UNIVERSITÉ DE LILLE

FACULTÉ DE MÉDECINE HENRI WAREMBOURG

Année : 2024

THÈSE POUR LE DIPLÔME D'ÉTAT

DE DOCTEUR EN MÉDECINE

Association entre composition corporelle et survie globale chez les patients atteints d'un carcinome rénal à cellules claires traités par immunothérapie.

Présentée et soutenue publiquement le 8 octobre 2024 à 18h
Au pôle recherche

Par

Tanguy BOUGET

JURY

Président :
Monsieur le Professeur Nicolas PENEL
Assesseurs :
Monsieur le Docteur Gautier MARCQ
Monsieur le Docteur Aurélien CARNOT
Directrice de thèse :
Madame le Docteur Alexandra FORESTIER

Avertissement

« La Faculté n'entend donner aucune approbation aux opinions émises dans les thèses : celles-ci sont propres à leurs auteurs. »

Liste des abréviations

AMM : Autorisation de Mise sur le Marché

ASCs : Adipose Stem Cells

BIA : Bioelectrical Impedance Analysis

CAAs : Cancer-Associated Adipocytes

CMH : Complexe Majeur d'Histocompatibilité

CPA : Cellules présentatrices d'antigènes

CT : Computed tomography

CTCAE : Common Terminology Criteria for Adverse Events

CTLA-4 : Cytotoxic T-lymphocyte antigen-4

DXA : Dual-Energy X-ray Absorptiometry

EMA: European Medicines Agency

ESMO : European Society for Medical Oncology

FLCN : Gène de la folliculine

HR : Hazard Ratio

IC : Confidence interval / intervalle de confiance

ICI / IPC : Immune checkpoint inhibitor / inhibiteurs de point de contrôle

IGF-1 : Insulin-like Growth Factor 1

IL-1β : Interleukin-1 beta

IL-6 : Interleukin-6

ILC1/2: Innate Lymphoid Cells type 1/2

IMDC : International Metastatic RCC Database Consortium

IQR : Interquartile range

irAE : Immune related adverse event

IFN-y : Interferon-gamma

L3 : Troisième vertèbre lombaire

LDH : Lactate Dehydrogenase

MAIT: Mucosal-Associated Invariant T cells

NF-κB : Nuclear Factor kappa-light-chain-enhancer of activated B cells

NK : Natural Killer cells

NSCLC : Non-Small Cell Lung Cancer

OMS : Organisation Mondiale de la Santé

ORR : Objective response rate

PD-1 : Programmed cell death 1

PD-L1 / PD-L2 : Programmed cell death-ligand 1/2

PFS: Progression free survival

STAT3 : Signal Transducer and Activator of Transcription 3

TCR : T Cell Receptor

Th : T helper cells

TKI : Tyrosine Kinase Inhibitor

TNF-α : Tumor Necrosis Factor-alpha

TNM : Tumor Node Metastasis classification of malignant tumors

Tregs : Regulatory T cells

VEGF : Vascular Endothelial Growth Factor

Table des matières

Abstract

Introduction: Immune checkpoint inhibitors (ICI) are widely prescribed for metastatic clear cell carcinoma renal cell. ICI can lead to heterogenous response patterns and various, severe toxicities. Despite the IMDC prognosis risk score, we lack routine clinical biomarkers to predict treatment response and adverse events (AE). Some authors who studied BMI as predictive biomarker highlight an obesity paradox which refers to the greater efficacy of ICI observed in obese subjects. To further investigate this paradox, authors studied the body composition (BC) parameters by measuring skeletal muscle and fat area on pre-treatment computed tomography (CT). Whereas loss of skeletal muscle demonstrated associations with poor outcomes, results on fat component are inconsistent. Thus, the aim of our study was to investigate correlations between CT-based BC-parameters, including subcutaneous fat and visceral fat, and overall survival in metastatic ccRCC treated by ICI. Secondly, we assessed the relationship between BC-parameters and immune-related AE and the benefit of a detailed body composition assessment compared to the use of BMI alone.

Methods: This retrospective multicenter study included ccRCC traited by ICI patients with available baseline enhanced CT scans. Clinical data at baseline were reviewed from medical record and CT body composition parameters were collected. The areas corresponding to skeletal muscle, subcutaneous, visceral and total adipose tissues at L3 vertebral level were normalized for height in square meters providing SMI, SFI, VFI and TFI, respectively. Correlations between BC parameters and overall survival (OS) were evaluated with Cox regressions models. After dichotomizing TFI by median, multivariate Cox models were built to identify predictive and prognostic factors.

Results: Between June 2017 and June 2022, 71 patients were included (53 men, mean age: 60.7), 24-months OS was 61.4, 95 %CI = [51.0-74.0]. TFI was not correlated with OS (multivariate HR 0.70, 95%CI = [0.33; 1.48]). TFI was strongly correlate with BMI (r = 0.81)

whereas weak association was found with between SFI and VFI (r = 0.53). TFI was not associated with irAEs.

Conclusions: Total fat index was not predictive of OS in patients with mRCC who received first-line ICI-based therapy. Given the strong correlation of TFI with BMI but the weak correlation of SFI with VFI, larger, prospective studies are warranted to investigate the predictive values of subcutaneous and visceral fat.

