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PRÉSENTÉE POUR LE DIPLÔME DE

DOCTEUR EN MÉDECINE

Diplôme d'État

Mention D.E.S Oncologie option Radiothérapie

PAR

Adrien PAIX

né le 25/09/1988 à Suresnes

Radiothérapie stéréotaxique des métastases cérébrales de mélanomes et de cancers colorectaux

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

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DEBRY Christian P0049	NRPô CS	• Pôle Tête et Cou - CETD - Serv. d'Oto-rhino-laryngologie et de Chirurgie cervico-faciale / HP	55.01	Oto-rhino-laryngologie
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GRUCKER Daniel (1) P0069	S/nb	• Pôle de Biologie - Labo. d'Explorations fonctionnelles par les isotopes in vitro / NHC • Institut de Physique biologique / Faculté de Médecine	43.01	Biophysique et médecine nucléaire
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MEZIANI Ferhat P0106	NRPô NCS	• Pôle Urgences - Réanimations médicales / Centre antipoison - Service de Réanimation Médicale / Nouvel Hôpital Civil	48.02	Réanimation
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NOEL Georges P0114	NCS	• Centre Régional de Lutte Contre le Cancer Paul Strauss (par convention) - Département de radiothérapie	47.02	Cancérologie ; **Radiothérapie** Option Radiothérapie biologique
OHLMANN Patrick P0115	NRPô NCS	• Pôle d'activité médico-chirurgicale Cardio-vasculaire - Service de Cardiologie / Nouvel Hôpital Civil	51.02	Cardiologie
Mme PAILLARD Catherine P0180	NRPô CS	• Pôle médico-chirurgicale de Pédiatrie - Service de Pédiatrie III / Hôpital de Hautepierre	54.01	Pédiatrie
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
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
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

NOM et Prénoms	CS*	Services Hospitaliers ou Institut / Localisation	Sous-section du Conseil National des Universités	
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 CS	• 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
WATTIEZ Arnaud P0161 (Dispo 31.07.2019)	NRPô NCS	• Pôle de Gynécologie-Obstétrique - Service de Gynécologie-Obstétrique / Hôpital de Hautepierre	54.03	**Gynécologie-Obstétrique** ; Gynécologie médicale / Opt Gynécologie-Obstétrique
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 WOLFRAM-GABEL (5) Renée P0165	S/nb	• Pôle de Chirurgie plastique reconstructrice et esthétique, Chirurgie maxillo-faciale, Morphologie et Dermatologie - Service de Morphologie appliquée à la chirurgie et à l'imagerie / Faculté • Institut d'Anatomie Normale / Hôpital Civil	42.01	Anatomie (option biologique)

NOM et Prénoms	CS*	Services Hospitaliers ou Institut / Localisation	Sous-section du Conseil National des Universités

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

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 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
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 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)
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

NOM et Prénoms	CS*	Services Hospitaliers ou Institut / Localisation	Sous-section du Conseil National des Universités	
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)
PELACCIA Thierry M0051		• Pôle d'Anesthésie / Réanimation chirurgicales / SAMU-SMUR - Service SAMU/SMUR	48.02	Réanimation et anesthésiologie Option : Médecine d'urgences
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)
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
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 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)

NOM et Prénoms	CS*	Services Hospitaliers ou Institut / Localisation	Sous-section du Conseil National des Universités	
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
ZOLL Joffrey M0077		• Pôle de Pathologie thoracique - Service de Physiologie et d'Explorations fonctionnelles / HC	44.02	Physiologie (option clinique)

B2 - PROFESSEURS DES UNIVERSITES (monoappartenant)

Pr BONAH Christian	P0166	Département d'Histoire de la Médecine / Faculté de Médecine	72.	Epistémologie - Histoire des sciences et des techniques
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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.

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Table des matières

Introduction

Les métastases cérébrales constituent bien souvent un virage dans l'évolution d'une maladie cancéreuse. Leur manifestation est variable mais induit le plus souvent une altération de la qualité de vie des patients et peuvent mettre en jeu le pronostique vital à court terme. Un des traitements possibles lorsque l'atteinte est limitée et que le pronostic vital n'est pas engagé à court terme est l'irradiation stéréotaxique.

La littérature rapporte des séries considérant les métastases cérébrales comme une entité unique ne prenant pas ou peu en compte l'histologie de la tumeur primitive. Par ailleurs, la plupart des études rapportent les résultats de la radiothérapie stéréotaxique mono fractionnée délivrée par le système Gamma Knife.

Nous avons choisi de nous intéresser à la prise en charge de métastases cérébrales de deux primitifs, le mélanome et le carcinome colo rectale. Dans un premier temps nous avons réalisé une revue systématique de la littérature selon les recommandations PRISMA et avec dépôt de protocoles d'étude au sein de la base PROSPERO. Dans un second temps, nous avons réalisés, sous l'égide de l'Association des Neuro-Oncologues de langue Française (ANOCEF), deux études multicentriques au sein de six centres en France et en Allemagne afin d'évaluer les résultats de la radiothérapie stéréotaxique mono et hypo fractionnée dans ces deux histologies. Enfin, nous avons réalisé une évaluation médico-économique dans la perspective du payeur français de ces deux techniques dans ces deux indications.

Stereotactic radiosurgery and hypofractionated stereotactic radiotherapy in melanoma brain metastasis management: a systematic review.

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Résumé

Introduction

Le mélanome est, en fréquence, le troisième cancer responsable de métastases cérébrales. La radiothérapie stéréotaxique mono fractionnée (SRS) et hypo fractionnée (HFSRT) sont des alternatives thérapeutiques à la chirurgie. Nous avons réalisé une revue systématique de la littérature évaluant l'efficacité et la sécurité de la SRS et de la HFSRT chez les patients présentant des métastases cérébrales de mélanome.

Méthodes

Un protocole de revue systématique de la littérature a été enregistré sur la base PROSPERO sous la référence CRD42017082477. Nous avons conduit nos recherches aux seins des bases PubMed EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) et Clinicaltrials.org. Les articles ont été évalués indépendamment par deux relecteurs. Le critère de jugement principal était le contrôle local. Les critères de jugement secondaires incluaient la survie globale, la survie sans récidive intra-cérébrale et les effets secondaires.

Résultats

Parmis les études rapportant l'efficacité de la SRS et HFSRT sans immunothérapie ou thérapie ciblée, le taux de réponse allait de 53 à 98,2%, la médiane de survie globale allait de 5,02 à 14,2 mois et la médiane de survie sans récidive intra-cérébrale allait de 3,74 à 30 mois, enfin le taux de radionécrose allait de 1,6% à 9,1%. Parmis les études rapportant l'efficacité de la SRS et HFSRT associée à l'immunothérapie ou une thérapie ciblée, une étude rapportait un taux de réponse de 63% (IC 95% [52,4% - 73,7%]), la médiane de survie globale allait de 8,2 à 21,3 mois, la médiane de survie sans progression allait de 4,4 à 5,4 mois, enfin deux études rapportaient le taux de radionécrose qui était de 4,4 et 16,4%.

Conclusion

Cette revue systématique de la littérature rapporte des résultats hétérogènes. Néanmoins, bien que les taux de réponses soient supérieurs à 80%, les médianes de survie globale et sans récidivie intra-cérébrale restent inférieurers à 15 et 6 mois respectivement. La plus part des études rapportent un taux de radionécrose inférieur à 5%.

Abstract

Introduction

Melanoma is, in frequency, the third main cancer responsible for brain metastases. Stereotactic radiosurgery (SRS) and hypofractionated stereotactic radiotherapy (HFSRT) are treatment alternatives to surgery. We conducted a systematic review of the literature evaluating the efficacity and safety of SRS and HFSRT in patients with melanoma brain metastasis.

Methods

A systematic review protocol has been registered in the PROSPERO database under the number: CRD42017082477. We searched in PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) and Clinicaltrials.org databases. Studies were screened by two independent reviewers. The primary outcome measure was local control. Secondary outcomes included overall survival (OS), brain progression-free survival (BPFS) and related toxicities.

Results

Among the studies reporting outcomes of SRS/HFSRT without immunotherapy or targeted therapy, the response rates ranged from 53 to 98.2%, the median OS intervals from the time of brain metastasis treatment ranged from 5.02 to 14.2 months, the median BPFS intervals ranged from 3.74 to 30 months, and radionecrosis (RN) rates ranged from 1.6 to 9.1%. Among the studies reporting outcomes of SRS/HFSRT with immunotherapy or targeted therapy, the response rate reported in only one study was 63% (CI 95% [52.4 – 73.7]), median OS intervals ranged from 8.2 to 21.3 months, median BPFS intervals were reported in only two studies were 4.4 and 5.4 months, and the reported RN rates in two studies were 4.4 and 16.4%.

Conclusion

This systematic review reports heterogeneous outcomes among the published studies. However, if the response rates reported are always over 80%, median of OS and BPFS intervals remains below 15 and 6 months, respectively. Most of the studies reported a radionecrosis rate below 5%.

Introduction

Melanoma is the third cancer responsible for brain metastases in frequency after breast and lung cancer, and brain metastases are known to be responsible for 20 to 54 percent of deaths in patients with melanoma [1,2]. According to the European Society for Medical Oncology (ESMO) guidelines, stereotactic radiotherapy should be preferred over whole brain radiotherapy (WBRT) mostly because melanoma is considered to be a radioresistant tumor and because of risk of neurocognitive decline following WBRT [3]. Historically, stereotactic irradiation of brain metastasis has been performed with Gamma knife in a single fraction, however, for some years, increasingly radiation oncology departments perform stereotactic radiotherapy with a linear accelerator and hypofractionated regimen, mostly delivered in 3 to 5 fractions. Moreover, the development of target therapy and immunotherapy increase the overall survival of patients with melanoma brain metastasis and few studies evaluated the association of such therapies with stereotactic radiosurgery (SRS) and hypofractionated stereotactic radiotherapy (HFSRT).

We conducted a systematic review of the literature evaluating the efficacity and safety of SRS and HFSRT in patients with melanoma brain metastasis.

Material and methods

Search strategy and selection criteria

This systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and a systematic review protocol has been registered in the PROSPERO database under the number: CRD42017082477 [4].

To identify the relevant studies, we searched PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) and Clinicaltrials.org, without date restriction, for studies evaluating SRS and/or HFSRT in melanoma brain metastasis. Search strategies are reported in Table 1.

Table 1: Search strategies

Table 1 – a: Pubmed data base

1	Melanoma [MeSH Terms]
2	brain metastasis[Title/Abstract]
3	((radiosurgery, stereotactic[MeSH Terms]) OR stereotactic radiotherapy[Title/Abstract]) OR stereotactic irradiation [Title/Abstract]
4	(English[Language]) OR French[Language]
5	#1 & #2 & #3 & #4

Table 1 – b : Embase data base

('metastatic melanoma'/exp AND 'brain metastasis'/exp AND ('stereotactic radiotherapy'/exp OR 'stereotactic radiosurgery'/exp OR 'stereotactic radiosurgery' OR 'stereotaxic radiosurgery')) AND ('clinical article'/de OR 'clinical trial'/de OR 'clinical trial (topic)'/de OR 'cohort analysis'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'human'/de OR 'major clinical study'/de OR 'multicenter study (topic)'/de OR 'phase 1 clinical trial (topic)'/de OR 'phase 2 clinical trial'/de OR 'phase 2 clinical trial (topic)'/de OR 'phase 3 clinical trial (topic)'/de OR 'prospective study'/de OR 'randomized controlled trial (topic)'/de OR 'retrospective study'/de) AND 'article'/it

Table 1 – c: The Cochrane central register of controlled trials (CENTRAL)

1	melanoma:ti,ab,kw (Word variations have been searched)
2	"brain":ti,ab,kw and "metastases":ti,ab,kw (Word variations have been searched)
3	"stereotactic irradiation":ti,ab,kw or "stereotactic radiosurgery":ti,ab,kw or "stereotactic radiotherapy":ti,ab,kw (Word variations have been searched)
4	#1 and #2 and #3

Table 1 – d: ClinicalTrials.gov

Condition / Disease	Melanoma
Other Terms	Brain
Intervention / Treatment	Stereotactic radiotherapy

To be considered for inclusion, studies should be either clinical trials, observational studies, randomized controlled trials, retrospective studies or prospective studies. Reviews, meta-analyses, abstract and case reports were not included. Moreover, we only included article written in English or French.

After removal of duplicates, studies were screened by title and abstract by two independent reviewers (A.P. and W.W.) and remaining studies were screened by full-text analysis by the same two independent reviewers. Differences between reviewers were solved by discussion.

Outcomes

The primary outcome measure was local control define as complete response, partial response or stabilization of the metastasis according to RECIST criteria [5]. Secondary outcomes included overall survival (OS), brain progression-free survival (BPFS), related toxicities and factors influencing local control, OS and BPFS.

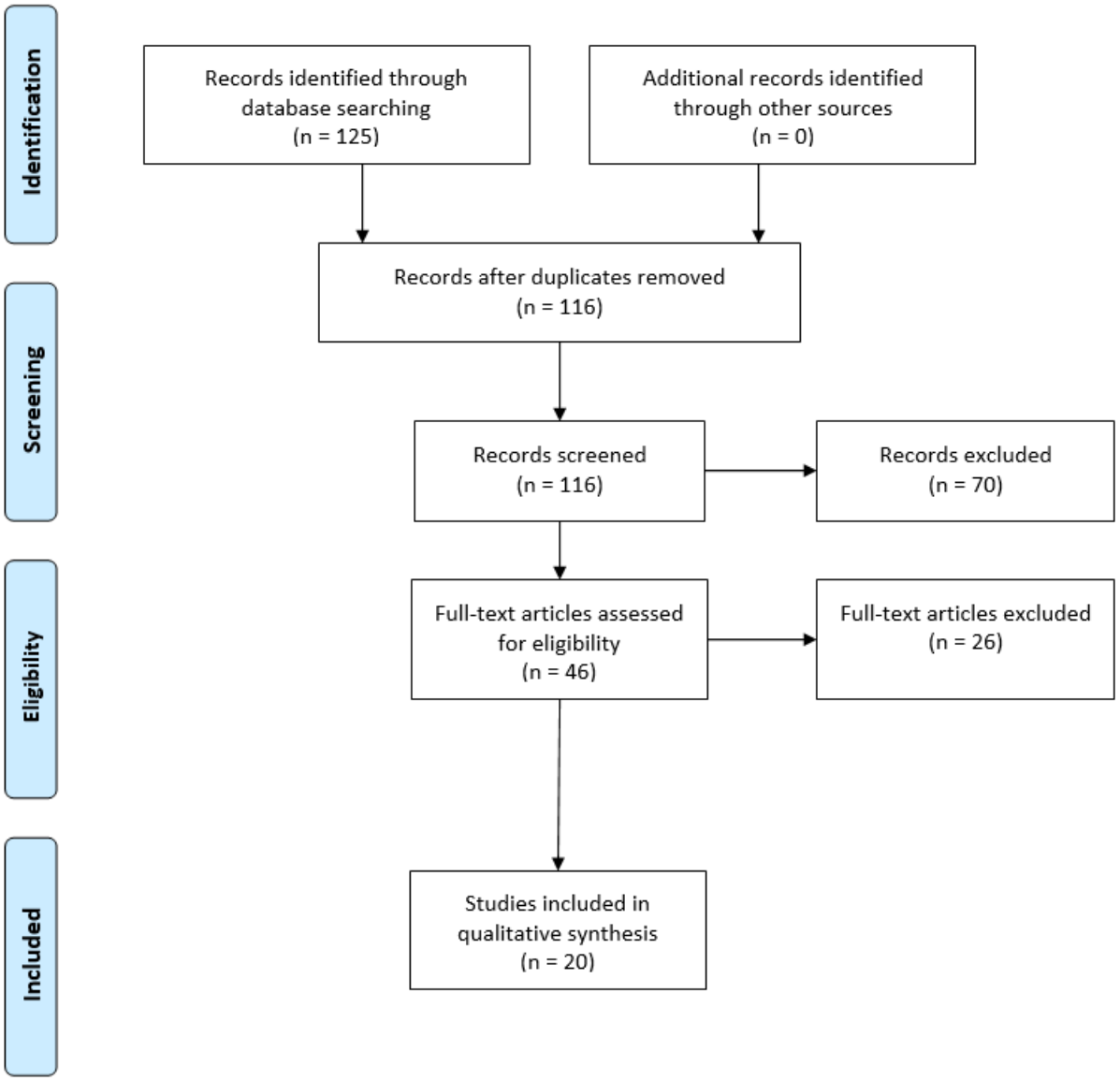
Data extraction

A.P. extracted the information from the full texts using a predefined form using Microsoft Access. Extracted data included study details (first author, title, journal, year of publication and study design), population details (number of patients, number of brain metastasis, BRAF mutational status, Karnofsky performance status, age, tumor volume, control of systemic disease and systemic treatment), treatment details (machine used to deliver radiotherapy and regimen: SRS or HFRT), and outcomes (overall survival, brain progression-free survival, radionecrosis and side effects).

Results

We identified 125 potentially relevant studies and then removed 9 duplicated studies. After screening for title and abstract, 70 records were excluded and after full-text assessment 20 studies were considered for qualitative analysis (Figure 1). All the studies included were retrospective.

Figure 1: Flowchart of the systematic review process



SRS and HFSRT without immunotherapy or targeted therapy

Among the 20 studies included, 17 reported outcomes of SRS and HFSRT on patients with melanoma brain metastases without a specific association of immunotherapy or targeted therapy [6–22].

Population

The included studies reported the outcomes of SRS and HFSRT in 1,568 patients and more than 4,530 melanoma brain metastases (in 2 studies the total number of metastasis was not reported). The median age of patients ranged from 47 to 64 years old (total range [16 – 93]), median Karnofsky performance status (KPS) ranged from 70 to 90 (total range [40 – 100]).

Median number of lesions by patient ranged from 1 to 3 (total range [1 – 30]). Median metastasis volume ranged from 1.05 to 3.63 mL (total range [0.004 – 37.2]). BRAF mutation was reported in 124 patients but mutational status was not reported in 13 studies.

Treatment was performed with Gamma knife in 12 studies, by a linear accelerator in 3 studies and by both Gamma knife and linear accelerator in 2 studies. Most of the patients were treated with SRS and one study did not report the radiotherapy regimen. Data are reported in Table 2.

Outcomes

The median follow-up of the included studies ranged from 4.4 to 37.4 months. Among the selected studies the response rate ranged from 53 to 98.2%, the median OS intervals from the time of brain metastasis treatment ranged from 5.02 to 14.2 months and the median BPFS intervals ranged from 3.74 to 30 months (Table 3).

Factor influencing OS in multivariate analysis are reported in table 4-a and 4-b. ECOG/KPS status and systemic disease status were the most frequently retrieved prognostic factors, 6 and 4 times, respectively. Single brain metastasis, high KPS, GPA > 2.5, high DS-GPA, systemic disease controlled, small metastasis volume and systemic treatment seems to be associated with longer OS, whereas infratentorial

location, Score Index for Radiosurgery in Brain Metastases (SIR) score ≤ 6 and metastasis hemorrhage seems to be associated with worst OS.

Local control prognosis factors have only been reported in one study, and hemorrhagic metastases seemed to be related with a poorest LC whereas largest metastases with a better LC (Table 4 – c).

Radionecrosis is one of the main and more clinical relevant toxicity of SRS and HFSRT as it can severely impact quality of life. Its diagnosis is based on magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT). In the selected studies, the radionecrosis rate ranged from 1.6 to 9.1%. Outcomes are reported in Table 3.

Finally, intra-tumoral bleeding is reported in 15% of patients undergoing SRS or HFSRT, with rates ranging from 1 to 30%.

SRS and HFSRT with immunotherapy or targeted therapy

Among the 20 studies included, 5 reported outcomes of SRS and HFSRT on patients with melanoma brain metastases with a specific association of immunotherapy or targeted therapy [17,18,23–25].

Population

The median age of patient ranged from 57 to 66 years, median KPS 90 but was reported in only one study.

Median lesions number by patient ranged from 2 to 5, and metastasis volume ranged from 0.15 to 0.6 mL. BRAF mutational status and control of systemic disease was only reported in one study.

Outcomes

The response rate was only reported in one study and was 63% (CI 95% [52.4 – 73.7]). Overall survival ranged from 8.2 to 21.3 months and brain progression-free reported only in two studies were 4.4 and 5.4 months. Radionecrosis rates, reported in two studies were 4.4 and 16.4%.

Table 2 – a: Population characteristics of the studies reporting the results of SRS and HFSRT without immunotherapy or targeted therapy

Study	Follow-up *median [range]* (months)	N	Age *median/mean [range] (yr)*		KPS *median [range] (%)*		Total brain metastasis	Radiation technique	Regimen	BRAF mutated	Metastasis/patient *median [range]*		Metastasis volume *median [range] (mL)*		ECD controlled *n (%)*
Mori et al [6]	9.3 [0.5 - 88]	60	49.1	[16 - 79]	90	[50 - 100]	118	GK	SRS		1		2.95	[0.1 - 25.5]	24 (40)
Grob et al [7]		35	56.6	[29 - 82]			70	GK	SRS						
Lavine et al [8]	12	45	53	[24 - 80]			93	GK	SRS		1	[1 - 5]			
Mingione et al [9]	8.6	45	53	[27 - 80]	80	[60 - 100]	92	GK	SRS				3.63	[0.1 - 57]	17 (38)
Noel et al [10]	12.6 [1 - 85]	25	47	[25 - 73]	80	[50 - 100]	61	Linac	SRS				1.7	[0.4 - 25.6]	10 (40)
Selek et al [11]	6 [2 - 46]	61	51	[18 - 93]	90	[50 - 100]	88	Linac	SRS		1		1.9	[0.06 - 22.3]	36 (59)
Chang et al [12]	7.4 [0.16 - 52]	103	52	[18 - 93]	80	[40 - 100]	153	Linac	SRS		1.5		1.9		
Gaudy-Marqueste et al [13]		106	56.5	[26 - 82]	90	[60 - 100]	221	GK	SRS				1.15	[0.004 - 33.5]	
Mathieu et al [14]	4.3 [0.3 - 114]	244	54.2	[16 - 87]	90	[50 - 100]	754	GK	SRS		2	[1 - 14]	3.4	[0.1 - 37.2]	48 (20)
Clarke et al [15]	[1.8 - 23.2]	18	56	[39 - 81]	70	[50 - 100]	18	GK	SRS		1				3 (17)
Liew et al [16]	3.8 [0.2 - 144.3]	333	53	[16 - 87]	90	[50 - 100]	1570	GK	SRS	0	2	[1 - 30]	1.4	[0.1 - 37.2]	70 (21)
Knisely et al [17]		50	61	[24 - 89]				GK							
Mathew et al[18]	6 [0.3 - 47]	33	57	[27 - 91]	90	[60 - 90]	99	GK	SRS		3	[1 - 9]	1.7	[0.2 - 8]	9 (27)
Neal et al [19]	4.4	129	57		80	[60 - 100]	550	GK	SRS		2				
Chowdhury et al [20]	37.4 [13.8 - 47.8]	86	56	[24 - 90]				GK		37					24 (28)

Ee Siang Choong et al [21]	8.6 [0.4 - 39.6]	108	64.3	[17 - 87]	339	Linac/GK	SRS	51			2.2	[0.04 - 53.5]	
Feng et al [22]	[1 - 28]	87	62	[26 - 85]	304	Linac/GK	SRS/HFSRT	36	2	[1 - 19]	1.05	[0.026 - 10.92]	16 (18)

GK : Gamma Knife ; SRS : stereotactic radiosurgery; HFSRT: hypofractionnated stereotactic radiotherapy; ECD: extracranial disease, N: number of patients

Table 2 – b: Population characteristics of the studies reporting the results of SRS and HFSRT with immunotherapy or targeted therapy.

