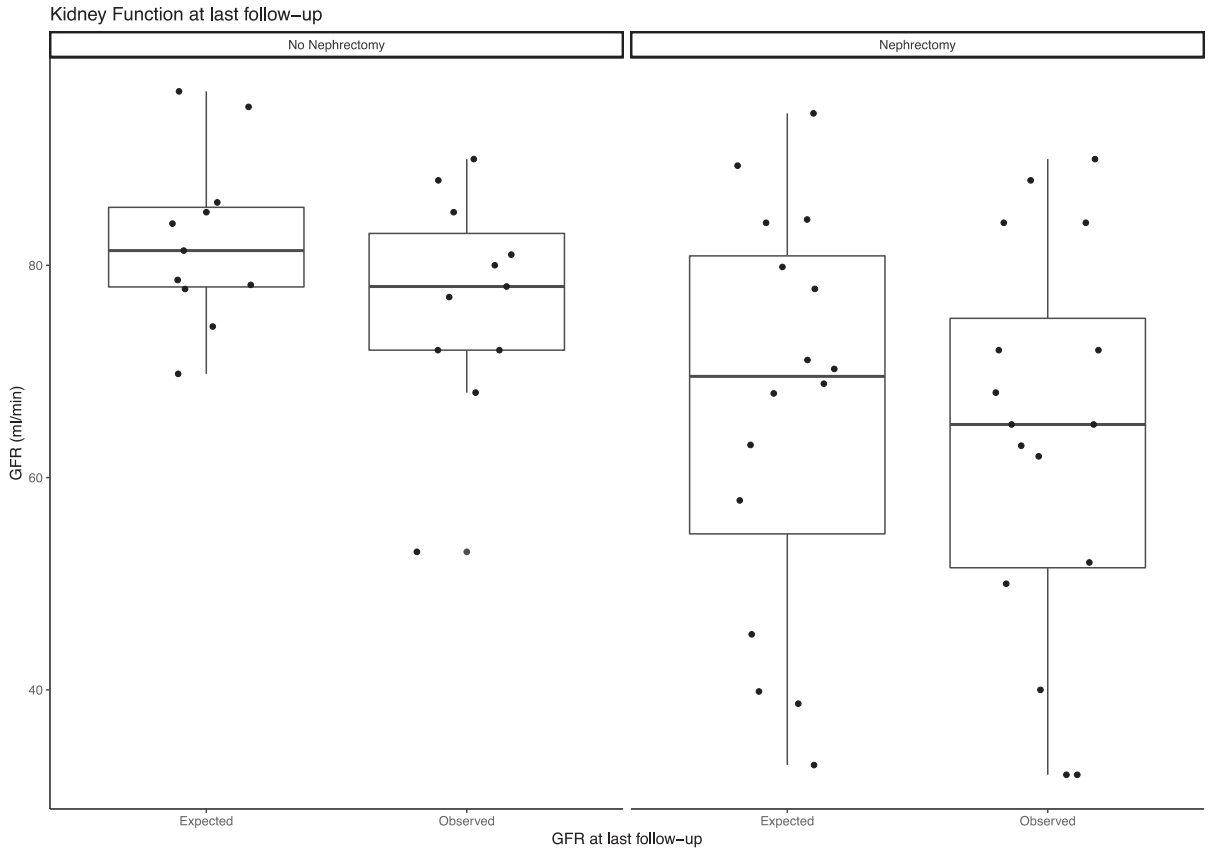
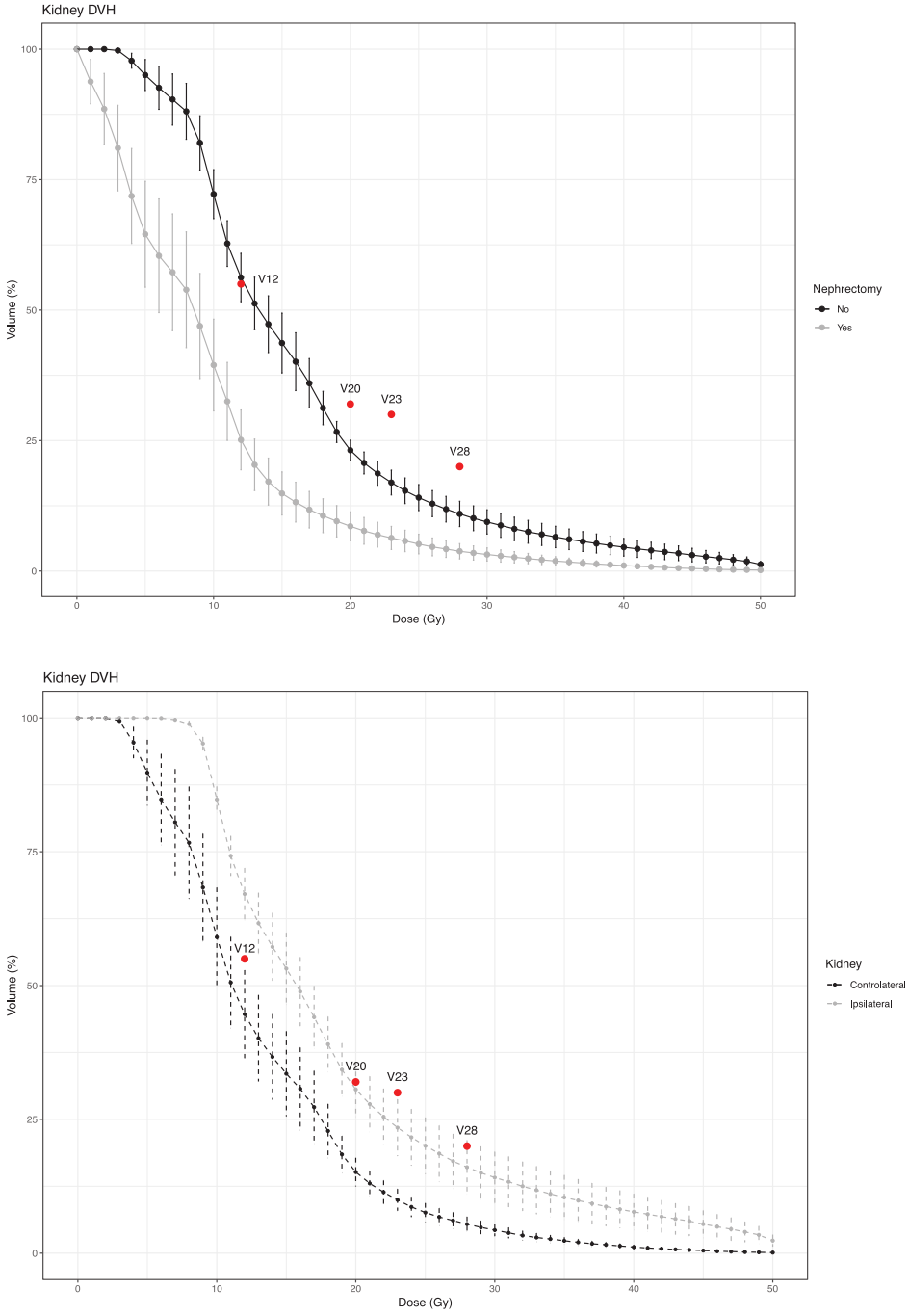