Study	Follow up *median [range] months*	N	Age *median/mean [range] (yr)*	KPS *median [range] (%)*	Total brain metastasis	Radiation technique	Regimen	BRAF mutated	Metastasis/patient median [range]	Metastasis volume *median [range] (mL)*	ECD controlled *n (%)*
Knisely et al [17]		27	61 [24 - 89]			GK					
Mathew et al [18]	6 [0.3 - 47]	25	62 [27 - 87]	90 [80 - 90]	85	GK	SRS		3 [1 - 9]	0.6 [0.1 - 4.6]	6 (24)
Kiess et al [24]	22 [6 - 89]	46	57 [24 - 76]		113	Linac	SRS				
Tazi et al [25]		10	66 [41 - 81]			Linac		5	2 [1 - 59]		
Cohen-Inbar et al [26	7.9 [3 - 42.6]	46	62 [24.3 - 83.6]		232	GK	SRS		5 [1 - 22]	0.15 [0.02 - 64.5]	

GK : Gamma Knife ; SRS : stereotactic radiosurgery; HFSRT: hypofractionnated stereotactic radiotherapy; ECD: extracranial disease; N: number of patients

Table 3 – a: Outcomes of SRS/HFSRT without immunotherapy or targeted therapy on melanoma brain metastases

Study	Reponse rate [range]	Overall survival (months) [range]	Brain progression free survival (months) [range]	Radionecrosis rate [range]
Mori et al [6]	0.844 [0.744 - 0.917]	7		0.083 [0.031 - 0.173]
Grob et al [7]	0.982 [0.904 - 0.999]	7		
Lavine et al [8]	0.969 [0.838 - 0.999]	8 [1 - 20]		
Mingione et al [9]	0.818 [0.704 - 0.902]	10.4		
Noel et al [10}	0.911 [0.804 - 0.97]	8		0.016 [0.0004 - 0.088]
Selek et al [11]	0.604 [0.492 - 0.705]	7.5	5.5	0.039 [0.015 - 0.083]
Chang et al [12]		6.8	4.7	
Gaudy – Marquestre et al [13]	0.838 [0.831 - 0.844]	5.09	3.74	0.017 [0.015 - 0.019]
Mathieu et al [14]	0.907 [0.879 - 0.931]	5.3 [0.2 - 114.3]	4.2 [0.5 - 41.1]	0 0
Clarke et al [15]	0.667 [0.615 - 0.718]	6		
Liew et al [16]	0.9 [0.881 - 0.916]	8.3 [7.18 - 9.36]	30 [14.61 - 44.53]	
Knisely et al [17]		4.9 [3.3 - 10.4]		
Mathew et al [18]	0.65 [0.544 - 0.740]	5.2	5.4	0 0
Neal et al [19]	0.53 [0.488 - 0.573]	6.7	4.6	
Chowdhury et al [20]		8.1 [4 - 19.2]		0.091 [0.084 - 0.098]
Ee Siang Choong et al [21]		14.2 [8.8 - 20.4]		0.028 [0.025 - 0.031]
Feng et al [22]	0.91 [0.908 - 0.911]	6 [5.9 - 9.9]		0 0

Table 3 – b: Outcomes of SRS/HFSRT with immunotherapy or targeted therapy on melanoma brain metastases

Study	Reponse rate [range]	Overall survival (months) [range]	Brain progression free survival (months) [range]	Radionecrosis rate [range]
Knisely et al [17]		21.3 [6.43 - 26.7]		
Mathew et al [18]	0.63 [0.524 - 0.737]	8.2	4.4	0 0
Kiess et al [24]		12.4 [2 - 89]		0.044 [0.041 - 0.048]
Tazi et al [25]		16.5 [10.4 - NA]		
Cohen-Inbar et al [26]		13.4 [1.2 - 43.2]	5.4 [0.4 - 34.7]	0.164 [0.16 - 0.167]

Table 4 – a: Prognosis factors for overall survival (Part 1)

Study	Age	Gender	ECOG PS	KPS	RPA	GPA	DS-GPA	SIR	Systemic disease	Primary to brain metastasis interval
Mori *et. al.* [6]	NS	NS		NS					***	
Mingione *et. al.* [9]				(> 80) **						
Noel *et. al.* [10]	NS	NS		NS						
Selek *et. al.* [11]	NS			NS				(≤ 6) HR = 1.8 *	NS	
Gaudy - Marqueste *et. al.* [13]				RR = 0.45***				(≤ 6) RR = 1.6 *		
Mathieu *et. al.* [14]	NS	NS		(<80) HR = 2***	NS				HR = 2.2 ***	NS
Liew *et. al.* [16]	NS	NS		HR = 0.987*	NS			NS	HR = 2.5 ***	NS
Knisely *et. al.* [17]							***			
Neal *et. al.* [19]										
Chowdhury *et. al.* [20]		(male) HR = 1.8*		(<80) HR = 8.1*					HR = 5.4 *	
Ee Siang Choong *et. al.* [22]			(>1) HR = 2.7**			(>2.5) HR = 0.13 **				

*NS : not significant; * p < 0.05 ; ** p < 0.005; *** p < 0.0005*

Table 4 – b: Prognosis factors for overall survival (Part 2)

Study	Neurological deficit	Single vs multiple metastases	Volume	Volume > 8cm3	Infratentoriale	Metastasis hemorrhage	Prior surgery	WBRT (before or after)	Chemo or immuno therapy after SR	Ipilimumab
Mori *et. al.* [6]	NS	NS	*		NS	NS	NS	NS	NS	
Mingione *et. al.* [9]		*								
Noel *et. al.* [10]		NS	NS		NS					
Selek *et. al.* [11]			NS							
Gaudy - Marqueste *et. al.* [13]		RR = 0.46 **			RR = 2 **					
Mathieu *et. al.* [14]	NS	NS	NS	HR = 0.379 *	HR = 1.6 *			NS	NS	
Liew *et. al.* [16]										
Knisely *et. al.* [17]	NS	NS	NS	NS	‡	HR = 1.6 *		(before) HR = 1.8***	NS	
Neal *et. al.* [19]										HR = 0.48 *
Chowdhury *et. al.* [20]		NS			‡	**		NS		
Ee Siang Choong *et. al.* [22]										
Mori *et. al.* [6]									Immunotherapy HR = 0.51, BRAFi HR = 0.3 *	

*NS : not significant ; ‡ 0.1 < p < 0.05; * p < 0.05 ; ** p < 0.005; *** p < 0.0005*

Table 4 – c: Prognosis factor for local control

Study	Age	Sex	Primary to brain interval	KPS	Prior chemotherapy	Prior immunotherapy	Vaccine therapy	PTV volume	Deep cerebral metastasis	Cerebellar metastasis	Brainstem metastasis	Hemorrhagic metastases
Liew *et. al.* [16]	NS	*	NS	NS	NS	NS	NS	HR = 0.039 **	NS	NS	NS	HR = 2.76 **

*NS : not significant ; * $p < 0.05$; ** $p < 0.005$;*

Discussion

We report the results of the first systematic review of the outcomes of SRS and HFSRT for melanoma brain metastases. It deviates from the published protocol on one inclusion factor, the minimum age of the patient in studies, which was not respected by 4 studies. However, it seems that it will not affect the conclusions of our analysis. This review was consistent with the rest of the published protocol. The database search was extensive, and the study selection was independently performed by 2 reviewers with conflict resolution by a discussion which is consistent with PRISMA guidelines[4].

This systematic review reports heterogeneous outcomes among the published studies. However, most of the response rate reported is over 80% and brain progression-free survival ranging from 3.74 to 5.5 months, which is consistent with the data reported in other primary tumors. These results are against the concept of radioresistant tumor, usually applied to melanoma metastases, which might not be relevant in case of high doses [26].

Overall survival remains low with most of the studies reporting OS ranging from 5 to 10 months. Immunotherapy trials in advanced melanoma reported OS ranging from 17 to 38 months, however patients with brain metastases were excluded or represented less than 4% of patients included in those studies [27,28]. Thus, the apparition of brain metastases could significate a later and more aggressive stage in the disease history.

The selected studies report a low rate of radionecrosis, generally lower than 5%., however, most of the studies included had a median follow-up shorter than 10 months which could explain that the reported radionecrosis rates are lower than in other studies not specific to melanoma but with a longer follow-up [29,30].

Finally, this systematic review analysis suggests that the association of immunotherapy or targeted therapy with SRS or HFSRT is feasible, do not increase the rate of radionecrosis and might enhance overall survival. However, the data are still very limited to make any definitive conclusion.

However, our systematic review has some drawback. One of the most important is the quality of the data reported in the study. First of all, the radiation protocol was often poorly reported, despites the

recommendations of the International Commission on Radiation Units and Measurements (ICRU) reports 83 and 91, and the population's characteristics were heterogeneously reported [31,32]. Secondly, most of the studies were conducted with Gamma knife system, which was for a long time the leading system for intracranial SRS and allowing, at the time of the reported treatment only monofractionated treatment but has now been supplanted by a linear accelerator system in term of use. Finally, all of these studies are retrospective analysis and all but one is monocentric, which could bias response rate analysis as it might be influenced by the follow-up schedule, the brain MRI frequency and the subjectivity of the physician.

This systematic analysis suggests that SRS and HFSRT are a safe and effective treatment option for melanoma brain metastasis, but further analysis is still required both for radiation alone and for radiation combined with immunotherapy or targeted therapy. Finally, a multicentric study, comparing SRS and HFSRT delivered with LINAC should be conducted to assess the efficiency of both the radiation regimen and their safety.

Conclusion

The included studies are heterogenous but report good local control rates, however, there are few evidences for hypofractionnated stereotactic radiotherapy, as most of the published studies are based on Gamma Knife. Finally, association of SRS and immunotherapy seems effective and safe but need to be validated in prospective trials, which will however be tough to set up.

References

[1] J.D. Johnson, B. Young, Demographics of brain metastasis, Neurosurg. Clin. N. Am. 7 (1996) 337–344.

[2] J.M. Skibber, S.J. Soong, L. Austin, C.M. Balch, R.E. Sawaya, Cranial irradiation after surgical excision of brain metastases in melanoma patients, Ann. Surg. Oncol. 3 (1996) 118–123.

[3] Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, Arbuckle RB, Swint JM, Shiu AS, Maor MH, Meyers CA, Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial, Lancet Oncol. 10 (2009) 1037–1044.

[4] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement, Int. J. Surg. 8 (2010) 336–341. doi:10.1016/j.ijsu.2010.02.007.

[5] E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij, New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), Eur. J. Cancer Oxf. Engl. 1990. 45 (2009) 228–247. doi:10.1016/j.ejca.2008.10.026.

[6] Y. Mori, D. Kondziolka, J.C. Flickinger, J.M. Kirkwood, S. Agarwala, L.D. Lunsford, Stereotactic radiosurgery for cerebral metastatic melanoma: factors affecting local disease control and survival., Int J Radiat Oncol Biol Phys. 42 (1998) 581–9.

[7] J.J. Grob, J. Regis, R. Laurans, M. Delaunay, P. Wolkenstein, K. Paul, P. Souteyrand, M.C. Koeppel, X. Murraciole, J.C. Perragut, J.J. Bonerandi, Radiosurgery without whole brain radiotherapy in melanoma brain metastases. Club de Cancérologie Cutanée., Eur J Cancer. 34 (1998) 1187–92.

[8] S.D. Lavine, Z. Petrovich, A.A. Cohen-Gadol, L.S. Masri, D.L. Morton, S.J. O'Day, R. Essner, V. Zelman, C. Yu, G. Luxton, M.L. Apuzzo, Gamma knife radiosurgery for metastatic

melanoma: an analysis of survival, outcome, and complications., Neurosurgery. 44 (1999) 59-64; discussion 64–6.

[9] V. Mingione, M. Oliveira, D. Prasad, M. Steiner, L. Steiner, Gamma surgery for melanoma metastases in the brain., J Neurosurg. 96 (2002) 544–51.

[10] G. Noël, J.M. Simon, C.-A. Valery, P. Cornu, G. Boisserie, D. Ledu, D. Hasboun, B. Tep, J.-Y. Delattre, C. Marsault, F. Baillet, J.-J. Mazeron, Linac radiosurgery for brain metastasis of melanoma., Ster. Funct Neurosurg. 79 (2002) 245–55.

[11] U. Selek, E.L. Chang, S.J. Hassenbusch, A.S. Shiu, F.F. Lang, P. Allen, J. Weinberg, R. Sawaya, M.H. Maor, Stereotactic radiosurgical treatment in 103 patients for 153 cerebral melanoma metastases., Int J Radiat Oncol Biol Phys. 59 (2004) 1097–106.

[12] E.L. Chang, U. Selek, S.J. Hassenbusch, M.H. Maor, P.K. Allen, A. Mahajan, R. Sawaya, S.Y. Woo, Outcome variation among “radioresistant” brain metastases treated with stereotactic radiosurgery., Neurosurgery. 56 (2005) 936–45; discussion 936.

[13] C. Gaudy-Marqueste, J.-M. Regis, X. Muracciole, R. Laurans, M.-A. Richard, J.-J. Bonerandi, J.-J. Grob, Gamma-Knife radiosurgery in the management of melanoma patients with brain metastases: a series of 106 patients without whole-brain radiotherapy., Int J Radiat Oncol Biol Phys. 65 (2006) 809–16.

[14] D. Mathieu, D. Kondziolka, P.B. Cooper, J.C. Flickinger, A. Niranjan, S. Agarwala, J. Kirkwood, L.D. Lunsford, Gamma knife radiosurgery in the management of malignant melanoma brain metastases., Neurosurgery. 60 (2007) 471-81; discussion 481–2.

[15] J.W. Clarke, S. Register, J.M. McGregor, J.C. Grecula, N.A. Mayr, J.Z. Wang, K. Li, N. Gupta, K.L. Kendra, T.E. Olencki, R. Cavaliere, A. Sarkar, S.S. Lo, Stereotactic radiosurgery with or without whole brain radiotherapy for patients with a single radioresistant brain metastasis., Am J Clin Oncol. 33 (2010) 70–4.

[16] D.N. Liew, H. Kano, D. Kondziolka, D. Mathieu, A. Niranjan, J.C. Flickinger, J.M. Kirkwood, A. Tarhini, S. Moschos, L.D. Lunsford, Outcome predictors of Gamma Knife surgery for melanoma brain metastases. Clinical article., J Neurosurg. 114 (2011) 769–79.

[17] J.P.S. Knisely, J.B. Yu, J. Flanigan, M. Sznol, H.M. Kluger, V.L.S. Chiang, Radiosurgery for melanoma brain metastases in the ipilimumab era and the possibility of longer survival., J Neurosurg. 117 (2012) 227–33.

[18] Mathew M., Tam M., Ott P.A., Pavlick A.C., Rush S.C., Donahue B.R., Golfinos J.G., Parker E.C., Huang P.P., Narayana A., Ipilimumab in melanoma with limited brain metastases treated with stereotactic radiosurgery, Melanoma Res. 23 (2013) 191–195. doi:10.1097/CMR.0b013e32835f3d90.

[19] M.T. Neal, M.D. Chan, J.T. Lucas, A. Loganathan, C. Dillingham, E. Pan, J.H. Stewart, J.D. Bourland, E.G. Shaw, S.B. Tatter, T.L. Ellis, Predictors of survival, neurologic death, local failure, and distant failure after gamma knife radiosurgery for melanoma brain metastases., World Neurosurg. 82 (2014) 1250–5.

[20] Chowdhury I.H., Ojerholm E., McMillan M.T., Miller D., Kolker J.D., Kurtz G., Dorsey J.F., Nagda S.N., Geiger G.A., Brem S., O'Rourke D.M., Zager E.L., Gangadhar T., Schuchter L., Lee J.Y.K., Alonso-Basanta M., Novel risk scores for survival and intracranial failure in patients treated with radiosurgery alone to melanoma brain metastases, Radiat. Oncol. 10 (2015). doi:10.1186/s13014-015-0553-y.

[21] E.S. Choong, S. Lo, M. Drummond, G.B. Fogarty, A.M. Menzies, A. Guminski, B. Shivalingam, K. Clarke, G.V. Long, A.M. Hong, Survival of patients with melanoma brain metastasis treated with stereotactic radiosurgery and active systemic drug therapies., Eur J Cancer. 75 (2017) 169–178.

[22] R. Feng, E.K. Oermann, R. Shrivastava, A. Gold, B.T. Collins, D. Kondziolka, S.P. Collins, Stereotactic Radiosurgery for Melanoma Brain Metastases: A Comprehensive Clinical Case Series., World Neurosurg. 100 (2017) 297–304.

[23] Kiess A.P., Wolchok J.D., Barker C.A., Postow M.A., Tabar V., Huse J.T., Chan T.A., Yamada Y., Beal K., Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: Safety profile and efficacy of combined treatment, Int. J. Radiat. Oncol. Biol. Phys. 92 (2015) 368–375. doi:10.1016/j.ijrobp.2015.01.004.

[24] Tazi K., Hathaway A., Chiuzan C., Shirai K., Survival of melanoma patients with brain metastases treated with ipilimumab and stereotactic radiosurgery, Cancer Med. 4 (2015) 1–6. doi:10.1002/cam4.315.

[25] Cohen-Inbar O., Shih H.-H., Xu Z., Schlesinger D., Sheehan J.P., The effect of timing of stereotactic radiosurgery treatment of melanoma brain metastases treated with ipilimumab, J. Neurosurg. 127 (2017) 1007–1014. doi:10.3171/2016.9.JNS161585.

[26] S.N. Badiyan, W.F. Regine, M. Mehta, Stereotactic Radiosurgery for Treatment of Brain Metastases, J. Oncol. Pract. 12 (2016) 703–712. doi:10.1200/JOP.2016.012922.

[27] J.S. Weber, S.P. D'Angelo, D. Minor, F.S. Hodi, R. Gutzmer, B. Neyns, C. Hoeller, N.I. Khushalani, W.H. Miller, C.D. Lao, G.P. Linette, L. Thomas, P. Lorigan, K.F. Grossmann, J.C. Hassel, M. Maio, M. Sznol, P.A. Ascierto, P. Mohr, B. Chmielowski, A. Bryce, I.M. Svane, J.-J. Grob, A.M. Krackhardt, C. Horak, A. Lambert, A.S. Yang, J. Larkin, Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial, Lancet Oncol. 16 (2015) 375–384. doi:10.1016/S1470-2045(15)70076-8.

[28] J.D. Wolchok, V. Chiarion-Sileni, R. Gonzalez, P. Rutkowski, J.-J. Grob, C.L. Cowey, C.D. Lao, J. Wagstaff, D. Schadendorf, P.F. Ferrucci, M. Smylie, R. Dummer, A. Hill, D. Hogg, J. Haanen, M.S. Carlino, O. Bechter, M. Maio, I. Marquez-Rodas, M. Guidoboni, G. McArthur, C. Lebbé, P.A. Ascierto, G.V. Long, J. Cebon, J. Sosman, M.A. Postow, M.K. Callahan, D. Walker, L. Rollin, R. Bhore, F.S. Hodi, J. Larkin, Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma, N. Engl. J. Med. 377 (2017) 1345–1356. doi:10.1056/NEJMoa1709684.

[29] A. Keller, M. Doré, H. Cebula, F. Thillays, F. Proust, I. Darié, S.-A. Martin, G. Delpon, F. Lefebvre, G. Noël, D. Antoni, Hypofractionated Stereotactic Radiation Therapy to the Resection Bed for Intracranial Metastases, Int. J. Radiat. Oncol. Biol. Phys. 99 (2017) 1179–1189. doi:10.1016/j.ijrobp.2017.08.014.

[30] X. Lin, L.M. DeAngelis, Treatment of Brain Metastases, J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 33 (2015) 3475–3484. doi:10.1200/JCO.2015.60.9503.

[31] ICRU, International Commission on Radiation Units and Measurements. Prescribing, recording, and reporting photon-beam intensity-modulated radiation therapy (IMRT). ICRU Report 83, 2010.

[32] ICRU, International Commission on Radiation Units and Measurements. Prescribing, Recording, and Reporting Stereotactic Treatments with Small Photo Beams. ICRU report 91., 2017.

Stereotactic radiation therapy in melanoma brain metastasis: a European multicentric cohort

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Résumé

Introduction

Quinze à 20% des patients présentent des métastases lors du diagnostic initiale de mélanome et le risque de développer des métastases cérébrales augmentent avec la durée de la maladie. Les recommandations de l'ESMO et de l'ANOCEF recommandent l'irradiation stéréotaxique des métastases cérébrales de mélanome non opérable chez les patients ayant une espérance de vie supérieure à 3 mois.

Nous avons conduit une étude rétrospective, multicentrique internationale afin d'évaluer les résultats de la radiothérapie stéréotaxique mono fractionnée et hypo fractionnée des métastases cérébrales de mélanome.

Méthodes

Nous avons recueilli les données cliniques de 150 patients et 298 métastases cérébrales traités entre le 01/01/2009 et le 31/12/2015 dans 6 départements de radiothérapie français et allemand. Pour être inclus les patients devaient avoir une confirmation histologique du diagnostic de mélanome et des métastases cérébrales < 50mm. Le taux de réponse et ses déterminant ont été étudié par un modèle de régression logistique multivarié, les survies globale et sans récidive intracrânienne ont été étudiée par la méthode de Kaplan Meier et par un modèle de Cox.

Résultats

La mutation BRAF (HR = 0,44), l'administration d'Ipilimumab (HR = 0,49), les métastases cérébrales multiples (HR = 0,37) et la durée entre l'IRM dosimétrique et le début du traitement (HR = 0,84) influent négativement sur la probabilité de réponse au traitement. La radiothérapie stéréotaxique mono fractionnée (HR = 3,63) et le contrôle de la maladie systémique (HR = 3,64) influent positivement sur la réponse au traitement. Le volume du PTV semble ne pas influer sur le taux de réponse (HR = 0,98).

La médiane de survie globale était de 11 mois (IC 95% [8 – 20 mois]). La médiane de survie sans récidive intra-cérébrale était de 9 mois (IC 95% [6 – 17 mois]).

Conclusion

Nous rapportons les résultats de la plus grosse série de radiothérapie stéréotaxique mono et hypo fractionnée de métastases cérébrales de mélanome délivré par accélérateur linéaire. Les résultats de notre analyse suggèrent que le traitement devrait être débuté rapidement après la réalisation de l'IRM dosimétrique et que la radiothérapie mono fractionnée devrait être préférée à la radiothérapie hypo fractionnée lorsque la taille de métastases le permet.

Abstract

Introduction

Melanoma brain metastasis represents 10% of brain metastasis, and current guidelines state that stereotactic radiosurgery (SRS) and stereotactic hypofractionated radiotherapy (HFSRT) should be preferred over whole brain irradiation (WBRT). On behalf of the ANOCEF, we conducted this international, multicentric analysis to evaluate and compare the outcomes of SRS and HFSRT in melanoma brain metastasis management.

Methods

We conducted a multicentric retrospective analysis involved 150 patients with 298 melanoma brain metastases treated from 01/01/2009 to 31/12/2015 in 6 radiation oncology departments in France and in Germany. The primary endpoint of the study was the radiological response rate define as a complete response, partial response or stability of the metastasis according to the RANO-BM criteria. Secondary endpoints included overall survival (OS) and brain progression-free survival (BPFS).

Results

BRAF mutation (HR = 0.44), Ipilimumab administration (HR = 0.49), multiple brain metastases (HR = 0.37) and longtime from dosimetric MRI to treatment (HR = 0.84) negatively affect the response rate, SRS (HR = 3.63) and control of the disease (HR = 3.64) positively impact the response rate. Finally, the PTV volume seems to have low influence on the response rate (HR = 0.98). The median OS from initial treatment was 11 months (CI 95% [8 – 20]). The median BPFS from initial treatment was 9 months (CI 95% [6 – 17]).

Conclusion

We report the results of the analysis of one of the largest multicentric cohort of patients with melanoma brain metastases treated with SRS or HFSRT delivered with LINAC. The results of our analysis suggest that treatment should be started closed from dosimetric MRI and that SRS should be preferred over HFSRT when safely feasible given the size of the metastases.

Introduction

Melanoma brain metastasis represents 10% of brain metastasis; melanoma is the third cause of brain metastasis following breast and lung cancer. Moreover, the risk of developing brain metastasis in melanoma patients rise with the duration of the disease [1,2]. Brain metastases occur in a median time of 2.2 to 3.8 years from the beginning of the disease, and 15 to 20% of patients are diagnosed with brain metastasis at initial staging [3–5].

Current European Society for Medical Oncology (ESMO) guidelines stated that stereotactic radiosurgery (SRS) and stereotactic hypofractionated radiotherapy (HFSRT) should be preferred over whole brain irradiation (WBRT) [6]. The French-speaking neuro-oncologist association – "*Association des neuro-oncologies de langue française*" (ANOCEF) guidelines concluded that SRS and HFSRT is a valid treatment option regardless of the number of metastasis when the life expectancy is at least 3 months [7]. A recent unpublished systematic review of the literature that we conducted reported metastasis response rates ranging from 53 to 98.2%. However, as stated in this analysis, all but one studies was monocentric and mostly based on the Gamma knife system. Moreover, a recent study reported significant differences in radiosensitivity on the basis of the primary histologic type of lung metastases. Thus a similar approach could be considered in brain metastases [8].

On behalf of the ANOCEF, we conducted this international, multicentric analysis to evaluate and compare the outcomes of SRS and HFSRT in melanoma brain metastasis management.

Materials and methods

Study design

This European, multicentric retrospective analysis involved 150 patients with 298 melanoma brain metastases treated from 01/2009 to 12/2015 in 6 radiation oncology departments in France and in Germany. A study protocol has been written, and a data collection form was given to each of the investigators to uniformize the data collection.

The scientific board of the ANOCEF has approved the study protocol.

Patients

To be eligible for SRS or HFSRT patients must have met the following criteria: 1) histologic diagnosis of primary melanoma, 2) metastasis less than 50 mm in greater dimension, 3) no age restriction, 4) No previous surgery of the metastases, 5) treatment delivered by linear accelerator (Linac) in 1 to 5 fractions. The patient could not be included in the study if one lesion diameter was greater than 50mm or if the radiotherapy prescription was missing.

Statistical methods

The number of patients included in this study was determined as any patient treated during the interval of the study and meeting the selection criteria. One person using a university hospital database performed data collection. The primary endpoint of the study was the radiological response rate define as a complete response, partial response or stability of the metastasis according to the RANO-BM criteria [9]. Secondary endpoints included overall survival (OS), with OS defined as the time between the beginning of the radiation therapy treatment and the date of death from any cause, brain progression-free survival (BPFS), where BPFS was defined as the time between the beginning of radiation therapy treatment and the date of brain recurrence diagnosed on CT scan or MRI, and safety.

Acute and late toxicities were assessed using Common Terminology Criteria for Adverse Events v4.0 (CTCAE) [10].

Statistical analyses

Statistical analyses were performed using R v3.4.3 and *Just Another Gibbs Sampler* (JAGS). Categorical data were analyzed as frequency counts and percentages; whereas, measured data were evaluated using medians and ranges. A Bayesian logistic regression was performed to evaluate explanatory variables for a response rate of metastases. Bayesian method allows to take into account prior information on the studied parameters, based on data available in the literature and on clinician experience, to produce a posterior belief of the parameters after observing the evidence [11]. The results are expressed as

probability distributions, and the credibility intervals, which can be compared to confidence intervals in the frequentist method could be adjusted given the clinical situation. Finally, no p-value is expressed, but be report the probability of the Odds Ratio to be superior or inferior to 1. To select the variables included in the model, we assessed the potential multicollinearity between variables with the Variation Inflation Factor and used a threshold of 4. OS and BPFS were determined using the Kaplan-Meier method. Factors influencing OS and BPFS were first evaluated with a univariate Cox analysis with a significant cutoff of $p<0.2$. Multicollinearity was also checked using a VIF threshold of 4. A stepwise backward procedure was used to build the multivariate Cox model to evaluate the impact of potential variables on OS and BPFS.

Results

Baseline patients and treatment characteristics are summarized in Table 1.

Treatment planning included dosimetric CT-scan and dosimetric MRI. A Gross Tumor Volume (GTV) was delineated on the dosimetric MRI and a 0.1 to 0.2mm geometric expansion was applied to generate the Planning Target Volume (PTV). Patient immobilization was ensured by thermoplastic mask. Treatment dosimetry was performed with Iplan® (Brainlab, Munich, Germany) in four departments, Eclipse™ (Varian, Palo Alto, USA) in one department and Multiplan™ (Accuray, Sunnyvale, USA). Treatment was delivered on the Novalis® (Varian, Palo Alto, USA), in one department, Novalis TX® (Varian, Palo Alto, USA) in two departments, Trilogy® (Varian, Palo Alto, USA) in one department, Cyberknife® (Accuray, Sunnyvale, USA) in one department and Truebeam Novalis STX® (Varian, Palo Alto, USA) in one department.

SRS median prescribed dose was 20Gy in one fraction (range [16Gy – 27.5Gy]). HFSRT median prescribed dose was 33Gy (range [24Gy – 35Gy]) in 3 fractions (range [3 - 7]) of 11Gy (range [5Gy – 11Gy]).

Table 1: Patients and metastases characteristics

	% (N)/Median	IQR	Min	Max
Departement				
a	6 (9)			
b	6 (9)			
c	38 (57)			
d	14 (21)			
e	10 (15)			
f	26 (39)			
Sex				
Femme	35 (52)			
Homme	65 (97)			
Age	58	19	0	86
WHO performans statut				
5	0 (0)			
4	0.72 (1)			
3	0.72 (1)			
2	4.3 (6)			
1	38 (53)			
0	56 (78)			
Karnofsky index				
0	0 (0)			
10	0 (0)			
20	0 (0)			
30	0 (0)			
40	0 (0)			
50	1.3 (1)			
60	1.3 (1)			
70	3.9 (3)			
80	16 (12)			
90	32 (24)			
100	46 (35)			
LDH	375	307	0	7219
BRAF mutated				
No	56 (59)			
Yes	44 (46)			
Extra-cranial metastases				
No	23 (34)			
Yes	77 (116)			
Extra-cranial disease controlled				
No	41 (59)			
Yes	59 (84)			
Multiple brain metastases				
No	52 (77)			
Yes	48 (72)			
History of whole brain irradiation				
No	94 (107)			

Yes	6 (7)			
Chemotherapy				
No	72 (77)			
Yes	28 (30)			
ipilimumab				
No	75 (104)			
Yes	25 (35)			
Fractionnation				
HFSRT	39 (117)			
SRS	61 (181)			
Time between MRI and treatment (days)	7	10	0	49
Volume of PTV (mL)	2.7	9.5	0.1	222

Response rate

Mean response rates for metastasis treated with SRS or HFSRT were 67.5% (CI 95% [57% – 77.9%]) and 47.8% (CI 95% [30.8% – 64.7%]), respectively. The results of the Bayesian multivariate logistic regression are reported in Table 2, and the distributions of the Odds Ratio are depicted in Figure 1.

Table 2: Results of the Bayesian multivariate logistic regression on the probability of response of melanoma brain metastases

	mean OR	**sd**	**2.5%**	**97.5%**	**p(OR<1)**	**p(OR>1)**
BRAF mutated	0.43	0.21	0.15	0.94	0.98	0.02
Disease controlled	3.74	2.78	0.92	10.87	0.03	0.97
Time from dosimetric MRI to treatment	0.86	0.04	0.78	0.93	1.00	0.00
Ipilimumab	0.46	0.25	0.14	1.1	0.96	0.04
Multiple brain metastases	0.43	0.25	0.12	1.06	0.97	0.03
PTV volume (cm3)	0.98	0.01	0.96	1	1.00	0.00
SRS	3.20	2.62	0.66	10.05	0.09	0.91

OR: odd ratio; PTV : planning target volume

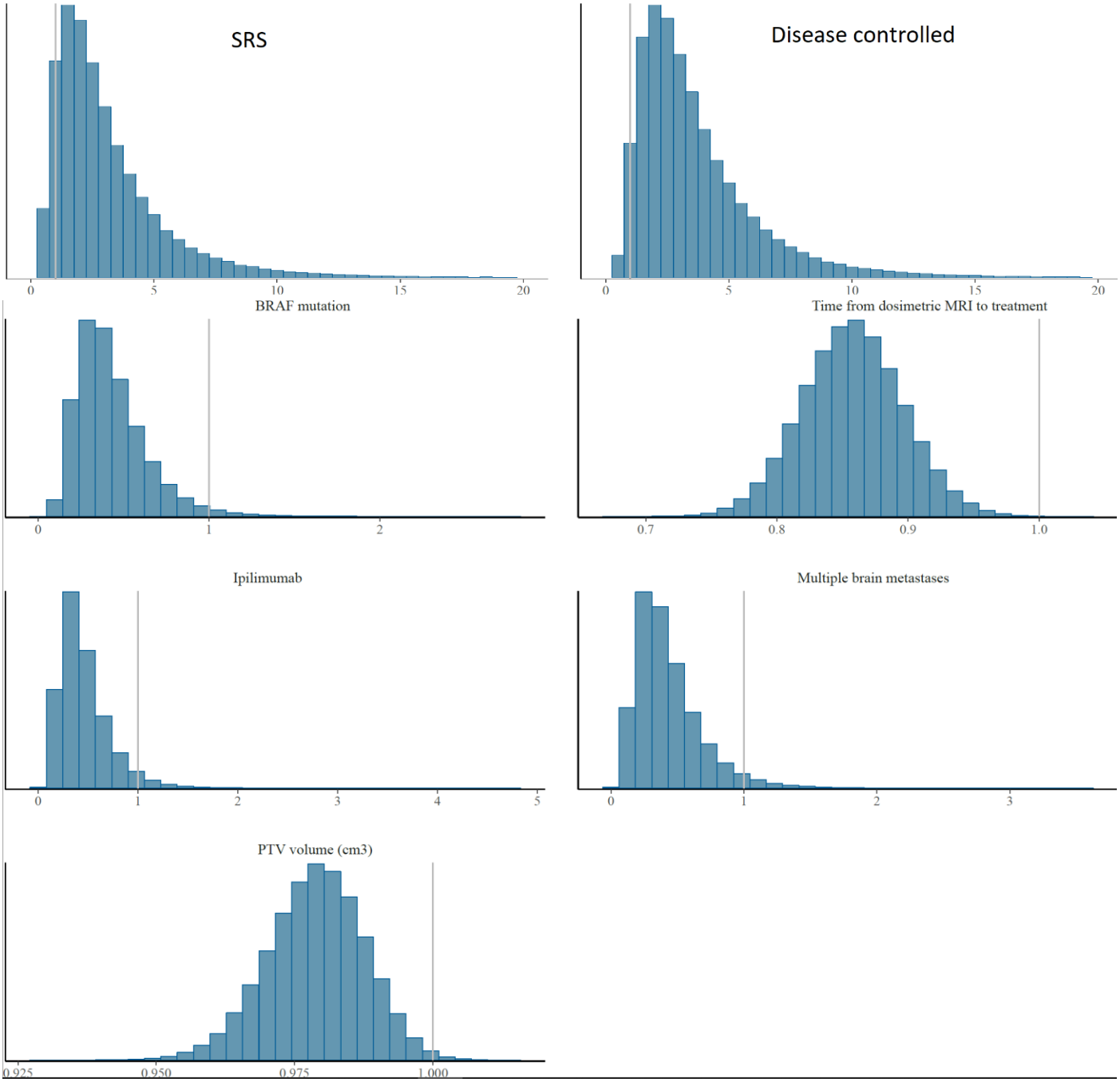

Figure 1: Distributions of Odds ratio estimated by the Bayesian multivariate logistic regression

Overall survival

The median follow-up from initial treatment was 31 months (CI 95% [26 - 39]). The median OS from initial treatment was 11 months (CI 95% [8 – 20]). Six, 12- and 18-months OS rates were 72.7%, 47.7% and 42.7% respectively. Kaplan-Meier survival curve is reported in Figure 2. According to the multivariate Cox analysis, the control of the systemic disease and the brain progression-free survival have an influence on OS with Hazard Ratios of 0.365 (sd = $3.76e^{-1}$, p = 0.0073) and

0.828 (sd = $4.02e^{-2}$, p < 0.001).

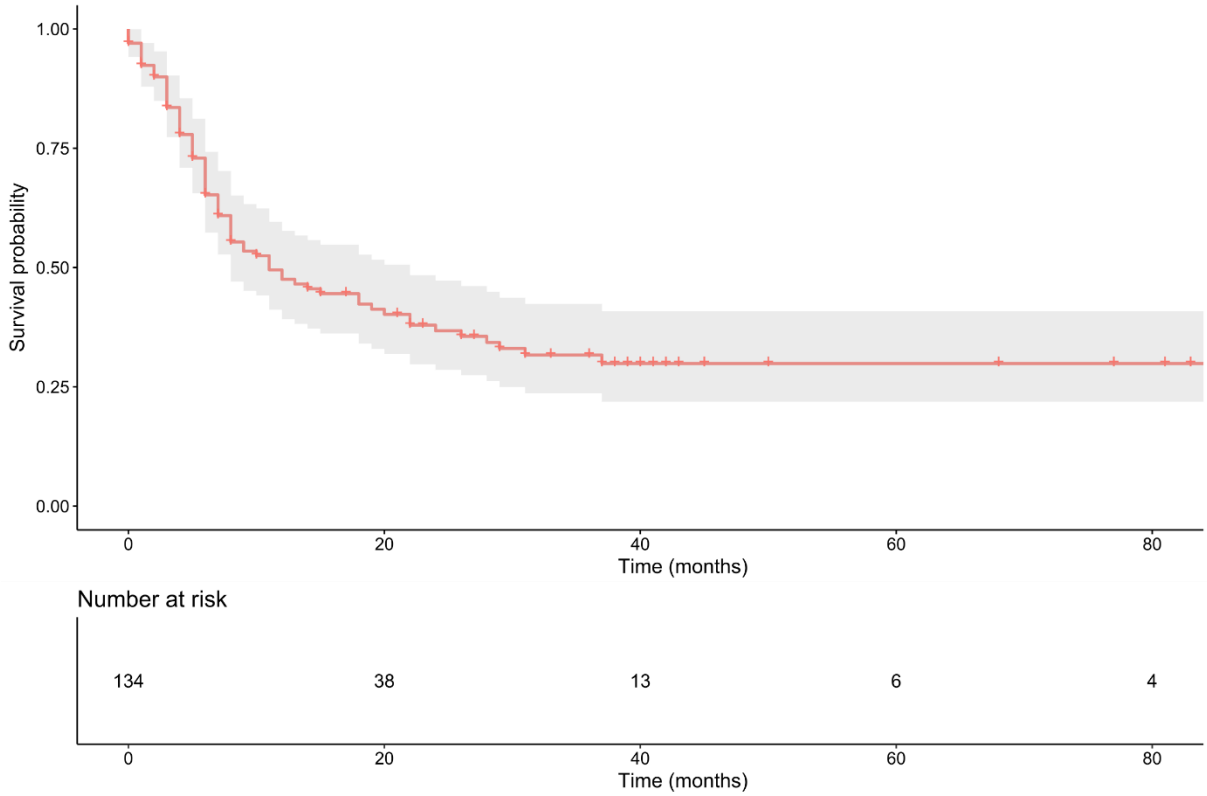

Figure 2: Kaplan Meier survival curve of overall survival

Brain progression-free survival

The median BPFS from initial treatment was 9 months (CI 95% [6 – 17]). Six, 12 and 18 months BPFS rates were 54.9%, 44.5% and 38% respectively. Kaplan Meier survival curve is reported in Figure 3. The multivariate Cox analysis did not report meaningful results for a predictive factor of survival.

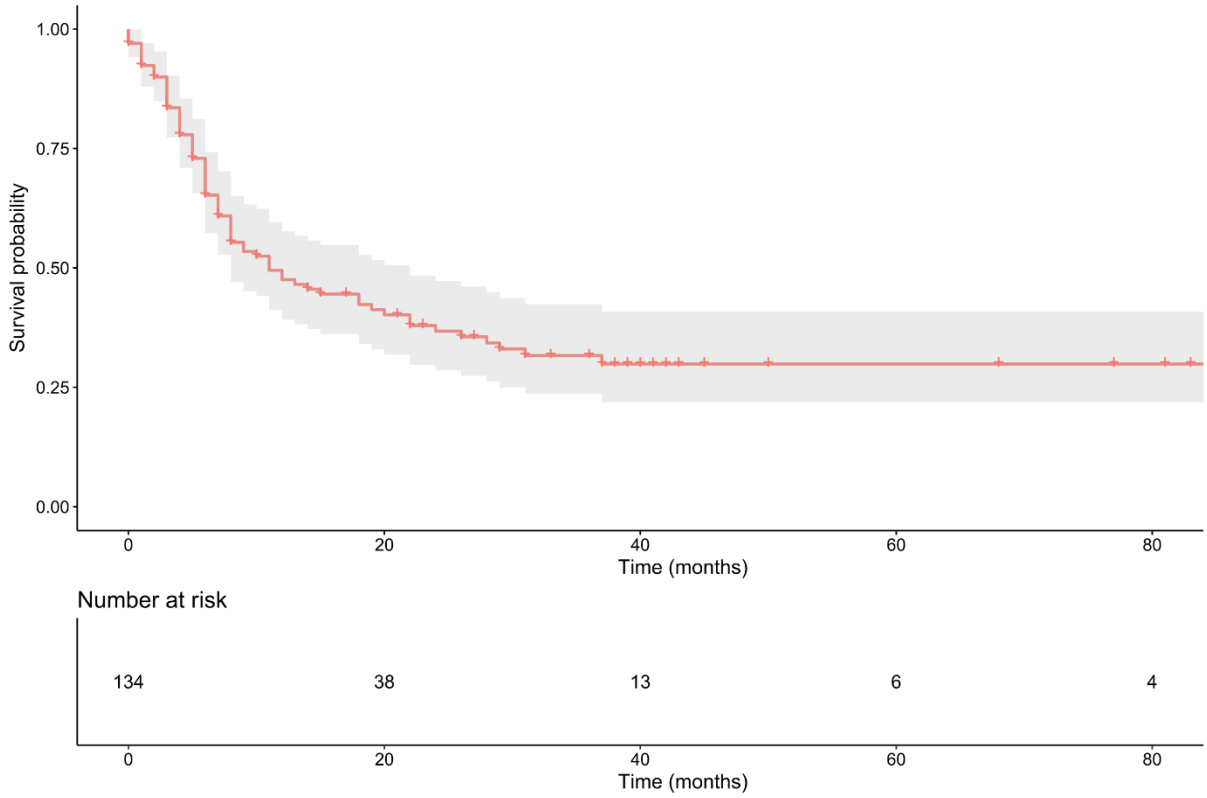

Figure 3: Kaplan Meier survival curve of brain progression free survival

Discussion

We report the results of the analysis of one of the largest multicentric cohort of patients with melanoma brain metastases treated with SRS or HFSRT delivered with LINAC.

A recent study compared SRS and HFSRT in melanoma and renal carcinoma brain metastasis and reported response rates of 73% and 68% respectively, which is consistent with our data for SRS and better for HFSRT. However, they had a smaller population and included renal cancer [12]. The mean response rates of 67.5% and 47.8% for SRS and HFSRT retrieve in our analysis are lower than the response rates published in other studies ranging from 67% to 83.6% [13], However, those studies included various primary histology. Thus, we can hypothesize that primary histology influence the response rate of brain metastases to SRS and HFSRT, which is consistent with the result of a recent study in lung metastases treated with stereotactic body radiotherapy [8].