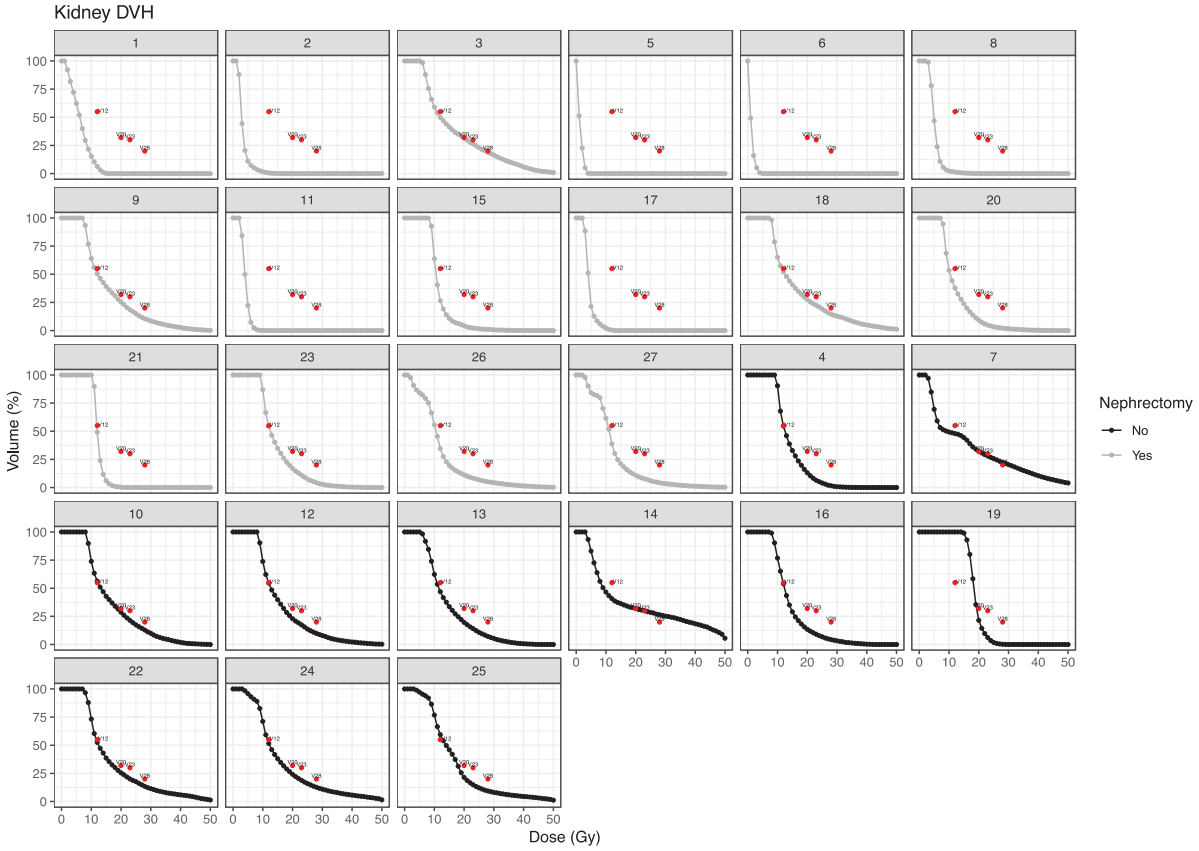