Our analysis suggests that BRAF mutation, Ipilimumab administration, multiple brain metastases and a long time from dosimetric MRI to treatment negatively affect the response rate and that SRS and control of the disease positively impact the response rate. PTV seems to have low influence on the probability of response to treatment.

The median, the 6-months and the 12-months OS of our cohort are higher than the values reported in the literature: 4 – 9.1 months, 38 – 69% and 24 – 45% respectively [12,14]. Those differences might be explained by the better overall condition of patients prior to treatment and the probable role of the targeted therapy recently introduced in the management of metastatic melanoma.

This study confirmed that regional control of melanoma brain metastases and control of the systemic disease impact on OS.

We have been able to identify some factors that lead to worst outcomes of SRS and HFSRT, and that should make consider a more aggressive treatment such as surgery and stereotactic irradiation of the tumoral bed. BRAF mutational status influence on treatment response has been reported in another publication, and it has been hypothesized that BRAF mutation leads to radiation resistance [15,16]. The timing of Ipilimumab administration has been reported as a prognostic factor of response to SRS/HFSRT in melanoma brain metastases [17,18]. However, we did not have access to this information in our analysis. Several studies reported an improvement of melanoma brain metastases when Ipilimumab was administrated, however, they also reported an increase of radionecrosis and treatment-related imaging changes (TRICs), which could have been interpreted has treatment failure in the data collected which can explain that our analysis reported that Ipilimumab administration was associated to a lower response probability [19–21].

Finally, the 1-year BPFS retrieves from our analysis is consistent with the literature, for primary of all types, with 1-year BPFS ranging from 24 to 74.2%. However, in our study 2-years BPFS rates seems to be worse than the rates retrieve in the literature which ranges from 67.6 to 82.4%, which can be explain by the better OS of our cohort [12–14].

Conclusion

The results of our analysis confirm that treatment should be started closed from dosimetric MRI. Our analysis suggests that SRS leads to better local control of MBM. Finally, the Bayesian approach allows a more clinically relevant analysis, by providing a probability of statically significant difference rather than a threshold as in frequentist statistics.

Furthermore, HFSRT induced transportation cost, whereas SRS requires most of the time a 24h hospitalization. Cost-effectiveness of both strategies should be assessed in order to set guidelines.

References

[1] J.D. Johnson, B. Young, Demographics of brain metastasis, Neurosurg. Clin. N. Am. 7 (1996) 337–344.

[2] J.M. Skibber, S.J. Soong, L. Austin, C.M. Balch, R.E. Sawaya, Cranial irradiation after surgical excision of brain metastases in melanoma patients, Ann. Surg. Oncol. 3 (1996) 118–123.

[3] M.A. Davies, P. Liu, S. McIntyre, K.B. Kim, N. Papadopoulos, W.-J. Hwu, P. Hwu, A. Bedikian, Prognostic factors for survival in melanoma patients with brain metastases, Cancer. 117 (2011) 1687–1696. doi:10.1002/cncr.25634.

[4] M.S. Carlino, G.B. Fogarty, G.V. Long, Treatment of melanoma brain metastases: a new paradigm, Cancer J. Sudbury Mass. 18 (2012) 208–212. doi:10.1097/PPO.0b013e31824b2890.

[5] A.Y. Bedikian, C. Wei, M. Detry, K.B. Kim, N.E. Papadopoulos, W.-J. Hwu, J. Homsi, M. Davies, S. McIntyre, P. Hwu, Predictive factors for the development of brain metastasis in advanced unresectable metastatic melanoma, Am. J. Clin. Oncol. 34 (2011) 603–610. doi:10.1097/COC.0b013e3181f9456a.

[6] R. Dummer, A. Hauschild, N. Lindenblatt, G. Pentheroudakis, U. Keilholz, Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up, Ann. Oncol. 26 (2015) v126–v132. doi:10.1093/annonc/mdv297.

[7] É. Le Rhun, F. Dhermain, G. Noël, N. Reyns, A. Carpentier, E. Mandonnet, S. Taillibert, P. Metellus, ANOCEF. l'Association des neuro-oncologies d'expression franc¸aise, [ANOCEF guidelines for the management of brain metastases], Cancer Radiother. J. Soc. Francaise Radiother. Oncol. 19 (2015) 66–71. doi:10.1016/j.canrad.2014.11.006.

[8] K.A. Ahmed, J.G. Scott, J.A. Arrington, A.O. Naghavi, G.D. Grass, B.A. Perez, J.J. Caudell, A.E. Berglund, E.A. Welsh, S.A. Eschrich, T.J. Dilling, J.F. Torres-Roca, Radiosensitivity of Lung Metastases by Primary Histology and Implications for Stereotactic Body Radiation Therapy Using the Genomically Adjusted Radiation Dose, J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer. 13 (2018) 1121–1127. doi:10.1016/j.jtho.2018.04.027.

[9] N.U. Lin, E.Q. Lee, H. Aoyama, I.J. Barani, D.P. Barboriak, B.G. Baumert, M. Bendszus, P.D. Brown, D.R. Camidge, S.M. Chang, J. Dancey, E.G.E. de Vries, L.E. Gaspar, G.J. Harris, F.S. Hodi, S.N. Kalkanis, M.E. Linskey, D.R. Macdonald, K. Margolin, M.P. Mehta, D. Schiff, R. Soffietti, J.H. Suh, M.J. van den Bent, M.A. Vogelbaum, P.Y. Wen, Response Assessment in Neuro-Oncology (RANO) group, Response assessment criteria for brain metastases: proposal from the RANO group, Lancet Oncol. 16 (2015) e270-278. doi:10.1016/S1470-2045(15)70057-4.

[10] National Cancer Institute, Common Terminology Criteria for Adverse Events v4.0 (CTCAE), (n.d.). http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

[11] L. Freedman, Bayesian statistical methods, BMJ. 313 (1996) 569–570.

[12] P. Lesueur, J. Lequesne, V. Barraux, W. Kao, J. Geffrelot, J.-M. Grellard, J.-L. Habrand, E. Emery, B. Marie, J. Thariat, D. Stefan, Radiosurgery or hypofractionated stereotactic radiotherapy for brain metastases from radioresistant primaries (melanoma and renal cancer), Radiat. Oncol. Lond. Engl. 13 (2018) 138. doi:10.1186/s13014-018-1083-1.

[13] S. Scoccianti, U. Ricardi, Treatment of brain metastases: review of phase III randomized controlled trials, Radiother. Oncol. J. Eur. Soc. Ther. Radiol. Oncol. 102 (2012) 168–179. doi:10.1016/j.radonc.2011.08.041.

[14] S.M. Nguyen, A. Castrellon, O. Vaidis, A.E. Johnson, Stereotactic Radiosurgery and Ipilimumab Versus Stereotactic Radiosurgery Alone in Melanoma Brain Metastases, Cureus. 9 (2017) e1511. doi:10.7759/cureus.1511.

[15] P. Fang, N.S. Boehling, E.J. Koay, A.D. Bucheit, J.A. Jakob, S.H. Settle, P.D. Brown, M.A. Davies, E.P. Sulman, Melanoma brain metastases harboring BRAF V600K or NRAS mutations are associated with an increased local failure rate following conventional therapy, J. Neurooncol. 137 (2018) 67–75. doi:10.1007/s11060-017-2695-2.

[16] M.J. Sambade, E.C. Peters, N.E. Thomas, W.K. Kaufmann, R.J. Kimple, J.M. Shields, Melanoma cells show a heterogeneous range of sensitivity to ionizing radiation and are radiosensitized by inhibition of B-RAF with PLX-4032, Radiother. Oncol. J. Eur. Soc. Ther. Radiol. Oncol. 98 (2011) 394–399. doi:10.1016/j.radonc.2010.12.017.

[17] Cohen-Inbar O., Shih H.-H., Xu Z., Schlesinger D., Sheehan J.P., The effect of timing of stereotactic radiosurgery treatment of melanoma brain metastases treated with ipilimumab, J. Neurosurg. 127 (2017) 1007–1014. doi:10.3171/2016.9.JNS161585.

[18] J.D. Schoenfeld, A. Mahadevan, S.R. Floyd, M.A. Dyer, P.J. Catalano, B.M. Alexander, D.F. McDermott, I.D. Kaplan, Ipilmumab and cranial radiation in metastatic melanoma patients: a case series and review, J. Immunother. Cancer. 3 (2015) 50. doi:10.1186/s40425-015-0095-8.

[19] K. Diao, S.X. Bian, D.M. Routman, C. Yu, P.E. Kim, N.A. Wagle, M.K. Wong, G. Zada, E.L. Chang, Combination ipilimumab and radiosurgery for brain metastases: tumor, edema, and adverse radiation effects, J. Neurosurg. (2018) 1–10. doi:10.3171/2017.7.JNS171286.

[20] K. Diao, S.X. Bian, D.M. Routman, C. Yu, J.C. Ye, N.A. Wagle, M.K. Wong, G. Zada, E.L. Chang, Stereotactic radiosurgery and ipilimumab for patients with melanoma brain metastases: clinical outcomes and toxicity, J. Neurooncol. (2018). doi:10.1007/s11060-018-2880-y.

[21] C. Nardin, C. Mateus, M. Texier, E. Lanoy, S. Hibat-Allah, S. Ammari, C. Robert, F. Dhermain, Tolerance and outcomes of stereotactic radiosurgery combined with anti-programmed cell death-1 (pembrolizumab) for melanoma brain metastases, Melanoma Res. 28 (2018) 111–119. doi:10.1097/CMR.0000000000000413.

Stereotactic radiation therapy in colorectal cancer brain metastasis: an European, multicentric cohort

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Résumé

Introduction

Le cancer colorectal (CCR) est le troisième en ordre de fréquence dans les pays développé, mais les métastases cérébrales de surviennent que dans 1% des cas. La survie globale des patients atteints de CCR augmente du fait des nouvelles thérapies systémiques, de ce fait l'incidence des métastases cérébrales va tendre à augmenter. Nous avons réalisé une étude multicentrique pour évaluer et comparer les résultats des la radiothérapie stéréotaxique mono (SRS) et hypo fractionnée (HFSRT) dans la prise en charge des métastases cérébrales de CCR.

Méthodes

Sous l'égide de l'association des Neuro-Oncologues de langue Française (ANOCEF), nous avons collecté rétrospectivement les données individuelles de patients traités par SRS ou HFSRT pour des métastases cérébrales de CCR au sein de 6 centres de radiothérapie en France et en Allemagne.

Le critère de jugement principal était le taux de réponse radiologique selon les critères RANO BM.

Résultats

La taux de réponse médian était de 65,9% (IC 95% [51,9% - 79,9%]) et était influencé positivement par le traitement par SRS, alors qu'il était négativement influencé par les métastases cérébrales multiples.

La médian de survie globale était de 10 mois (IC 95% [5 – 22 mois]) et était influencée négativement par l'existence de métastases extra-cérébrales, le sexe masculin et était influencée positivement par la survie sans récidive intra-cérébrales.

Conclusion

Cette analyse suggère que la radiothérapie stéréotaxique mono fractionnée est plus efficace dans le traitement des métastases cérébrales de CCR. De plus, elle démontre que la survie sans récidive intra-cérébrale influe sur la survie globale.

Abstract

Introduction

Colorectal cancer (CRC) is the third most common cancer in western countries, but brain metastases only occur in 1% of CRC patients. Overall survival in CRC patients rises as new systemic drugs became available. Thus the incidence of brain metastases in CRC patients will likely increase. We conducted a multicentric analysis to evaluate and compare the outcomes of stereotactic radiosurgery (SRS) and hypofractionated stereotactic radiotherapy (HFSRT) in CRC brain metastasis management.

Methods

On behalf of the association of French-speaking neuro-oncologist (ANOCEF), we retrospectively collected individual data of patients treated with SRS or HFSRT for CRC brain metastases in 6 hospitals in France and Germany. The primary endpoint of the study was the radiological response rate define as a complete response, partial response or stability of the metastasis according to RANO BM criteria.

Results

The median response rate for metastasis treated was 65.9% (CI 95% [51.9% – 79.9%]) and was positively influenced by SRS whereas multiple brain metastases were related to poorest response rates. The median overall survival (OS) from initial treatment was ten months (CI 95% [5 – 22]). OS was negatively influenced by extra-cranial metastases, male gender, whereas it influenced positively by brain progression-free survival (BPFS).

Conclusion

This analysis suggests that SRS should prefer over HFSRT in patients with limited CRC brain metastases. Moreover, it demonstrates that BPFS directly impact OS.

Introduction

Colorectal cancer (CRC) is the third most common cancer in western countries. Visceral metastases are common in CRC as 20% of CRC patients have metastases at initial staging and 25% of CRC patients will develop metastases [1,2]. However, brain metastases only occur in 1% of CRC patients. Overall survival in CRC patients rises as new systemic drugs became available. Thus the incidence of brain metastases in CRC patients will likely increase which is also favored by the fact that many systemic therapies do not cross the blood-brain barrier [3]. Brain metastases from CRC are always the last occurrence and poor prognostic factor of the disease, with median survival, ranges from 1.0 to 5.7 months [4].

According to the American Society for Radiation Oncology (ASTRO) and to the French-speaking neuro-oncologist association – "*Association des neuro-oncologies de langue française*" (ANOCEF) guidelines, stereotactic radiosurgery (SRS) and hypofractionated stereotactic radiotherapy (HFSRT) are a treatment options for single metastasis smaller than 30 – 40 mm and for multiple metastases smaller than 30 – 40 mm if the patient has an expected survival of 3 months or more. However, despite an increased risk of radionecrosis for metastasis larger than 30 mm treated with SRS, there is no consensus in which regimen to use in smaller metastases [5]. A recent study reported significant differences in radiosensitivity on the basis of the primary histologic type of lung metastases, thus a similar approach could be considered in brain metastases [6]. Moreover, the rise of health expenses related to technologic development, there is a need to rationalize our decision based on treatment efficiency.

We conducted this multicentric analysis to evaluate and compare the outcomes of SRS and HFSRT in CRC brain metastasis management.

Materials and methods

Study design

This international, multicentric retrospective analysis involved 58 patients and 69 metastases treated from 01/01/2009 to 31/12/2015 in 6 radiation oncology departments in France and Germany. A study

protocol has been written, and a data collection form was given to each of the investigators to uniformize the data collection. The scientific board of the ANOCEF has approved the study protocol.

Patients

To be eligible for SRS or HFSRT patients must have met the following criteria: 1) histologic diagnosis of primary colorectal cancer, 2) less than 50 mm in greater dimension, 3) no age restriction, 4) no previous surgery of the metastases, 5) treatment delivered by linac in 1 to 5 fractions. The patient could not be included in the study if one lesion diameter was greater than 50 mm or if the radiotherapy prescription was missing.

Statistical methods

The number of patients included in this study was determined as any patient treated during the interval of the study and meeting the selection criteria. Data collection was performed by one person using a university hospital database. The primary endpoint of the study was the radiological response rate define as a complete response, partial response or stability of the metastasis according to RANO BM criteria [7]. Secondary endpoints included overall survival (OS), with OS defined as the time between the beginning of the radiation therapy treatment and the date of death from any cause, brain progression-free survival (BPFS), where BPFS was defined as the time between the beginning of radiation therapy treatment and the date of brain recurrence diagnosed on CT scan or MRI, and safety.

Acute and late toxicities were assessed using Common Terminology Criteria for Adverse Events v4.0 (CTCAE) [8].

Statistical analysis

Statistical analyses were performed using R v3.4.3. Categorical data were analyzed as frequency counts and percentages; whereas, measured data were evaluated using medians and ranges. Bayesian logistic regression was performed to evaluate explanatory variables for a response rate of metastases. To select the variables included in the model, we assessed the potential multicollinearity between variables with the Variation Inflation Factor and used a threshold of 4. OS and BPFS were determined using the

Kaplan-Meier method. Factors influencing OS and BPFS were first evaluated with a univariate Cox analysis with a significant cutoff of $p < 0.2$. Multicollinearity was also assessed using a VIF threshold of 4. A stepwise backward procedure was used to build the multivariate Cox model to evaluate the impact of potential variables on OS and BPFS.

Results

Baseline patients and treatment characteristics are summarized in Table 1.

Treatment planning included dosimetric CT-scan and dosimetric MRI. A Gross Tumor Volume (GTV) was delineated on the dosimetric MRI and a 0.1 to 0.2mm geometric expansion was applied to generate the Planning Target Volume (PTV). Patient immobilization was ensured by thermoplastic mask. Treatment dosimetry was performed with Iplan® (Brainlab, Munich, Germany) in four departments, Eclipse™ (Varian, Palo Alto, USA) in one department and Multiplan™ (Accuray, Sunnyvale, USA). Treatment was delivered on the Novalis® (Varian, Palo Alto, USA), in one department, Novalis TX® (Varian, Palo Alto, USA) in two departments, Trilogy® (Varian, Palo Alto, USA) in one department, Cyberknife® (Accuray, Sunnyvale, USA) in one department and Truebeam Novalis STX® (Varian, Palo Alto, USA) in one department.

The median prescribed dose for SRS was 20Gy (range [17 – 20]), with 14Gy delivered to the 70% isodose line. The median prescribed dose for HFSRT was 33Gy (range [15 – 35] with 23.1Gy delivered to the 70% isodose line.

Response rate

The median response rate for metastasis treated was 65.9% (CI 95% [51.9% – 79.9%]). Response rate were 65.9% (CI 95% [51.4% - 80.4%]) and 66.7% (CI 95% [13.4% - 100%]) for HFSRT and SRS respectively.

The results of the Bayesian multivariate logistic regression are reported in Table 2, and the distributions of the Odds Ratio are depicted in Figure 1.

Table 1: Patients and metastases characteristics

	%/Median	IQR	Min	Max
Centre				
A	11 (6)			
B	8.8 (5)			
C	7 (4)			
D	21 (12)			
E	35 (20)			
F	18 (10)			
Sex				
Female	35 (20)			
Male	65 (37)			
Age	65	16	40	87
WHO Performans status				
5	0 (0)			
4	0 (0)			
3	1 (1)			
2	13 (7)			
1	56 (30)			
0	30 (16)			
Karnofsky index	90	20	40	100
Extra cranial metastasis				
No	26 (15)			
Yes	74 (42)			
Disease controlled				
No	60 34)			
Yes	40 (23)			
Number of brain metastases	1	1	0	4
Multiple brain metastases				
No	65 (37)			
Yes	35 (20)			
PTV volume (mL)	5	7.5	0.43	65
SRS				
No	72 (50)			
Yes	28 (19)			
Time between dosimetric MRI and treatment	8	9.5	1	62
Previous whole brain irradiation				
No	75 (43)			
Yes	25 (14)			

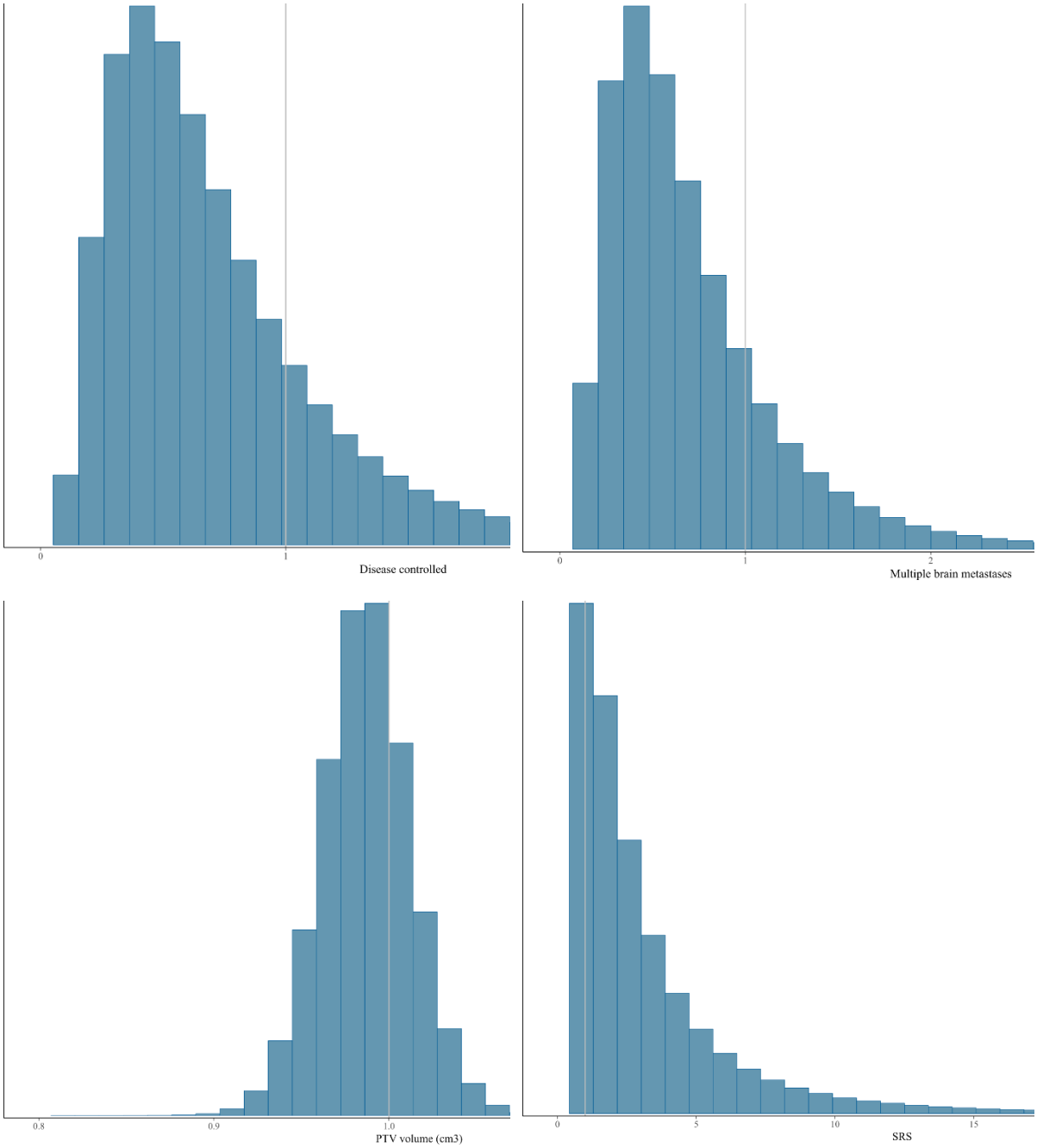

Figure 1: Bayesian multivariate logistic regression results for treatment response

Overall survival

The median follow-up from initial treatment was 31 months. The median OS from initial treatment was 10 months (CI 95% [5 – 22]). Six, 12 and 18-months OS were 69%, 38.7% and 27.4% respectively. Kaplan Meier survival curve is reported Figure 2. According to the multivariate Cox analysis, the existence of extra-cranial metastases, male gender and the brain progression free survival have an influence on OS with Hazard Ratios of 5.1 (sd = 0.63, p = 0.009), 2.76 (sd = 5.02, p = 0.43) and 0.86 (sd = 0.0037, p = 4.9e-5) respectively. Multiple brain metastases was close from statistical significance with HR = 2.43 (sd = 0.49, p = 0.07).