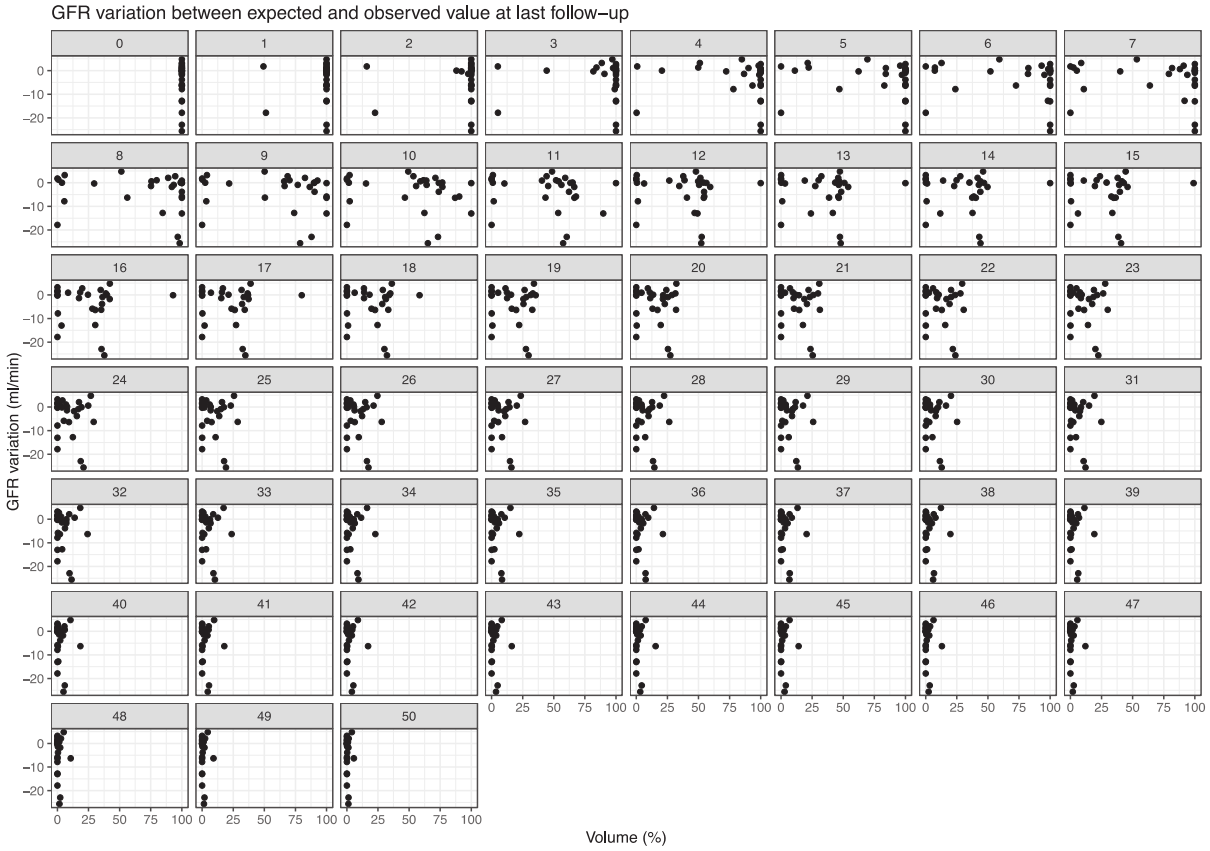
Figure 5 : Kidneys dose Volume Histogram representing mean and standard error for patient with nephrectomy compared to patients without nephrectomy (top). Kidneys dose Volume Histogram representing mean and standard error of ipsilateral (grey) and contralateral (black) for patient without nephrectomy (bottom). Red points shows QUANTEC dose constraints: V_{12Gy}=55%; V_{20Gy}=32%; V_{23Gy}=30%; V_{28Gy}=20%



Supplementary Figure 1 : Kidneys dose volume histogram of 27 patients treated with postoperative helical tomotherapy for retroperitoneal sarcoma. Red points shows QUANTEC dose constraints : V_{12Gy}=55%; V_{20Gy}=32%; V_{23Gy}=30%; V_{28Gy}=20%



Supplementary Figure 2: Scatter plot representing GFR variation between expected and observed value at last follow-up according to kidney volume (0-100%) receiving a certain dose (0-50 Gy).



Conclusions et perspectives

Les sarcomes du retropéritoine sont des tumeurs rares et hétérogènes. Leur prise en charge doit être organisée dans des centres experts. En l'absence de résultats d'essais cliniques randomisés, la chirurgie d'exérèse maximale reste le traitement de référence des sarcomes retropéritonéaux. Toutefois, la rechute loco-régionale est la principale cause de décès. De nombreuses études rétrospectives et l'analyse de base de données prospectives ont montré un bénéfice de l'irradiation peri-opératoire (pré- ou post-opératoire) dans la réduction du risque de récidive loco-régionale mais sans bénéfice en survie globale. Ces études ont aussi mis en évidence une augmentation du risque de toxicité principalement digestive. L'essor des techniques modernes de radiothérapie (radiothérapie guidée par l'image, radiothérapie conformationnelle avec modulation d'intensité) a permis, dans d'autres types de cancer, d'améliorer la tolérance sans effet négatif sur l'efficacité. Dans le cas des sarcomes rétropéritonéaux, les volumes d'irradiation sont souvent complexes et la proximité d'organes à risque, très radiosensibles, (tube digestif) justifient l'utilisation de ces techniques d'irradiation.

Cette étude rétrospective mono-centrique a permis de colliger 56 patients traités pour un sarcome rétropéritonéal ou pelvien par irradiation conformationnelle avec modulation d'intensité hélicoïdale sous Tomotherapy® et d'analyser cette prise en charge..

Dans un premier temps, notre étude a permis de mettre en évidence la faisabilité du traitement en situation pré- ou post-opératoire. En effet, compte tenu des volumes d'irradiation complexe, la tomothérapie hélicoïdale permet d'avoir une meilleure couverture de volume cible avec une meilleure préservation des organes à risques. De plus, nous avons mis en évidence que les taux de contrôle locaux, de survie sans maladie et de survie globale sont concordants avec la littérature. Nous avons aussi analysé les deux principaux risques de toxicité lors d'irradiation abdominale : la toxicité digestive et rénale. Bien que les doses délivrées dans la cavité péritonéale soient plus importantes que lors d'autres types d'irradiation abdominale, nous avons montré que le taux de toxicité digestive restait faible. Cependant la tolérance de l'irradiation était meilleure en pré-opératoire. Ceci était principalement lié au fait que la dose reçue par le tube digestif en pré-opératoire était sensiblement plus faible. L'analyse dosimétrique a permis de mettre en évidence un nouveau facteur dosimétrique permettant de prédire le risque de diarrhée $\geq$ grade 2 : le volume de cavité péritonéale recevant 35 Gy. Par ailleurs, avec un suivi médian de 41 mois pour l'ensemble de la cohorte et de 39 mois pour les patients opérés, nous n'avons mis en évidence qu'une seule toxicité digestive tardive de grade 3. Dans notre série, une majorité des patients traités pour un sarcome rétropéritonéal a bénéficié d'une néphrectomie. Dans ce contexte le risque de développer une insuffisance rénale aurait pu sembler plus important et l'irradiation abdominale pouvait augmenter ce risque. En dépit de cette situation, nous avons pu montrer qu'aucun patient n'a présenté une insuffisance rénale terminale et n'a été dialysé.