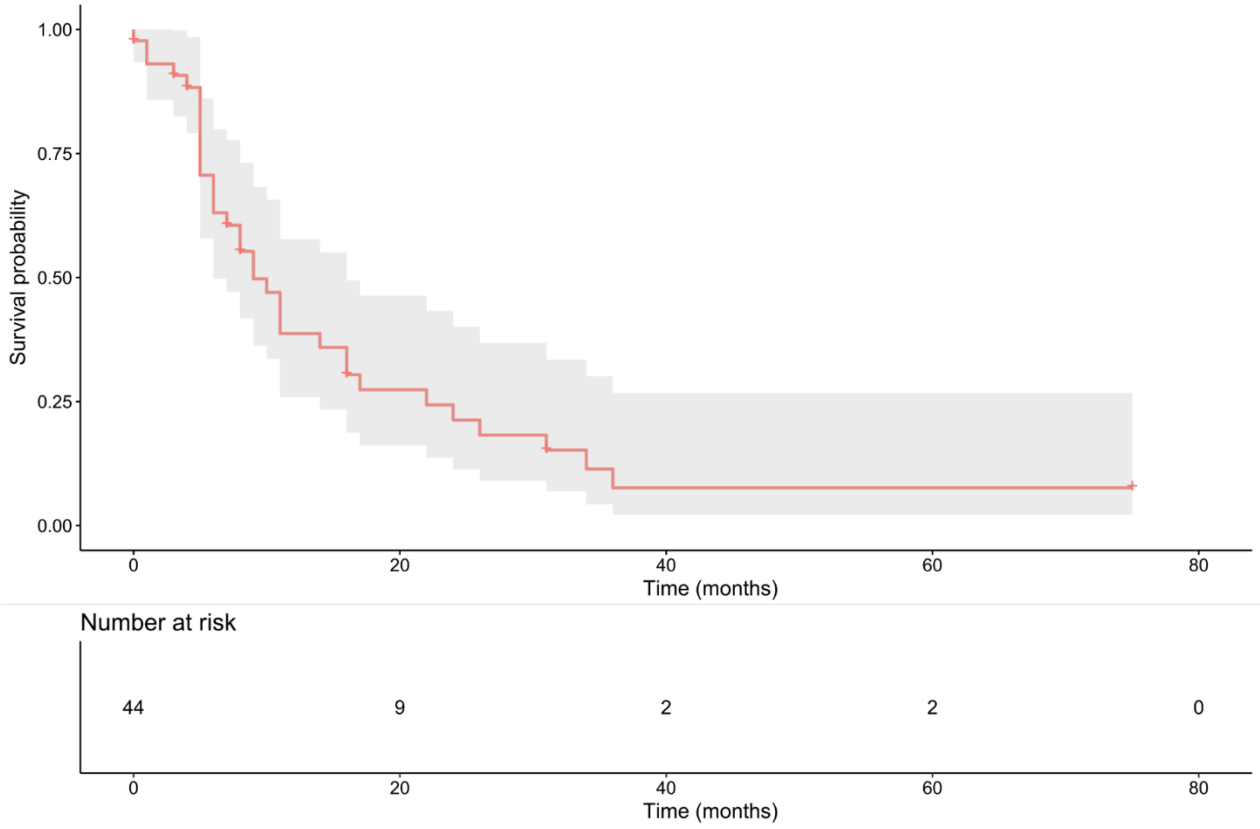

Figure 2: Kaplan Meier survival curve of overall survival

Brain progression-free survival

The median BPFS from initial treatment has not been reached. Kaplan Meier survival curve is reported in Figure 3. Six, 12 and 18-months BPFS were 71.9%, 65.3% and 58.9% respectively. The multivariate Cox analysis did not report meaningful results for a predictive factor of BPFS.

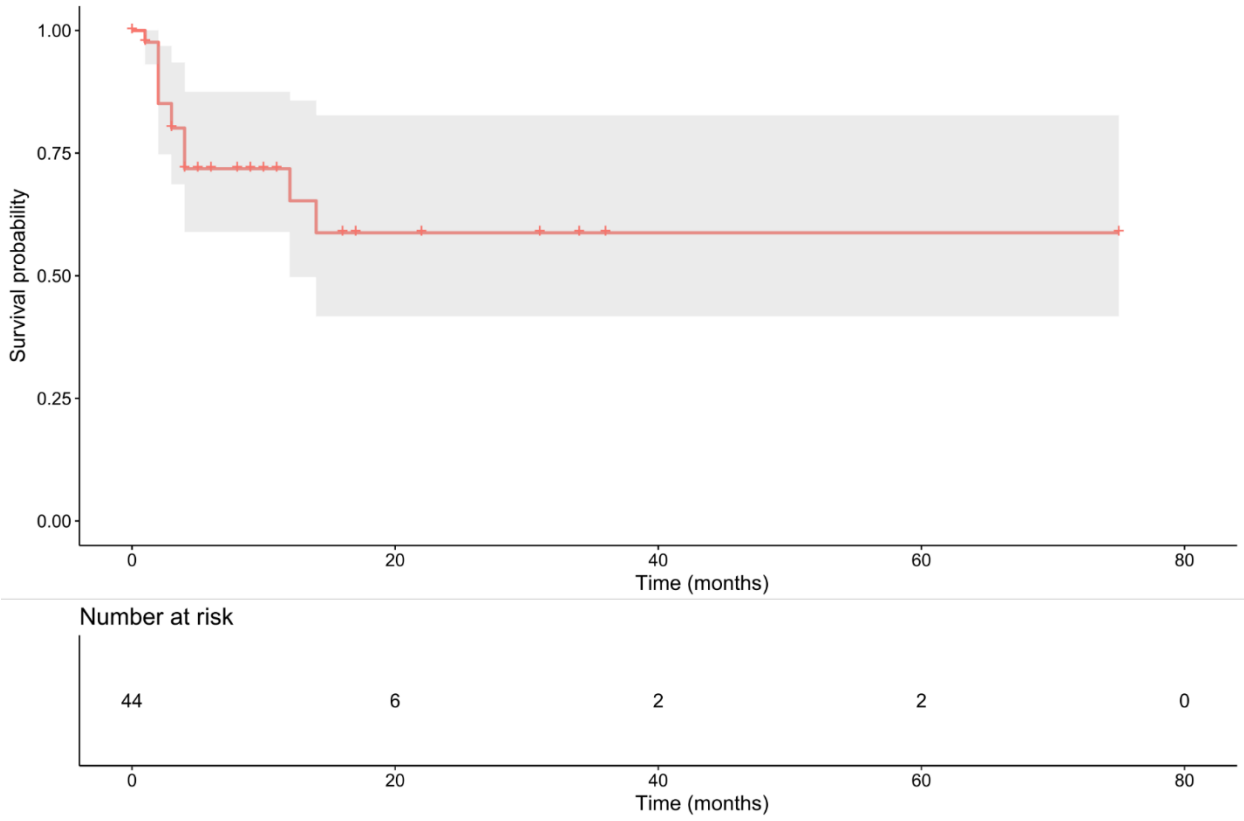

Figure 3: Kaplan Meier survival curve of brain progression free survival

Discussion

We report the results of the largest multicentric cohort of patients treated with linear accelerator-based stereotactic irradiation for CRC brain metastases.

Our analysis reported a low response rate of CRC brain metastasis compared to published studies reported response rates ranging from 71 to 91%, however they did not take into account the primary cancer histology [9–12].

We have been able to identify several factors influencing the response to treatment. Multiple brain metastases and control of the systemic disease seem to have a negative impact on the probability of response. As control of the systemic disease influence OS, thus we can hypothesize that patients with a longer OS have an highest probability of being diagnosed with an infield recurrence or a progression. CRC brain metastases treated with SRS seems to have a better probability of response to treatment compared to HFSRT, which has not been reported in the literature to our knowledge[9]. PTV volume does not seem to have an impact on the probability of response.

OS was consistent with the data published in previous study, which were not specific to CRC brain metastasis, with median OS ranging from 7 to 13.4 months [9–11].

Extra-cranial metastases and male gender seem to have a negative impact on OS, whereas BPFS seems to have a positive impact on OS. It has been reported that extra-cranial metastases and control of the systemic disease influence OS [9,10].

Given the results of the analysis of those individual treatments data we recommend to prefers SRS over HFSRT when feasible. Moreover, this analysis confirms that SRS and HFSRT should be proposed for a patient with a limited number of brain metastases as the probability of treatment failure rise with the number of brain metastases. Finally, for metastases smaller than 50 mm, the volume of the PTV is not a prognosis factor of response and thus should not influence the choice of delivering SRS or HFSRT, however according to the RTOG trial 90-05 radionecrosis rate is directly related to metastasis size [5].

Data related to SRS and HFSRT of CRC brain metastases scarce, and despite a multicentric data collection, the number of patients included in our analysis remains low. However, we address this potential lack of power by performing a Bayesian logistic regression which provides results with a probability of accuracy.

Finally, even though some studies reported an impact of the *RAS* mutational status on OS, we have not been able to evaluate it in our analysis because it has rarely been researched in the patients included [13].

Conclusion

Our analysis suggests that CRC brain metastases have a higher response probability when treated with SRS compared to HFSRT. While HFSRT induced transportation cost, whereas SRS requires most of the time a 24h hospitalization, cost-effectiveness of both strategies should be assessed in order to set guidelines.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2017, CA. Cancer J. Clin. 67 (2017) 7–30. doi:10.3322/caac.21387.

[2] L.J. Schouten, J. Rutten, H.A.M. Huveneers, A. Twijnstra, Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma, Cancer. 94 (2002) 2698–2705.

[3] M. Jung, J.B. Ahn, J.H. Chang, C.O. Suh, S. Hong, J.K. Roh, S.J. Shin, S.Y. Rha, Brain metastases from colorectal carcinoma: prognostic factors and outcome., J Neurooncol. 101 (2011) 49–55.

[4] M. Michl, J. Thurmaier, G. Schubert-Fritschle, M. Wiedemann, R.P. Laubender, N.C. Nüssler, R. Ruppert, J. Kleeff, W. Schepp, C. Reuter, F. Löhe, M. Karthaus, J. Neumann, T. Kirchner, J. Engel, V. Heinemann, Brain Metastasis in Colorectal Cancer Patients: Survival and Analysis of Prognostic Factors., Clin. Colorectal Cancer. 14 (2015) 281–290. doi:10.1016/j.clcc.2015.05.009.

[5] E. Shaw, C. Scott, L. Souhami, R. Dinapoli, R. Kline, J. Loeffler, N. Farnan, Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05, Int. J. Radiat. Oncol. Biol. Phys. 47 (2000) 291–298.

[6] K.A. Ahmed, J.G. Scott, J.A. Arrington, A.O. Naghavi, G.D. Grass, B.A. Perez, J.J. Caudell, A.E. Berglund, E.A. Welsh, S.A. Eschrich, T.J. Dilling, J.F. Torres-Roca, Radiosensitivity of Lung Metastases by Primary Histology and Implications for Stereotactic Body Radiation Therapy Using the Genomically Adjusted Radiation Dose, J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer. 13 (2018) 1121–1127. doi:10.1016/j.jtho.2018.04.027.

[7] N.U. Lin, E.Q. Lee, H. Aoyama, I.J. Barani, D.P. Barboriak, B.G. Baumert, M. Bendszus, P.D. Brown, D.R. Camidge, S.M. Chang, J. Dancey, E.G.E. de Vries, L.E. Gaspar, G.J. Harris, F.S. Hodi, S.N. Kalkanis, M.E. Linskey, D.R. Macdonald, K. Margolin, M.P. Mehta, D. Schiff, R. Soffietti, J.H. Suh, M.J. van den Bent, M.A. Vogelbaum, P.Y. Wen, Response Assessment in Neuro-Oncology (RANO) group, Response assessment criteria for brain metastases: proposal from the RANO group, Lancet Oncol. 16 (2015) e270-278. doi:10.1016/S1470-2045(15)70057-4.

[8] National Cancer Institute, Common Terminology Criteria for Adverse Events v4.0 (CTCAE), (n.d.). http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

[9] E. Fokas, M. Henzel, G. Surber, G. Kleinert, K. Hamm, R. Engenhart-Cabillic, Stereotactic radiosurgery and fractionated stereotactic radiotherapy: comparison of efficacy and toxicity in 260 patients with brain metastases, J. Neurooncol. 109 (2012) 91–98. doi:10.1007/s11060-012-0868-6.

[10] Y.-J. Kim, K.H. Cho, J.-Y. Kim, Y.K. Lim, H.S. Min, S.H. Lee, H.J. Kim, H.S. Gwak, H. Yoo, S.H. Lee, Single-dose versus fractionated stereotactic radiotherapy for brain metastases, Int. J. Radiat. Oncol. Biol. Phys. 81 (2011) 483–489. doi:10.1016/j.ijrobp.2010.05.033.

[11] G. Minniti, C. Scaringi, S. Paolini, G. Lanzetta, A. Romano, F. Cicone, M. Osti, R.M. Enrici, V. Esposito, Single-Fraction Versus Multifraction (3 × 9 Gy) Stereotactic Radiosurgery for Large (>2 cm) Brain Metastases: A Comparative Analysis of Local Control and Risk of Radiation-Induced Brain Necrosis, Int. J. Radiat. Oncol. Biol. Phys. 95 (2016) 1142–1148. doi:10.1016/j.ijrobp.2016.03.013.

[12] Y. Higuchi, M. Yamamoto, T. Serizawa, H. Aiyama, Y. Sato, B.E. Barfod, Modern management for brain metastasis patients using stereotactic radiosurgery: literature review and the

authors' gamma knife treatment experiences, Cancer Manag. Res. 10 (2018) 1889–1899. doi:10.2147/CMAR.S116718.

[13] R. Yaeger, E. Cowell, J.F. Chou, A.N. Gewirtz, L. Borsu, E. Vakiani, D.B. Solit, N. Rosen, M. Capanu, M. Ladanyi, N. Kemeny, RAS mutations affect pattern of metastatic spread and increase propensity for brain metastasis in colorectal cancer, Cancer. 121 (2015) 1195–1203. doi:10.1002/cncr.29196.

Cost-effectiveness analysis of radiosurgery and hypofractionated stereotactic radiotherapy in melanoma brain metastases.

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Résumé

Introduction

Le mélanome est, par fréquence, le troisième cancer responsable de métastases cérébrales. Lorsqu'une chirurgie ne peut être réalisée, la radiothérapie stéréotaxique est préférée à l'irradiation de l'encéphale en totalité lorsque le nombre de métastases le permet afin de préserver les fonctions neuro-cognitives. Nous avons conduit une évaluation médico-économiques de la radiothérapie stéréotaxique mono (SRS) et hypo (HFSRT) fractionnée dans le traitement des métastases cérébrales de mélanome.

Méthodes

Nous avons développé un modèle de Markov, basé sur les données de traitement rétrospectives de patients traités dans 6 centres en France et en Allemagne, pour décrire la survie et les complications liées au traitement de patients traités pour une métastase cérébrales unique de mélanome.

Cette analyse a été conduite dans la perspective du payeur français sur un horizon de temps vie entière. Les utilités, risque de réccurence et coûts ont été obtenu de la littérature publiée. Des études de sensibilité déterministe (DSA) et probabiliste (PSA) ont été réalisée pour évaluer l'influence des hypothèses réalisées.

Résultats

Dans l'analyse de base, les coûts totaux de la SRS et de la HFSRT étaient de 5444,68€ et 7349,83€, et les QALY (*quality adjusted life years*) étaient de 1,4641 et 1,4763 respectivement. Dans l'analyse de sensibilité probabiliste, les coûts totaux de la SRS et de la HFSRT étaient de 5258,77€ et 7138,91€, et les QALY étaient de 1,4709 et 1,4928 respectivement. La SRS était moins chère de 1880,14€ que la HFSRT avec une perte de 0,0219 QALYs. La courbe d'acceptabilité rapporte une probabilité de coût-efficacité de 85,1% et 36,5% pour la SRS pour des propensions à payer de 30000 et 100000€/QALY respectivement.

Conclusion

Il s’agit de la première évaluation médico-économique évaluant SRS et HFSRT dans le traitement des métastases cérébrales de mélanome et ses résultats suggèrent que la HFSRT est coût-efficace.

Abstract

Introduction

Melanoma is the third cancer responsible for brain metastases in frequency. To treat these metastases, when a safe surgery could not be performed, there is a global agreement to prefer stereotactic radiotherapy, performed in either one single fraction (SRS) or several fractions (HFSRT), over whole brain irradiation, to preserve cognitive function with a better metastases response to treatment.

Methods

We developed a Markov model based on retrospectively collected data of treatment delivered in 6 hospitals in France and Germany, to describe survival and treatment-related complications of patients treated for a single melanoma brain metastasis. This analysis was conducted from the French payer perspective on a lifetime horizon. Utility values, recurrence risks, and costs were adapted from the literature. Deterministic (DSA) and probabilistic (PSA) sensitivity analyses were performed to assess the influence of the assumptions made.

Results

In the base case analysis, SRS and HFSRT total costs were 5,444.68€ and 7,349.83€, and the quality-adjusted life expectancies were 1.4641 and 1.4763. In the probabilistic sensitivity analysis, SRS and HFSRT were associated with a mean total cost of 5,258.77€ and 7,138.91€, and a quality-adjusted life expectancy of 1.4709 and 1.4928 QALYs, respectively. SRS appeared to be 1,880.14€ cheaper than HFSRT with a decrease of quality-adjusted life expectancy of 0.0219 QALYs. The acceptability curves reported a probability of cost-effectiveness of nearly 85.1% and 36.5% for SRS for willingness thresholds of 30,000 and 100,000€/QALY respectively.

Conclusion

This is the first medico-economic evaluation of SRS and HFSRT in melanoma brain metastases and its results suggest that HFSRT is cost-effective over SRS.

Introduction

Melanoma is third cancer responsible for brain metastases in frequency [1]. Brain metastases are known to be responsible for 95% of death for patients with brain metastases of melanoma [2]. When a safe surgery could not be performed, there is a global agreement to prefer stereotactic radiotherapy over whole brain irradiation, to preserve cognitive function and with the poorest efficiency [3–5]. Stereotactic radiotherapy of brain metastasis could be performed in one single fraction, usually called stereotactic radiosurgery (SRS) or in several fractions, usually called hypofractionated stereotactic radiotherapy (HFSRT) [6]. Arguments to use HFSRT are multiple; goals are improvement of radiation efficiency by tumor re-oxygenation, decreasing of the healthy brain dose at risk of complications, increase of the differential repair effect of post irradiation between tumor cells and normal cell. However, despite an increased risk of radionecrosis for metastasis larger than 30 mm treated with SRS, there is no consensus in which regimen to use in smaller metastases. A recent study reported significant differences in radiosensitivity on the basis of primary histologic type of lung metastases, thus a similar approach could be considered in brain metastases [7].Moreover, the rise of health expenses related to technologic development, there is a need to rationalize our decision based on treatment efficiency [8].

In this study, we developed a Markov model to compare the cost-effectiveness of SRS and HFSRT in patients with melanoma brain metastases.

Methods

We designed a Markov model to simulate the clinical trajectory of a patient with a single melanoma brain metastasis. Markov simulation is a statistical method that allows the simulation of the transition of a hypothetical cohort of patients between different health states in fixed increments of time. The model was created and analyzed with the Heemod package for R [9].

Strategies

Two stereotactic radiotherapy regimens were compared: 1 single fraction of 20 Gy (SRS) and 3 fractions of 11 Gy (HFSRT) prescribed on the 70% isodose. SRS delivered during a hospitalization of 1 day, while HFSRT delivered without hospitalization in three fractions. However, SRS might be delivered for

outpatient or hospitalized patient (according to the hospital health care rules), we include this probability in our model. Patients began in the treatment state in which he could receive either SRS or HFSRT. After the first cycle, he progressed to either response, early complications, including seizure and intratumoral bleeding, or non-response state, where the non-response state was equivalent to progression and the response state was equivalent to stabilization, partial or complete response. Patients in the progression state could stay in the same state or progress to the death state. Patients in the response state could stay in the same state, progress to death or to radionecrosis. Patients in the radionecrosis could undergo three treatment options: corticosteroids oral therapy, bevacizumab infusion in day hospital or surgery. Those treatments could fail, and the patients remain in the radionecrosis state or succeed and the patient progress to the response state. Cycle length is 1 month.

Decision model

We assumed that patients in the response state and in the non-response state underwent a similar follow-up with brain MRI and clinical examination every three months.

We assumed that early complications impact the length of the hospitalization for SRS and require a hospitalization for HFSRT, which is usually delivered without hospitalization, thus induce hospitalization costs and monthly costs.

We assumed that patients in the symptomatic radionecrosis state were firstly diagnosed with a brain PET/CT and then could be treated with a 2 months corticosteroid therapy at a dose of 1mg per kilogram or with bevacizumab at a dose of 7.5 mg per kilogram every 2 weeks for 2 months and delivered at a day hospital [10].

The Markov model is represented in Figure 1.