Les facteurs pronostiques que nous avons identifiés se rapprochent de ceux déjà décrits dans la littérature, tels que le grade de la tumeur ou encore la présentation du sarcome (initiale ou en récidive). Compte tenu du faible nombre de patients, nous n'avons pas pu identifier d'autres facteurs de risques.

Les résultats de l'essai de l'EORTC (STRASS), comparant la radiothérapie pré-opératoire des sarcomes rétropéritonéaux à la chirurgie exclusive, pourront permettre de mieux définir la place de la radiothérapie. En attendant les résultats de cet essai clinique, les indications d'irradiation doivent être discutés au cas par cas en réunion de concertation pluridisciplinaire et si l'indication est retenue, une irradiation préopératoire doit être préférée et ceci avec des techniques optimales de radiothérapie.

Vu
Strasbourg le 11/12/2018
Le Président du jury de Thèse

Professeur Georges NOËL

Vu
Strasbourg, le 18 DEC. 2018
Le Doyen de la Faculté de médecine de STRASBOURG

Professeur Jean SIBILIA

Université de Strasbourg

Faculté de médecine

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RESUME :

Introduction : Les sarcomes des tissus mous représentent 1% de l'ensemble des cancers. Les sarcomes rétropéritonéaux représentent environ 15% des sarcomes des tissus mous de l'adulte. La place de la radiothérapie reste débattue dans la prise en charge de cette pathologie rare. Les nouvelles techniques d'irradiation associant la modulation d'intensité et le guidage par l'image ont démontré un bénéfice dosimétrique comparativement à la radiothérapie 3D. Cependant peu d'études se sont intéressées aux résultats cliniques de ces nouvelles techniques d'irradiation.
L'objectif de ce travail était d'évaluer l'efficacité et la tolérance clinique de la radiothérapie conformationnelle avec modulation d'intensité hélicoïdale sous Tomotherapy® dans le traitement peri-opératoire des sarcomes rétropéritonéaux et pelviens.

Matériels et méthodes : Entre Août 2008 et Janvier 2017, 56 patients ont été traités pour un sarcome rétropéritonéal ou pelvien par radiothérapie conformationnelle avec modulation d'intensité hélicoïdale. Parmi ces patients, 49 ont bénéficié d'un traitement chirurgical dont 39 avant radiothérapie. Nous avons analysé le contrôle local, la survie sans maladie et la survie globale ainsi que la toxicité digestive et rénale aigue et tardive.

Résultats : Avec un suivi médian de 39 mois pour les patients opérés, nous avons pu montrer que la survie sans récidive locale, la survie sans maladie et la survie globale à 3 ans étaient respectivement de 88,9 %, 73,7 %, et 88,3%. L'analyse dosimétrique a permis de mettre en évidence un nouveau facteur dosimétrique permettant de prédire le risque de diarrhée ≥ grade 2 : le volume de cavité péritonéale recevant 35 Gy. Enfin, nous n'avons pas montré de toxicité rénale à long terme pour ces patients dont une partie a bénéficié d'une néphrectomie.

Conclusions : La radiothérapie conformationnelle avec modulation d'intensité hélicoïdale (Tomotherapy®) permet d'avoir des résultats cliniques proches de ceux observés dans la littérature. La toxicité digestive et rénale, à court et long terme reste faible. Pour diminuer la toxicité digestive, nous proposons d'intégrer une nouvelle donnée dosimétrique : la V_{35Gy}.

Rubrique de classement : ONCOLOGIE option Onco-Radiothérapie

Mots-clés : Sarcome, Rétropéritoine, Radiothérapie avec modulation d'intensité, Radiothérapie guidée par l'image.

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