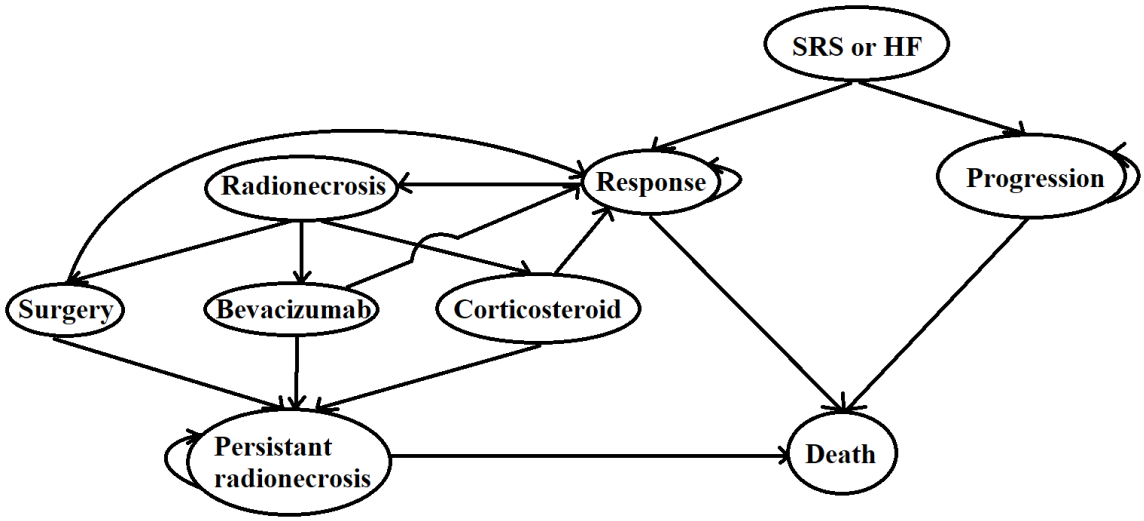

Figure 1: Markov model graphical representation (*SRS: stereotactic radiosurgery; HF: hypofractionnated stereotactic radiotherapy*)

Disease and treatment assumptions

We derived probabilities of transition of overall survival from a retrospective, multicentric database of 150 patients treated for melanoma brain metastasis. We derived probabilities of transition to the response and the non-response state from the same database, using the data of 298 melanoma brain metastases treated with SRS or HFSRT. We derived to probabilities of transition to the radionecrosis state from a retrospective cohort of 587 brain metastases treated with SRS and applied a hazard ratio (HR) for sensitivity analysis [11]. We retrieved the raw data using the using the statistical method described by Guyot e*t al.* [12].

We retrieved the probability of seizure and bleeding for metastases treated with SRS from a 316 patients cohort [13].

Utilities

There are no specific utilities related to health states and radionecrosis in patients treated for melanoma brain metastases. Thus, we retrieved utilities related to health state from a prospective study evaluating health state utilities of patients treated with radiosurgery for brain metastasis using the Standard Gamble technique [14].

Costs

We conducted our analysis in the French payer perspective, using payment data applicable in public hospitals in 2017. For treatments delivered at the hospital, the French payer defined diagnosis-related groups called *Groupes Homogènes des Malades* translated in English to "Homogeneous Groups of Patients" (HGPs). HGPs are defined by the major diagnostic category (MDC) and patient's comorbidities; for the same MDC, four HGPs were defined depending on the severity of the patient related to the comorbidities[15]. The HGP code used for SRS and HFSRT were 17K041 and 28Z11Z respectively.

Drug prices were determined to perform a search in the national database of drug prices [16].

Brain MRI and PET/CT costs were retrieved from the *Classification Commune des Actes Médicaux* (CCAM) database [17]. A medical consultation fee with a specialist physician costs 28€ [18]. Costs for transportation were estimated for a patient living 70 km away from the hospital where the treatment was delivered and based on reimbursement fee of the French payer [19]. Costs are summarized in Table 1.

Table 1: Inputs used in the Markov model: probabilities. utilities and costs.

Parameter		Base case value	Deterministic sensitivity analysis		Probabilistic sensitivity analysis
			Min	Max	
Discount rate		0.04	0	0.05	Normal
Distance: home - hospital			5	200	Gamma
Weight (Kg)			30	150	Normal
Costs					
Initial treatment	HFSRT	4054.59			
	SRS	4240.66			
	Hospitalization probability	0.8	0.5	1	Normal
	Transportation/km	2.19			
Complication	Grade 2 seizure initial cost	336.6			
	Grade 3 seizure initial cost	2513.51			
	Grade4 seizure initial cost	6751.1			
	Seizure/month	20.52	10	50	Normal

	Bleeding initial cost	336.6			
	Bleeding/month	0	0	30	Normal
Radionecrosis	PET CT	89.54			
	Corticosteroid/kg	0.13			
	Bevacizumab (400 mg)	913.75			
	Day hospital	403.53			
	Neurosurgery	3762.49	1776.42	8128.98	Multinomial
Follow - up	Brain MRI	69			
	Clinical examination	23			
Transition probabilities					
Response probability					
	SRS	p_srs	CI 95%	CI 95%	Beta
	HFSRT	p_hfsrt	CI 95%	CI 95%	Beta
Complication	SRS – Grade 2 seizure	0.07	0	0.1	Normal
	SRS – Grade 3 seizure	0.05	0	0.08	Normal
	SRS – Grade 4 seizure	0.009	0	0.02	Normal
	SRS – Bleeding	0.13	0	0.15	Normal
	HR seizure	1	0	1	Normal
	HR bleeding	1	0	1	Normal
Radionecrosis	Hazard ratio	1	0.4	1.2	Normal
	Probability of bevacizumab	0.1			
	Probability of corticosteroid	0.7			
	Probability of surgery	0.2			
	Surgical mortality	0.017			
Probability of response	Bevacizumab	0.9	0.5	1	Beta
	Corticosteroid	0.7	0.5	1	Normal
	Surgery	1	0.85	1	Normal
Utility					
	Response	0.85			
	Complication	0.75	0.75	0.85	Normal
	Progression	0.75			
	Radionecrosis	0.5			
	Death	0			

Base case and sensitivity analysis

For both SRS and HFSRT, we projected QALYS and costs and then compared those projections. We also estimated the incremental cost-effectiveness ratio (ICER), which was calculated over a 5 years horizon with an annual discounted rate of 4% for both costs and QALYs.

As the *Haute Autorité de Santé* (French National Authority for Health), does not set a willingness to pay threshold, we considered the threshold recommended by the World Health Organization, which is that an intervention is cost-effective if its ICER is below three times the national annual growth domestic product per capita [20]. Hence, we considered a willingness to pay threshold of 100,000€ for the French payer. To assess the impact of the assumptions made to build our model, we performed deterministic sensitivity analysis (DSA) for the parameters listed in Table 1. Overall, model uncertainty was tested in the probabilistic sensitivity analysis (PSA), in which we drew 1,000 random values from specified probability distributions for each parameter.

Results

Base case

SRS was associated with a mean total cost of 5,444.68€, including 3,553.67€ for initial treatment including transportation, 422.27€ for early complications, 68.59€ for radionecrosis related costs and 1,400.24€ for follow-up related costs. HFSRT was associated with a mean total cost of 7,349.83€, including 4,568.40€ for initial treatment including transportation, 1,478.36€ for early complications, 44.95€ for radionecrosis related costs and 1,258.19€ for follow-up related costs.

SRS and HFSRT were associated with a quality-adjusted life expectancy of 1.4641 and 1.4763 QALYs, respectively. Thus, the ICER was -156,504.4€/QALY.

Thus, SRS appeared to be 1,905.15€ cheaper than HFSRT with a decrease of quality-adjusted life expectancy of 0.012 QALYs; hence SRS was dominant over HFSRT in melanoma brain metastases treatment.

Deterministic sensitivity analysis

We ran a deterministic sensitivity analysis on every assumption made in our model. The results are depicted in figure 2. This sensitivity analysis revealed that the incremental cost-effectiveness ratio (ICER) was highly sensitive to the Hazard Ratio of radionecrosis between SRS and HFSRT and to the utility associated to early complications. Finally, it was little sensitive to the probability of response after HFSRT or SR, the rate of hospitalization for SR, and the HR of seizure and bleeding between SRS and HFSRT.

The ICER was little sensitive to the hazard ratio applied to the probability of radionecrosis, to the discount rate, and to the cost of the surgery of radionecrosis, but not sensitive to the probability of efficiency of corticosteroids, bevacizumab and surgery in radionecrosis treatment, to the surgery-related mortality when performed to treat radionecrosis and to the weight of the patient. Results are displayed in figure 2.

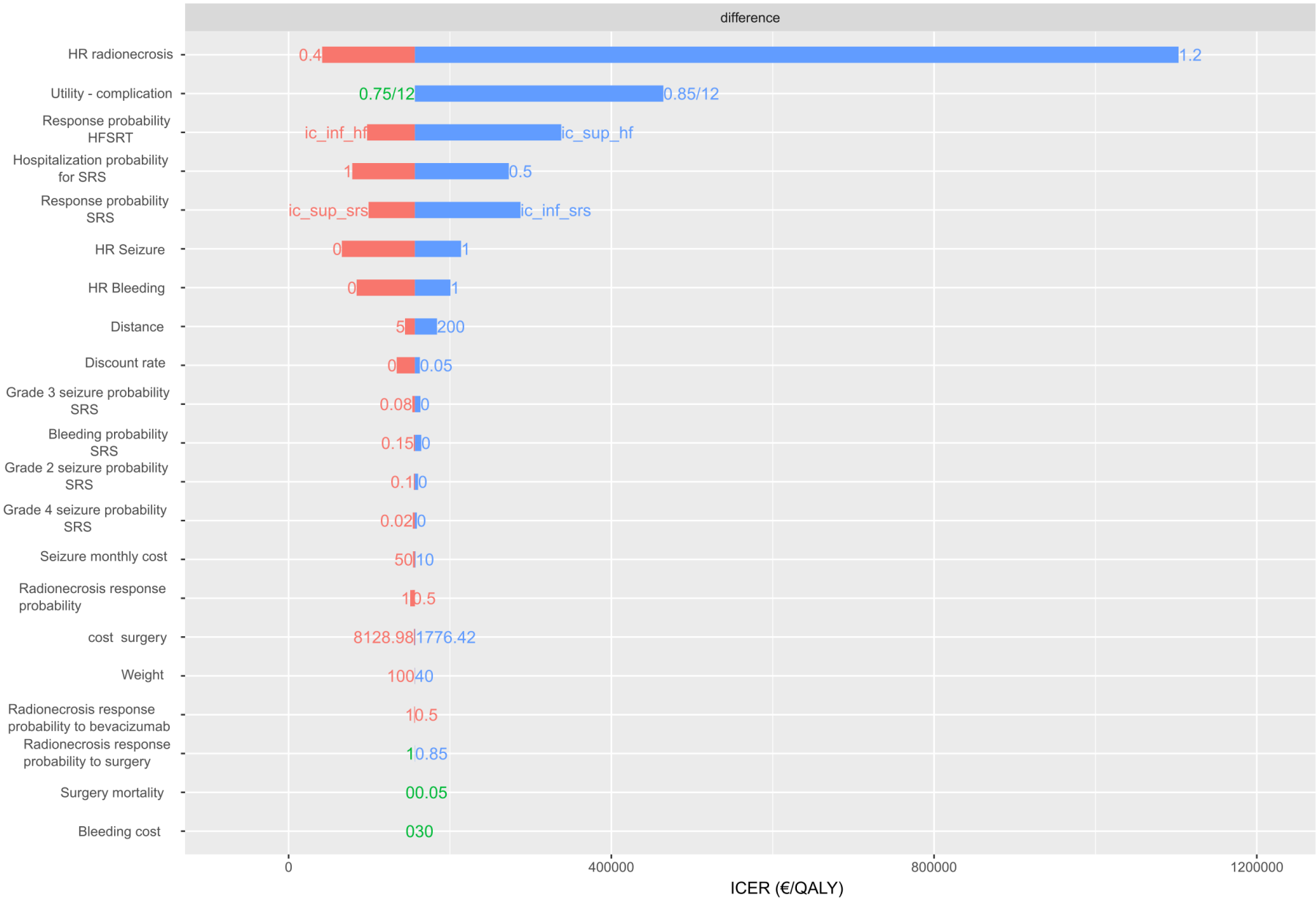

Figure 2: Tornado Plot representing the results of the Deterministic Sensitivity Analysis (DSA).

Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis are shown in the scatter plot and the cost-effectiveness acceptability curves (Figure 3, 4). Those curves evaluate the probability of cost-effectiveness for each willingness to pay thresholds. From the French payer perspective, there was not a defined threshold; we estimated on the basis of WHO recommendations that an ICER below 100,000€/QALY was cost-effective, and an ICER below 30,000€/QALY was very cost-effective.

SRS was associated with a mean total cost of 5,258.77€, including 3,515.24€ for initial treatment including transportation, 428.27€ for early complications, 72.06€ for radionecrosis related costs and 1,243.28€ for follow-up related costs. HFSRT was associated with a mean total cost of 7,138.91€, including 4,480.42€ for initial treatment including transportation, 1,507.98€ for early complications, 36.61€ for radionecrosis related costs and 1,113.95€ for follow-up related costs. The difference of complications related cost between SRS and HFSRT is related to the fact that a complication occurring during SRS induces a supplementary cost to the hospitalization cost, but when it occurs in HFSRT it induces a full hospitalization cost.

SRS and HFSRT were associated with a quality-adjusted life expectancy of 1.4709 and 1.4928 QALYs, respectively.

Thus, SRS appeared to be 1,880.14€ cheaper than HFSRT with a decrease of quality-adjusted life expectancy of 0.022 QALYs. Thus, the ICER was 85,762.7€/QALY.

The scatter-plot (Figure 3) shows that most of the simulations have an ICER located in the northeast and north-west quarter.

The acceptability curves (Figure 4) drawn from the Monte Carlo simulation does not cross, with a higher probability of cost-effectiveness of SRS. The probabilities of the cost-effectiveness of SRS compared to HFSRT for willingness to pay threshold of 10,000€, 30,000€ and 100,000€ were 93%, 85.1%, 36.5%.

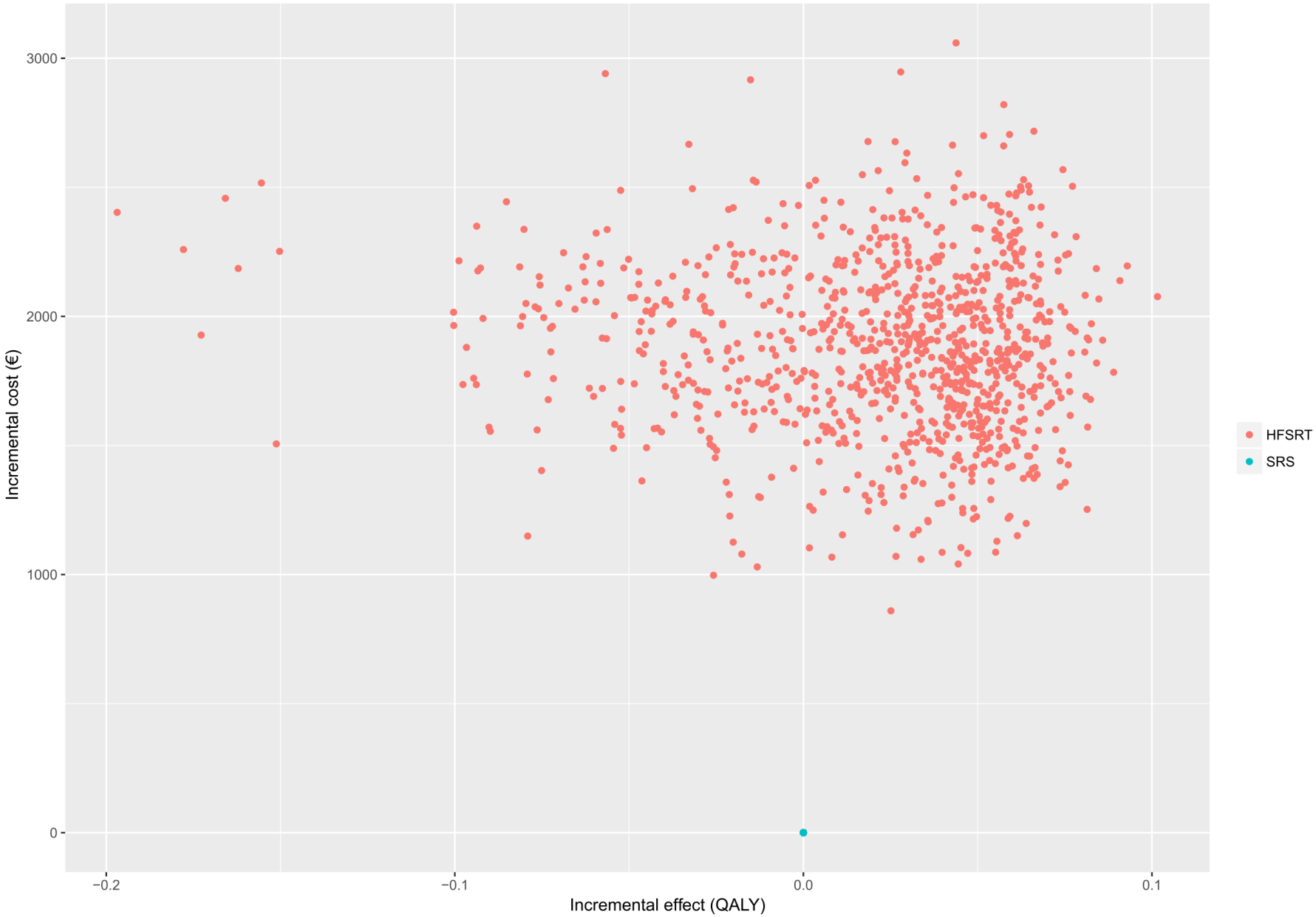

Figure 3: Scatter plot of the 1,000 Monte Carlo simulations ran in the Probabilistic Sensitivity Analysis (PSA)

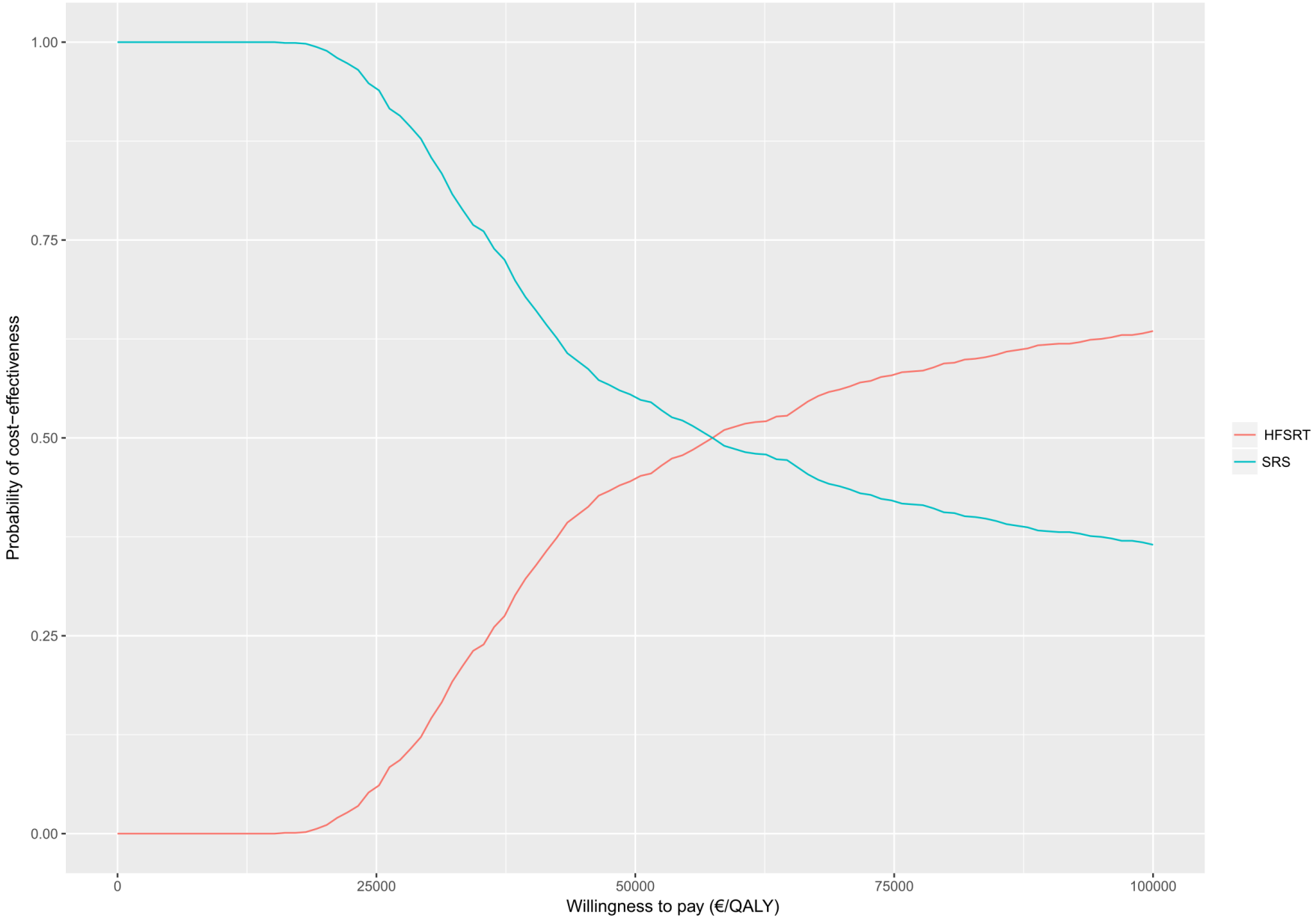

Figure 4: Acceptability curves of the Probabilistic Sensitivity Analysis (PSA)

Discussion

We report the results of the first medico-economics analysis evaluating SRS and HFSRT in melanoma brain metastases. Our analysis suggests that from a French payer perspective, with a willingness-to-pay threshold of 30,000€/QALY SRS is cost-effective over HFSRT. However, for a willingness-to-pay of 100,000€/QALY HFSRT appeared to be cost-effective over SRS.

This analysis relies on one of the largest multicentric cohorts of patients treated with linear accelerator-based SRS/HFSRT. While the utility data used in our analysis are not specific to a French population, it is likely that they do not differ significantly from the utilities that could be observed in a French population. Finally, the evaluation of cost could have been more precise if integrating into a piggyback study, however, those kinds of study are more complicated to conduct and the results are likely to be closed from the one we reported.

Moreover, we performed DSA and PSA to assess potential bias induced by the assumptions made in the Markov model building.

While the saving at an individual level could seem insignificant, they result in appreciable savings at a national level and medico-economics evaluation should drive public policies.

Several studies already demonstrated that stereotactic radiotherapy alone was cost-effective over whole brain irradiation or whole brain irradiation plus stereotactic radiotherapy [21–25]. Our cost-effectiveness analysis provides new data to help precising the most cost-effectiveness strategy to manage melanoma brain metastases. However, the results of our analysis are valid from a French payer perspective, thus a Graphical User Interface of the Markov model developed to conduct this analysis is being developed to help other team conducting the same analysis from a different perspective.

Conclusion

With this first medico-economic evaluation of SRS and HFSRT in melanoma brain metastases, results suggest that for a willingness to pay threshold below 87,132.84€/QALY SRS is cost-effective over HFSRT, but for a willingness to pay threshold over 87,132.84 HFSRT become to cost-effective treatment.

References

[1] J.D. Johnson, B. Young, Demographics of brain metastasis, Neurosurg. Clin. N. Am. 7 (1996) 337–344.

[2] J.H. Sampson, J.H. Carter, A.H. Friedman, H.F. Seigler, Demographics, prognosis, and therapy in 702 patients with brain metastases from malignant melanoma, J. Neurosurg. 88 (1998) 11–20. doi:10.3171/jns.1998.88.1.0011.

[3] Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, Arbuckle RB, Swint JM, Shiu AS, Maor MH, Meyers CA, Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial, Lancet Oncol. 10 (2009) 1037–1044.

[4] G. Noël, J.M. Simon, C.-A. Valery, P. Cornu, G. Boisserie, D. Ledu, D. Hasboun, B. Tep, J.-Y. Delattre, C. Marsault, F. Baillet, J.-J. Mazeron, Linac radiosurgery for brain metastasis of melanoma., Ster. Funct Neurosurg. 79 (2002) 245–55.

[5] É. Le Rhun, F. Dhermain, G. Noël, N. Reyns, A. Carpentier, E. Mandonnet, S. Taillibert, P. Metellus, ANOCEF. l'Association des neuro-oncologues d'expression franc¸aise, [ANOCEF guidelines for the management of brain metastases], Cancer Radiother. J. Soc. Francaise Radiother. Oncol. 19 (2015) 66–71. doi:10.1016/j.canrad.2014.11.006.

[6] A. Carpentier, F. Dhermain, E. Le Rhun, E. Mandonnet, P. Metellus, G. Noel, N. Reyns, S. Taillibert, Référentiel ANOCEF: métastases cérébrales de l'adulte., (2014).

[7] K.A. Ahmed, J.G. Scott, J.A. Arrington, A.O. Naghavi, G.D. Grass, B.A. Perez, J.J. Caudell, A.E. Berglund, E.A. Welsh, S.A. Eschrich, T.J. Dilling, J.F. Torres-Roca, Radiosensitivity of Lung Metastases by Primary Histology and Implications for Stereotactic Body Radiation Therapy Using the Genomically Adjusted Radiation Dose, J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer. 13 (2018) 1121–1127. doi:10.1016/j.jtho.2018.04.027.

[8] Y. Lievens, J.M. Borras, C. Grau, Cost calculation: a necessary step towards widespread adoption of advanced radiotherapy technology, Acta Oncol. Stockh. Swed. 54 (2015) 1275–1281. doi:10.3109/0284186X.2015.1066932.

[9] A. Filipovic Pierucci, K. Zarca, I. Durand Zaleski, Markov Models for Health Economic Evaluations: The R Package heemod, (n.d.). https://arxiv.org/abs/1702.03252.

[10] D. Delishaj, S. Ursino, F. Pasqualetti, A. Cristaudo, M. Cosottini, M.G. Fabrini, F. Paiar, Bevacizumab for the Treatment of Radiation-Induced Cerebral Necrosis: A Systematic Review of the Literature, J. Clin. Med. Res. 9 (2017) 273. doi:10.14740/jocmr2936e.

[11] Z.A. Kohutek, Y. Yamada, T.A. Chan, C.W. Brennan, V. Tabar, P.H. Gutin, T.J. Yang, M.K. Rosenblum, Å. Ballangrud, R.J. Young, Z. Zhang, K. Beal, Long-term risk of radionecrosis and imaging changes after stereotactic radiosurgery for brain metastases, J. Neurooncol. 125 (2015) 149–156. doi:10.1007/s11060-015-1881-3.

[12] P. Guyot, A. Ades, M. Ouwens, N. Welton, Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves., BMC Med. Res. Methodol. 12 (2012).

[13] B.J. Williams, D. Suki, B.D. Fox, C.E. Pelloski, M.V.C. Maldaun, R.E. Sawaya, F.F. Lang, G. Rao, Stereotactic radiosurgery for metastatic brain tumors: a comprehensive review of complications, J. Neurosurg. 111 (2009) 439–448. doi:10.3171/2008.11.JNS08984.

[14] N.H. Lester-Coll, A.P. Dosoretz, J.A. Hayman, J.B. Yu, Health State Utilities for Patients with Brain Metastases, Cureus. 8 (2016) e667. doi:10.7759/cureus.667.

[15] Z. Or, M. Bellanger, France: Implementing homogeneous patient groups in a mixed market, in: Diagn.-Relat. Groups Eur. Mov. Transpar. Effic. Qual. Hosp., 2011: pp. 221–241.

[16] www.base-donnes-publique.medicaments.gouv.fr, (accessed June 3, 2017).

[17] www.ameli.fr/accueil-de-la-ccam/trouver-un-acte/index.php, (accessed June 3, 2017).

[18] www.ameli.fr/assure/remboursements/rembourse/consultations/metropole, (accessed June 3, 2017).

[19] www.ameli.fr/transporteur-sanitaire/exercice-professionnel/facturation/tarifs/ambulances-tarifs-conventionnels, (accessed June 3, 2017).

[20] Geneva: World Health, Choosing interventions that are cost-effective [Internet]., (2014). http://www.who.int/choice/en/ (accessed June 17, 2017).

[21] M.D. Hall, J.L. McGee, M.C. McGee, K.A. Hall, D.M. Neils, J.D. Klopfenstein, P.W. Elwood, Cost-effectiveness of stereotactic radiosurgery with and without whole-brain radiotherapy for the treatment of newly diagnosed brain metastases, J. Neurosurg. 121 Suppl (2014) 84–90. doi:10.3171/2014.7.GKS14972.

[22] H. Kim, M.S. Rajagopalan, S. Beriwal, K.J. Smith, Cost-effectiveness Analysis of Stereotactic Radiosurgery Alone Versus Stereotactic Radiosurgery with Upfront Whole Brain Radiation Therapy for Brain Metastases, Clin. Oncol. R. Coll. Radiol. G. B. 29 (2017) e157–e164. doi:10.1016/j.clon.2017.05.001.

[23] L.S. Lal, S.D. Byfield, E.L. Chang, L. Franzini, L.-A. Miller, R. Arbuckle, L. Reasonda, C. Feng, A. Adamus, J.M. Swint, Cost-effectiveness analysis of a randomized study comparing radiosurgery with radiosurgery and whole brain radiation therapy in patients with 1 to 3 brain metastases, Am. J. Clin. Oncol. 35 (2012) 45–50. doi:10.1097/COC.0b013e3182005a8f.

[24] N.H. Lester-Coll, A.P. Dosoretz, W.J. Magnuson, M.S. Laurans, V.L. Chiang, J.B. Yu, Cost-effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for up to 10 brain metastases, J. Neurosurg. 125 (2016) 18–25. doi:10.3171/2016.7.GKS161499.

[25] N.H. Lester-Coll, A.P. Dosoretz, J.B. Yu, Decision analysis of stereotactic radiation surgery versus stereotactic radiation surgery and whole-brain radiation therapy for 1 to 3 brain metastases, Int. J. Radiat. Oncol. Biol. Phys. 89 (2014) 563–568. doi:10.1016/j.ijrobp.2014.03.001.

Cost-effectiveness analysis of radiosurgery and hypofractionated stereotactic radiotherapy in colorectal cancer brain metastases.

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Résumé

Introduction

Le cancer colorectal (CCR) est le troisième par ordre de fréquence dans les pays développé mais les métastases cérébrales ne surviennent que chez 1% des patients. Néanmoins, l'incidence des métastases cérébrales est susceptible d'augmenter du fait de l'augmentation de la survie globale liée aux nouvelles thérapies systémiques. La radiothérapie stéréotaxique mono (SRS) et hypo (HFSRT) fractionnée sont des options thérapeutiques dans la prise en charge des métastases cérébrales.

Nous avons réalisé une évaluation médico-économique de ces 2 traitements dans la prise en charges des métastases cérébrales de CCR.

Méthodes

Nous avons réalisé un modèle de Markov pour simuler la trajectoire clinique d'un patient traité pour une métastase cérébrale de CCR en utilisant les données collectées rétrospectivement dans 6 centres de radiothérapie en France et en Allemagne. Cette analyse a été conduit dans la perspective du payeur français sur un horizon temporel vie entière. Les utilités, risques de récidive et coûts ont été adapté à partir de la littérature. Des analyses de sensibilité déterministes (DSA) et probabilistes (PSA) ont été réalisées afin d'évaluer l'influence des hypothèses faites.

Résultats

L'analyse de base rapporte des coûts totaux de 4404,76€ et 5921,34€ et des utilités de 1,2545 et 1,2589 QALYs pour la SRS et la HFSRT respectivement. L'analyse de sensibilité probabiliste rapporte des coûts totaux de 4407,80€ et 5817,33€ et des utilités de 1,2597 et 1,2987 QALYs pour la SRS et la HFSRT respectivement.

SRS est moins chère que la HFSRT de 1409,53€ et entraine une diminution de la qualité de vie de 0,039 QALYs. La HFSRT a une probabilité d'être coût efficace de 33,2% and 94% pour des propensions à payer de 30000€ et 100000€ respectivement.

Conclusion

Il s’agit de la première évaluation médico-économique de la SRS et de la HFSRT dans la prise en charge des métastases cérébrales de CCR et ses résultats suggèrent que la HFSRT est coût-efficace.

Abstract

Introduction

Colorectal cancer (CRC) is the third most common cancer in developed countries and brain metastases only occur in 1% of CRC patients, however this rate is likely to raise due to the increase of the overall survival as new systemic drugs became available. Stereotactic radiosurgery (SRS) and hypofractionated stereotactic radiotherapy (HFSRT) are treatment options. We developed a Markov model to evaluate the cost-effectiveness of SRS and HFSRT in patients with CRC brain metastases.

Methods

We designed a Markov model to simulate the clinical trajectory of a patient with a single CRC brain metastasis using data retrospectively collected in 6 hospitals in France and Germany. This analysis was conducted in a French payer perspective on a lifetime horizon. Utility values, recurrence risks, and costs were adapted from the literature. Deterministic (DSA) and probabilistic (PSA) sensitivity analyses were performed to assess the influence of the assumptions made.

Results

In the base case analysis, SRS and HFSRT total costs were 4,404.76€, and 5,921.34€, and the quality-adjusted life expectancies were 1.2545 and 1.2589. In the probabilistic sensitivity analysis, SRS and HFSRT were associated with a mean total cost of 4,407.80 € and 5,817.33€, and a quality-adjusted life expectancies 1.2597 and 1.2987 QALYs, respectively. SRS appeared to be 1,409.53€ € cheaper than HFSRT with a decrease of quality-adjusted life expectancy of 0.039 QALYs. HFSRT had a probability of cost-effectiveness for willingness-to-pay threshold of 30,000€ and 100,000€ of 33.2% and 94% respectively.

Conclusion

This is the first medico-economic evaluation of SRS and HFSRT in CRC brain metastases and its results suggest that HFSRT is cost-effective compare to SRS.

Introduction

Colorectal cancer (CRC) is the third most common cancer in developed countries. Visceral metastases are common in CRC as 20% of patients have metastases at initial staging and 25% of CRC patients will develop metastases [1,2]. However, brain metastases occur only in 1% of CRC patients. Overall survival in CRC patients rise as new systemic drugs became available, thus the incidence of brain metastases in CRC patients will likely increase, which is also favored by the fact that many systemic therapies do not cross the blood-brain barrier [3]. Brain metastases from CRC are always the last occurrence and are considered poor prognostic factor of the disease, with median survival, ranges from 1.0 to 5.7 months [4].

According to the American Society for Radiation Oncology (ASTRO) and to the French-speaking neuro-oncologist association (ANOCEF) guidelines, stereotactic radiosurgery (SRS) and hypofractionated stereotactic radiotherapy (HFSRT) are a treatment options for single metastasis smaller than 3 – 4 cm and for multiple metastases smaller than 3 – 4 cm if the patient has an expected survival of 3 months or more. However, despite an increased risk of radionecrosis for metastasis larger than 30 mm treated with SRS, there is no consensus in which regimen to use in smaller metastases [5]. A recent study reported differences of radiosensitivity in lung metastases depending on the primary histology and this difference might also apply in brain metastases [6]. Moreover, the rise of health expenses related to technologic development, there is a need to rationalize treatment decision based on treatment efficiency.

In this study, we developed a Markov model to evaluate the cost-effectiveness of SRS and HFSRT in patients with CRC brain metastases.

Methods

We designed a Markov model to simulate the clinical trajectory of a patient with a single CRC brain metastasis. Markov simulation is a statistical method that allows the simulation of the transition of a hypothetical cohort of patients between different health states in fixed increments of time. The model was created and analyzed with the Heemod package for R [7].

Strategies

Two stereotactic radiotherapy regimens were compared, one single fraction of 20 Gy (SRS) and three fractions of 11 Gy (HFSRT) prescribed on the 70% isodose. SRS delivered during an one-day hospitalization, while HFSRT delivered without hospitalization in three fractions. The patient enters the model in the treatment state, where he could receive SRS or HFSRT. At the time of the initial treatment, patient could experience intra-tumoral bleeding or seizure. Bleeding and seizure rates were retrieved from a comprehensive review of complications of SRS [8]. For patient receiving SRS, complications could influence the length and the cost of the hospitalization, and for patient receiving HFSRT, this could require an hospitalization. After the first cycle, patient progressed to either response or non-response state, where the non-response state was equivalent to progression and the response state was equivalent to stabilization, partial or complete response. Patients in the progression state could stay in the same state or progress to the death state. Patients in the response state could stay in the same state, progress to death or to radionecrosis. Patients in the radionecrosis could undergo three treatment options: corticosteroids oral therapy, bevacizumab infusion in day hospital or surgery. Those treatments could fail, and the patients remain in the radionecrosis state or succeed and the patient progress to the response state. Cycle length is 1 month.

Decision model

We assumed that patients in the response state and in the non-response state underwent a similar follow-up with brain MRI and clinical examination every three months. We supposed that patients in the symptomatic radionecrosis state were firstly diagnosed with a brain PET/CT and then could be treated with a two-month corticosteroid therapy at a dose of 1 mg per kilogram or with bevacizumab at a dose of 7.5 mg per kilogram every 2 weeks for 2 months and delivered at a day hospital [9]. The Markov model is represented in Figure 1.

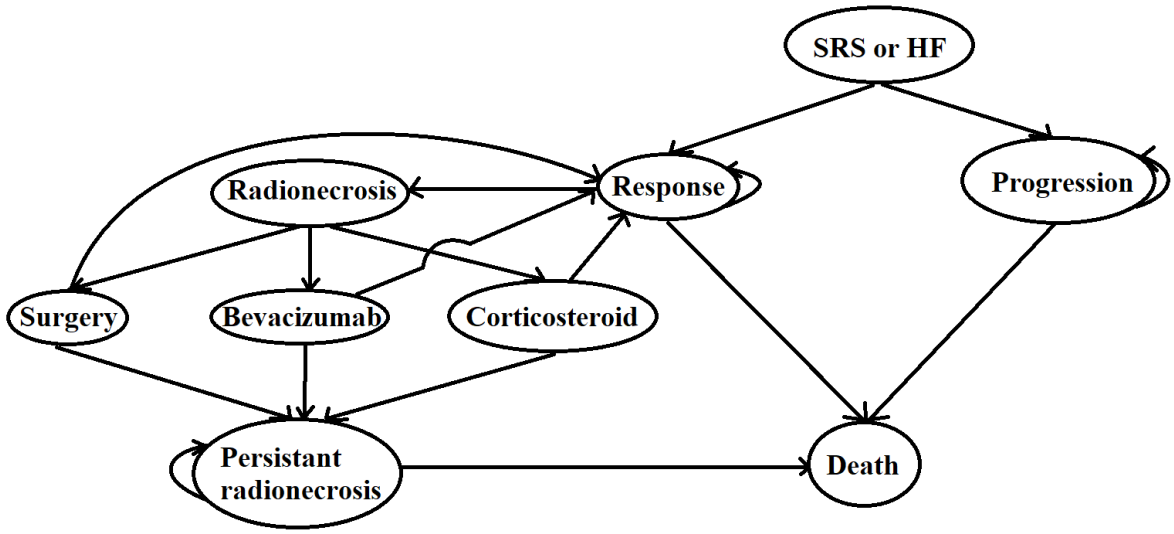


Figure 1 : Markov model graphical representation (*SRS: stereotactic radiosurgery; HF: hypofractionnated stereotactic radiotherapy*)

Disease and treatment assumptions

We derived probabilities of transition of overall survival from a retrospective, multicentric database of 57 patients treated for CRC brain metastasis. We derived probabilities of transition to the response and the non-response state from the same database, using the data of 69 CRC brain metastases treated with SRS or HFSRT. We derived to probabilities of transition to the radionecrosis state from a retrospective cohort of 587 brain metastases treated with SRS and applied a hazard ratio (HR) for sensitivity analysis [10]. We retrieved the raw data using the using the statistical method described by Guyot e*t al* [11].

Utilities

There are no specific utilities related to health states and radionecrosis in patients treated for CRC brain metastases. Thus, we retrieved utilities related to health state from a prospective study evaluating health state utilities of patients treated with radiosurgery for brain metastasis using the Standard Gamble technique [12].

Costs

We conducted our analysis in the French payer perspective, using payment data applicable in public hospitals in 2017. For treatments delivered at the hospital, the French payer defined diagnosis-related groups called *Groupes Homogènes des Malades* translated in English to "Homogeneous Groups of Patients" (HGPs). HGPs are defined by the major diagnostic category (MDC) and patient's comorbidities; for the same MDC, four HGPs were defined depending on the severity of the patient related to the comorbidities [13]. The HGP code used for SRS and HFSRT were 17K041 and 28Z11Z respectively.

Drug prices were determined to perform a search in the national database of drug prices [14].

Brain MRI and PET/CT costs were retrieved from the *Classification Commune des Actes Médicaux* (CCAM) database [11]. A medical consultation fee with a specialist physician costs 28€ [16]. Costs for transportation were estimated for a patient living 70 km away from the hospital where the treatment was delivered and based on reimbursement fee of the French payer [17]. Costs are summarized in Table 1.

Base case and sensitivity analysis

For both SRS and HFSRT, we projected QALYS and costs and then compared those projections. We also estimated the incremental cost-effectiveness ratio (ICER), which was calculated over a lifetime horizon with an annual discounted rate of 4% for both costs and QALYs.

As the *Haute Autorité de Santé* (in English, *French National Authority for Health*), does not set a willingness to pay threshold, we considered the threshold recommended by the World Health Organization, which is that an intervention is cost-effective if its ICER is below three times the national annual growth domestic product per capita [18]. Hence, we considered a willingness to pay threshold of 100,000€ for the French payer. To assess the impact of the assumptions made to build our model, we performed deterministic sensitivity analysis (DSA) for the parameters listed in Table 1. Overall, model uncertainty was tested in the probabilistic sensitivity analysis (PSA), in which we drew 1,000 random values from specified probability distributions for each parameter.

Table 1: Inputs used in the Markov model: probabilities, utilities and costs.

Parameter		Base case value	Deterministic sensitivity analysis		Probabilistic sensitivity analysis
			Min	Max	
Discount rate		0,04	0	0,05	Normal
Distance: home - hospital			5	200	Gamma
Weight (Kg)			30	150	Normal
Costs					
Initial treatment	HFSRT	4054,59			
	SRS	4240,66			
	Transportation/km	2,19			
Complications	Grade 2 seizure – SRS	336.6			
	Grade 3 seizure – SRS	2,513.51			
	Grade 4 seizure - SRS	6,751.1			
	Grade 2 seizure – HFSRT	4,577.6			
	Grade 3 seizure – HFSRT	6,754.51			
	Grade 4 seizure – HFSRT	10,992.1			
	Bleeding – SRS	336.6			
	Bleeding - HFSRT	4,577.6			
radionecrosis	PET CT	89,54			
	Corticosteroid/kg	0,13			
	Bevacizumab (400 mg)	913,75			
	Day hospital	403,53			
	Neurosurgery	3762,49	1776,42	8128,98	Multinomial
follow - up	Brain MRI	69			
	Clinical examination	23			
Transition probabilities					
Response probability					
	SRS	p_srs	CI 95%	CI 95%	Beta
	HFSRT	p_hfsrt	CI 95%	CI 95%	Beta
Complications	Grade 2 seizure – SRS	0.07	0	0.1	Normal
	Grade 3 seizure – SRS	0.05	0	0.08	Normal
	Grade 4 seizure – SRS	0.009	0	0.02	Normal
	HR seizure HFSRT	0.7	0	1	Normal
	Bleeding – SRS	0.03	0	0.15	Normal

	HR bleeding – HFSRT	0.7	0	1	Normal
Radionecrosis	Hazard ratio	1	0,4	1,2	Normal
	Probability of Bevacizumab	0,1			
	Probability of corticosteroid	0,7			
	Probability of surgery	0,2			
	Surgical mortality	0,017			
Probability of response					
	Bevacizumab	0,9	0,5	1	Beta
	Corticosteroid	0,7	0,5	1	Normal
	Surgery	1	0,85	1	Normal
Utility					
	Response	0,85			
	Progression	0,75			
	Radionecrosis	0,5			
	Death	0			

Results

Base case

SRS was associated with a mean total cost of 4,404.76 €, including 3,553.68 € for initial treatment including transportation, 115.98 € for radionecrosis related costs, 244.04 € for complications and 491.16 € for follow-up related costs. HFSRT was associated with a mean total cost of 5,921.34 €, including 4,568.44 € for initial treatment including transportation, 114.31€ for radionecrosis related costs, 750.31 € for complications and 488.38 € for follow-up related costs.

SRS and HFSRT were associated with a quality-adjusted life expectancy of 1.4485 and 1.4472 QALYs, respectively. The ICER was -511,801.1€/QALY for SRS versus HFSRT.

Thus, SRS appeared to be 659.90€ cheaper than HFSRT with an increase of quality-adjusted life expectancy of 0.0013 QALYs; hence SRS was dominant over HFSRT in colorectal cancer brain metastases treatment.

Deterministic sensitivity analysis

We ran a deterministic sensitivity analysis on every assumption made in our model. The results are depicted in figure 2. This sensitivity analysis revealed that the incremental cost-effectiveness ratio

(ICER) was highly sensitive to the radionecrosis hazard ratio, the probability of response related to both strategies, to the utility related to complication of treatment, to the hospitalization for SRS probability, to the seizure hazard ratio and to the bleeding hazard ratio.

The ICER was little sensitive to the discount rate and the distance from home to hospital. The ICER was not sensitive to the other assumptions made to build the Markov model Results are displayed in figure 2.

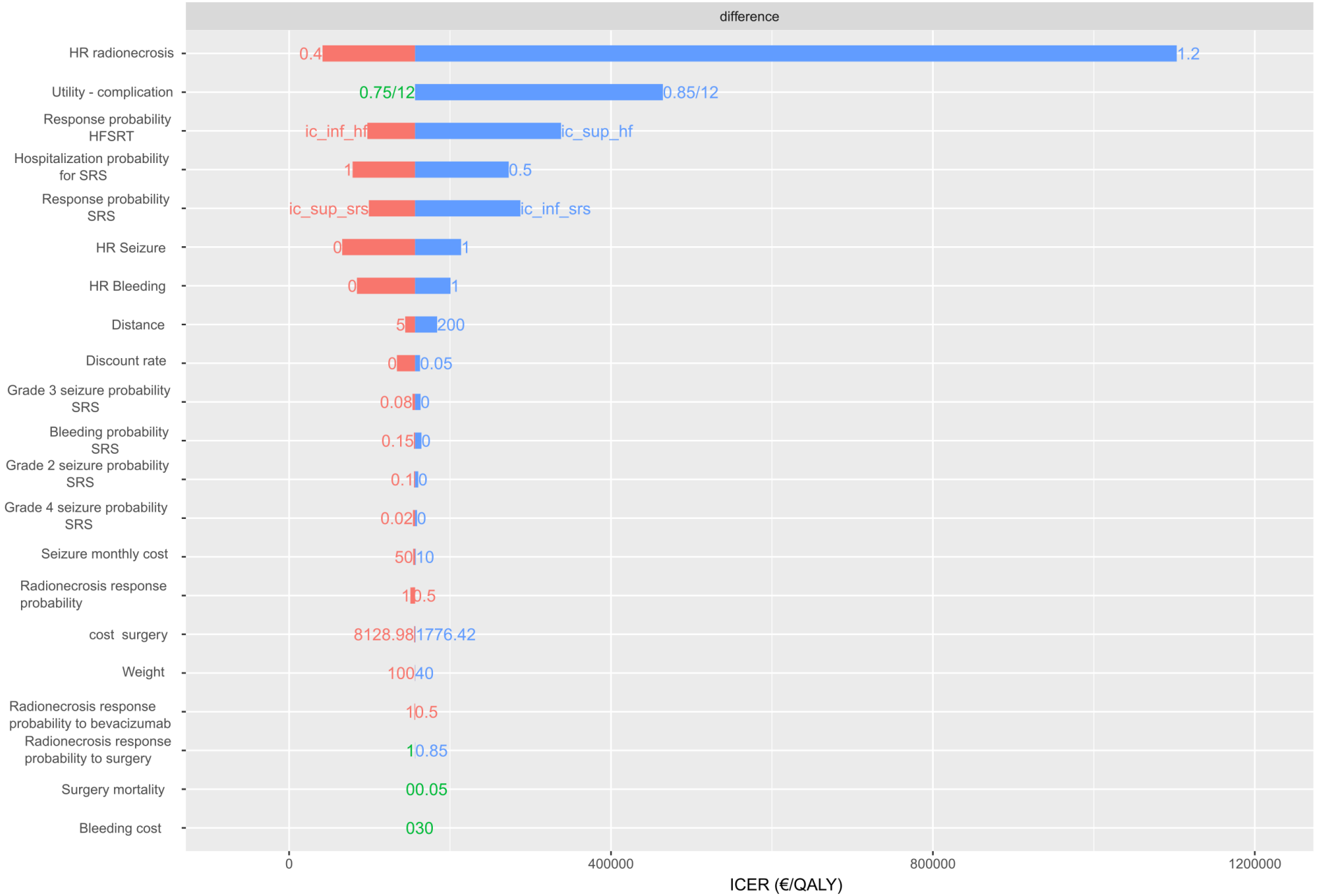


Figure 2: Tornado diagram representing the results of the Deterministic Sensitivity Analysis (DSA)

Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis are shown in the scatter plot and the cost-effectiveness acceptability curves (Figure 3, 4). Those curves evaluate the probability of cost-effectiveness for each willingness to pay thresholds. From the French payer perspective, there was not a defined threshold; we estimated on the basis of WHO recommendations that an ICER below 100,000€/QALY was cost-effective, and an ICER below 30,000€/QALY was very cost-effective.

SRS was associated with a mean total cost of 4,407.80€, including 3,556.62€ for initial treatment including transportation, 116.65€ for radionecrosis related costs, 243,45€ for complications and 491,18€ for follow-up related costs. HFSRT was associated with a mean total cost of 5,817.33€, including 4,521.74€ for initial treatment including transportation, 76.69€ for radionecrosis related costs, 730.87€ for complications, and 488.10€ for follow-up related costs. The difference of complications related cost between SRS and HFSRT is related to the fact that a complication occurring during SRS induces a supplementary cost to the hospitalization cost, but when it occurs in HFSRT it induces a full hospitalization cost.

SRS and HFSRT were associated with a quality-adjusted life expectancy of 1.2597 and 1.2987 QALYs, respectively.

Thus, SRS appeared to be 1,409.53€ cheaper than HFSRT with a decrease of quality-adjusted life expectancy of 0.039 QALYs, the ICER was 36,132.28€/QALY for HFSRT versus SRS.

The scatter-plot (Figure 3) shows that most of the simulations have an ICER located in the northeast and north-west quarter.

The acceptability curves (Figure 4) drawn from the Monte Carlo simulation does not cross, with a higher probability of cost-effectiveness of SRS. The probabilities of the cost-effectiveness of HFSRT compared to SRS for willingness to pay threshold of 10,000€, 30,000€ and 100,000€ are 24.7%, 33.2%, and 94% respectively.

Figure 3: Scatter Plot representing the 1,000 Monte Carlo simulations ran for the Probabilistic Sensitivity Analysis (PSA).

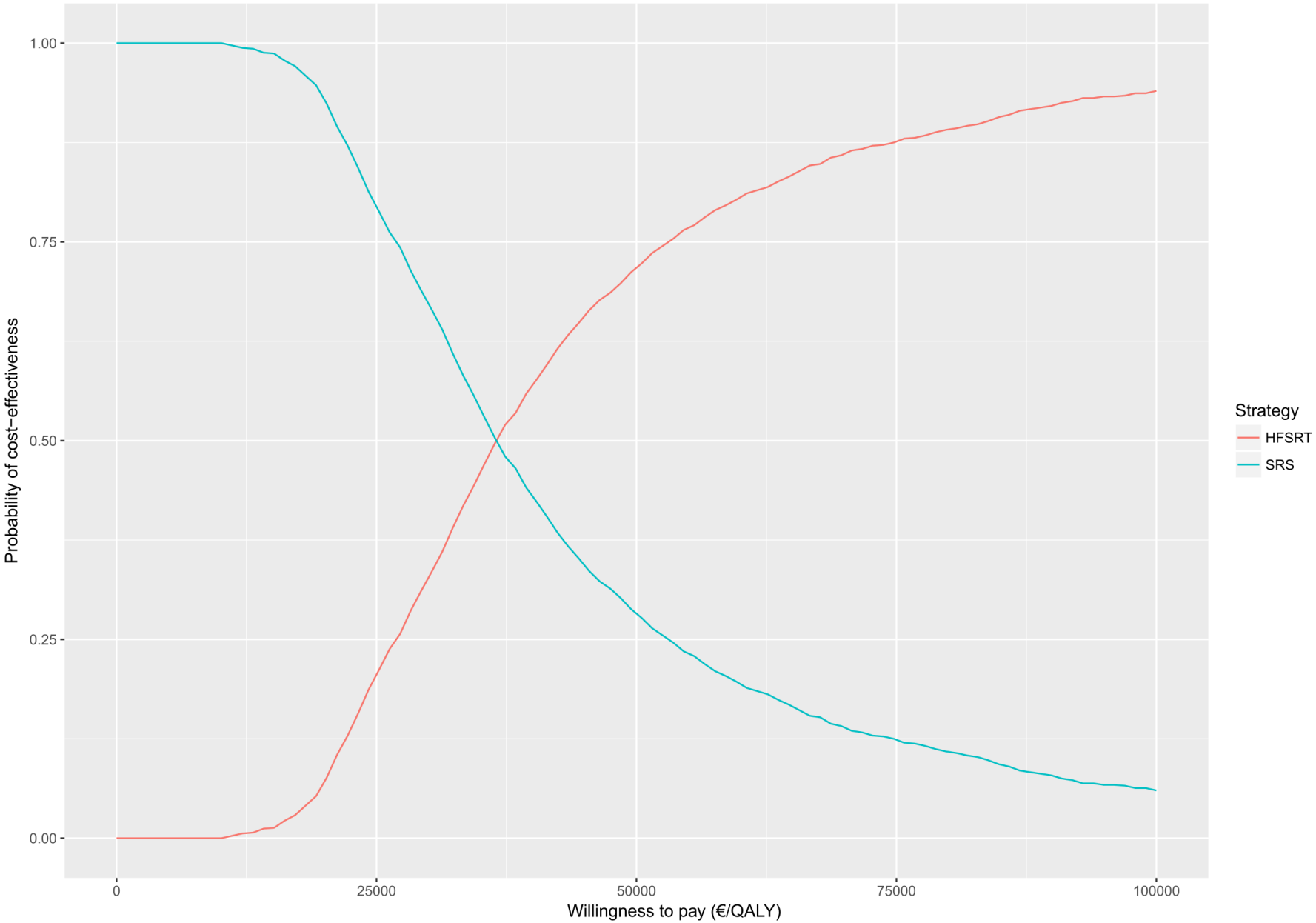


Figure 4: Acceptability curves representing the probability of cost-effectiveness of each strategy given a willingness-to-pay threshold

Conclusion

We report the results of the first medico-economic evaluation of SRS and HFSRT in CRC brain metastases. The results of our analysis suggest that while being more expensive than SRS, HFSRT give an increase of QALY. Moreover, with an ICER of 36,132.28€ per QALY gained, HFSRT is cost-effective over SRS. The probability of cost-effectiveness of HFSRT over SRS is 94%. Our analysis suggests that in a French payer perspective, HFSRT should be preferred over SRS, in patient with CRC brain metastases.

While being limited, the data used to simulate the clinical trajectory of a patient treated for a single CRC brain metastasis are one of the biggest multicentric databases. The utilities used in our model are not specific to a French population, however, it is likely that they would have not significantly differed from what could have been observed in a French population.

Moreover, we evaluate the potential bias induced by the hypothesis made to build the model thru both deterministic and probabilistic sensitivity analysis.

Several studies already demonstrated that stereotactic radiotherapy alone was cost-effective over whole brain irradiation or whole brain irradiation plus stereotactic radiotherapy [19–23]. Our cost-effectiveness analysis provides new data to help precising the most cost-effectiveness strategy to manage melanoma brain metastases. However, the results of our analysis are valid from a French payer perspective, thus a Graphical User Interface of the Markov model developed to conduct this analysis is being developed to help other team conducting the same analysis from a different perspective.

The results of our analysis are dependant of the overall survival of the patient, which might keep increasing in the coming years. Thus, it is likely that patients will undergo several rounds of SRS or HFSRT for intra cerebral relapse thus the cost difference between both strategies will increase. The increase of the overall survival might also lead to an increase of the rate of radionecrosis. Finally, costs could increase because of an increasing use of expensive exams such as F-DOPA PET/CT.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2017, CA. Cancer J. Clin. 67 (2017) 7–30. doi:10.3322/caac.21387.

[2] L.J. Schouten, J. Rutten, H.A.M. Huveneers, A. Twijnstra, Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma, Cancer. 94 (2002) 2698–2705.

[3] M. Jung, J.B. Ahn, J.H. Chang, C.O. Suh, S. Hong, J.K. Roh, S.J. Shin, S.Y. Rha, Brain metastases from colorectal carcinoma: prognostic factors and outcome., J Neurooncol. 101 (2011) 49–55.

[4] M. Michl, J. Thurmaier, G. Schubert-Fritschle, M. Wiedemann, R.P. Laubender, N.C. Nüssler, R. Ruppert, J. Kleeff, W. Schepp, C. Reuter, F. Löhe, M. Karthaus, J. Neumann, T. Kirchner, J. Engel, V. Heinemann, Brain Metastasis in Colorectal Cancer Patients: Survival and Analysis of Prognostic Factors., Clin. Colorectal Cancer. 14 (2015) 281–290. doi:10.1016/j.clcc.2015.05.009.

[5] E. Shaw, C. Scott, L. Souhami, R. Dinapoli, R. Kline, J. Loeffler, N. Farnan, Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05, Int. J. Radiat. Oncol. Biol. Phys. 47 (2000) 291–298.

[6] K.A. Ahmed, J.G. Scott, J.A. Arrington, A.O. Naghavi, G.D. Grass, B.A. Perez, J.J. Caudell, A.E. Berglund, E.A. Welsh, S.A. Eschrich, T.J. Dilling, J.F. Torres-Roca, Radiosensitivity of Lung Metastases by Primary Histology and Implications for Stereotactic Body Radiation Therapy Using the Genomically Adjusted Radiation Dose, J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer. 13 (2018) 1121–1127. doi:10.1016/j.jtho.2018.04.027.

[7] A. Filipovic Pierucci, K. Zarca, M. Wiener, Z. Kabat, V. Filipec, J. Amdahl, Heemod: Models for Health Economic Evaluation, (n.d.). https://CRAN.R-project.org/package=heemod.

[8] B.J. Williams, D. Suki, B.D. Fox, C.E. Pelloski, M.V.C. Maldaun, R.E. Sawaya, F.F. Lang, G. Rao, Stereotactic radiosurgery for metastatic brain tumors: a comprehensive review of complications, J. Neurosurg. 111 (2009) 439–448. doi:10.3171/2008.11.JNS08984.

[9] D. Delishaj, S. Ursino, F. Pasqualetti, A. Cristaudo, M. Cosottini, M.G. Fabrini, F. Paiar, Bevacizumab for the Treatment of Radiation-Induced Cerebral Necrosis: A Systematic Review of the Literature, J. Clin. Med. Res. 9 (2017) 273. doi:10.14740/jocmr2936e.

[10] Z.A. Kohutek, Y. Yamada, T.A. Chan, C.W. Brennan, V. Tabar, P.H. Gutin, T.J. Yang, M.K. Rosenblum, Å. Ballangrud, R.J. Young, Z. Zhang, K. Beal, Long-term risk of radionecrosis and imaging changes after stereotactic radiosurgery for brain metastases, J. Neurooncol. 125 (2015) 149–156. doi:10.1007/s11060-015-1881-3.

[11] P. Guyot, A. Ades, M. Ouwens, N. Welton, Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves., BMC Med. Res. Methodol. 12 (2012).

[12] N.H. Lester-Coll, A.P. Dosoretz, J.A. Hayman, J.B. Yu, Health State Utilities for Patients with Brain Metastases, Cureus. 8 (2016) e667. doi:10.7759/cureus.667.

[13] Z. Or, M. Bellanger, France: Implementing homogeneous patient groups in a mixed market, in: Diagn.-Relat. Groups Eur. Mov. Transpar. Effic. Qual. Hosp., 2011: pp. 221–241.

[14] www.base-donnes-publique.medicaments.gouv.fr, (accessed March 6, 2017).

[15] www.ameli.fr/accueil-de-la-ccam/trouver-un-acte/index.php, (accessed March 3, 2017).

[16] www.ameli.fr/assure/remboursements/rembourse/consultations/metropole, (accessed March 3, 2017).

[17] www.ameli.fr/transporteur-sanitaire/exercice-professionnel/facturation/tarifs/ambulances-tarifs-conventionnels, (accessed December 20, 2017).

[18] Geneva: World Health, Choosing interventions that are cost-effective [Internet]., (2014). http://www.who.int/choice/en/ (accessed June 17, 2017).

[19] M.D. Hall, J.L. McGee, M.C. McGee, K.A. Hall, D.M. Neils, J.D. Klopfenstein, P.W. Elwood, Cost-effectiveness of stereotactic radiosurgery with and without whole-brain radiotherapy for the treatment of newly diagnosed brain metastases, J. Neurosurg. 121 Suppl (2014) 84–90. doi:10.3171/2014.7.GKS14972.

[20] H. Kim, M.S. Rajagopalan, S. Beriwal, K.J. Smith, Cost-effectiveness Analysis of Stereotactic Radiosurgery Alone Versus Stereotactic Radiosurgery with Upfront Whole Brain Radiation Therapy for Brain Metastases, Clin. Oncol. R. Coll. Radiol. G. B. 29 (2017) e157–e164. doi:10.1016/j.clon.2017.05.001.

[21] L.S. Lal, S.D. Byfield, E.L. Chang, L. Franzini, L.-A. Miller, R. Arbuckle, L. Reasonda, C. Feng, A. Adamus, J.M. Swint, Cost-effectiveness analysis of a randomized study comparing radiosurgery with radiosurgery and whole brain radiation therapy in patients with 1 to 3 brain metastases, Am. J. Clin. Oncol. 35 (2012) 45–50. doi:10.1097/COC.0b013e3182005a8f.

[22] N.H. Lester-Coll, A.P. Dosoretz, W.J. Magnuson, M.S. Laurans, V.L. Chiang, J.B. Yu, Cost-effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for up to 10 brain metastases, J. Neurosurg. 125 (2016) 18–25. doi:10.3171/2016.7.GKS161499.

[23] N.H. Lester-Coll, A.P. Dosoretz, J.B. Yu, Decision analysis of stereotactic radiation surgery versus stereotactic radiation surgery and whole-brain radiation therapy for 1 to 3 brain metastases, Int. J. Radiat. Oncol. Biol. Phys. 89 (2014) 563–568. doi:10.1016/j.ijrobp.2014.03.001.

Conclusions

La revue systématique de la littérature conduite sur l'efficacité et la tolérance de la radiothérapie stéréotaxique des métastases cérébrales de mélanome a inclus 20 études. Leurs résultats sont hétérogènes, néanmoins le taux de réponse est supérieur à 80% et la survie sans progression intra-cérébrale varie de 3,74 à 5,5 mois. La survie globale reste médiocre variant de 5 à 10 mois. Enfin, la tolérance du traitement est bonne avec un taux de radionécrose inférieur à 5% et un taux d'hémorragie intra-tumoral de 15%, variant entre 1 et 30% selon les études.

L'étude clinique de l'efficacité de la radiothérapie stéréotaxique des métastases cérébrales de mélanomes a inclus 150 patients avec 298 métastases traités dans 6 centres de radiothérapie en France et en Allemagne. Le taux de réponse moyen était de 67,5% (IC95% = [57 – 77,9%]) pour l'irradiation stéréotaxique mono fractionnée et de 47,8% (IC95% = [30,8 – 64,7%]) pour l'irradiation stéréotaxique hypo fractionnée. Avec un suivi médian de 31 mois (IC95% = [26 – 39 mois]), la médiane de survie globale était de 11 mois (IC95% = [8 – 20 mois]), influencée par le contrôle de la maladie systémique (HR = 0,365, p = 0,0073) et par la survie sans récidive intra cérébrale (HR = 0,828, p < 0,001). Enfin la médiane de survie sans récidive intra cérébrale était de 9 mois (IC95% = [6 – 17 mois]).

L'évaluation médico-économique comparant radiothérapie stéréotaxique mono versus hypo fractionnée montrait que la radiothérapie hypo fractionnée était coût efficace.

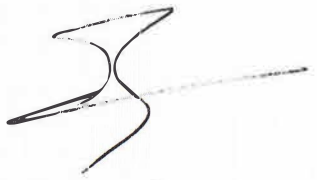
L'étude clinique de l'efficacité de la radiothérapie stéréotaxique des métastases cérébrales de carcinomes colorectaux a inclus 58 patients avec 69 métastases traités dans 6 centres de radiothérapie en France et en Allemagne. Le taux de réponse moyen était de 65,9% (IC95% = [51,9 – 79,9%]). Avec un suivi médian de 31 mois, la médiane de survie globale était de 10 mois (IC95% = [5 – 22 mois]), influencée par l'existence de métastases extra cérébrales (HR = 5,1, p = 0,009), le sexe masculin (HR = 2,76, p = 0,043) et la survie sans récidive intra-cérébrale (HR = 0,86, p < 0,001). La médiane de survie sans récidive intra cérébrale n'a pas été atteinte.

L'évaluation médico-économique comparant radiothérapie stéréotaxique mono versus hypofractionnée était en faveur de la radiothérapie hypo fractionnée.

Vu

Strasbourg, le 27 juillet 2018.

Le président du Jury de Thèse



Professeur Georges NOEL

VU et approuvé

Strasbourg, le..... 17 AOUT 2018

Le Doyen de la Faculté de Médecine de Strasbourg

(signature)

Professeur Jean SIBILIA

Pour le Doyen,
L'Assesseur
Pr Bernard GOICHOT

Rubrique de classement : Oncologie - radiothérapie

Mots-clés : radiothérapie stéréotaxique ; métastase cérébrale ; mélanome; carcinome colorectal; évaluation médico-économique

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RESUME : Les métastases cérébrales correspondent généralement à une phase tardive de l'évolution d'un cancer. La plus part des études publiées à ce jour s'intéresse à leur prise en charge en tant qu'entité individuelle en prenant peu ou pas en compte l'histologie du cancer primitif.

La radiothérapie stéréotaxique a supplanté l'irradiation de l'encéphale en totalité dans le cadre d'atteinte limité à moins de 5 métastases cérébrales. Néanmoins, la plus part des études rapportent des résultats prenant peu ou pas en compte l'histologie de la tumeur primitive. Les mélanomes et carcinomes colorectaux sont traditionnellement décrite comme des tumeurs radioresistantes et en ce sens nécessite une approche particulière.

Nous avons dans un premier temps conduit une revue systématique de la littérature sur le sujet.

Dans un second temps, nous avons conduit sous l'égide de l'Association des Neuro-Oncologues de langue Française (ANOCEF), deux études rétrospectives multicentriques en France et en Allemagne, afin d'évaluer l'efficacité et la tolérance de la radiothérapie stéréotaxique sur les métastases cérébrales et leurs déterminants.

Enfin, nous avons réalisé une évaluation médico-économique comparant les différents régimes de radiothérapie stéréotaxique dans le cadre de ces deux pathologies.

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