1. Introduction Générale

1.1. Généralités sur le cancer du rein

Le cancer du rein est le 6ème cancer le plus fréquent en France avec 15 323 nouveaux cas diagnostiqués en 2018 pour 5 589 décès. Entre 1990 et 2018 l'incidence a augmenté de 1,7%/an chez l'homme et 1,4%/an chez la femme alors que la mortalité est restée globalement stable (1). Cette discordance peut s'expliquer par l'amélioration des performances diagnostiques en imagerie multipliant les diagnostiques fortuits aux stades plus précoces mais aussi grâces aux innovations thérapeutiques conférant un meilleur pronostic.

Les facteurs de risques connus et non modifiables sont l'âge et le sexe. Une proportion plus faible des cas est expliquée par des syndromes de prédisposition héréditaire avec plusieurs gènes identifiés (dont VHL ; FLCN) (2). Les facteurs de risques modifiables, accessibles à la prévention primaire sont : le tabagisme, l'obésité, l'hypertension artérielle et l'insuffisance rénale (3).

La maladie est diagnostiquée à un stade localisé dans 70 à 80% des cas. L'objectif du traitement est curatif, au moyen d'une chirurgie d'exérèse complète. Malgré l'intention curative de la chirurgie 30% à 40% des cas récidivent sous forme métastatique (4).

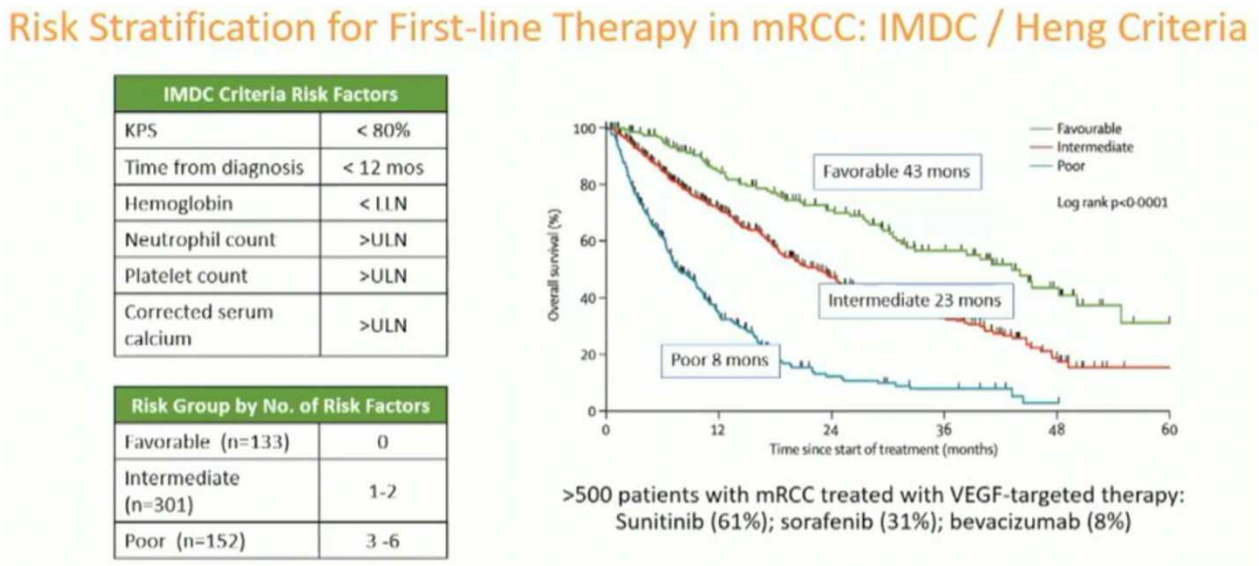
L'analyse histologique de la tumeur primitive ou d'un site métastatique conditionnant le choix de la première ligne thérapeutique est indispensable. La classification OMS 2022 décrit trois principaux sous types de tumeurs malignes rénales. Les carcinomes rénaux à cellules claires sont le sous type histologique le plus fréquent représentant 80% des cas. Seul ce sous-type histologique bénéficie d'une AMM pour les inhibiteurs du point de contrôle immunitaire (ICI). Les principales autres histologies sont représentées par le carcinome papillaire (15% des cas) et les carcinomes chromophobes (5% des cas). Concernant ces

deux types histologiques il existe peu de données de forts niveaux de preuves quant à leur traitement en raison de leur faible prévalence (5)(6).

En cas de maladies oligométastatiques, ou lentement évolutives, le traitement systémique peut être différé après une phase initiale de surveillance. Les traitements focaux comme la radiothérapie stéréotaxique ou la chirurgie des métastases permettent également de retarder l'instauration d'un traitement systémique (7).

Les carcinomes à cellules rénales ont en effet un pronostic très variable estimé par la classsification pronostique de Heng calculée par le score de risque IMDC (International Metastatic Renal Cell Carcinoma Database Consortium) (**Figure 1).** Ce score, développé à l'ère des thérapies ciblées reste utilisé pour définir le choix de la première ligne thérapeutique en situation métastatique. Il prend en compte: l'index de Karnofsky, le délai entre le diagnostic et l'introduction du traitement systémique, le taux d'hémoglobine, le taux de plaquettes, le taux de neutrophiles, la calcémie corrigée et le taux de LDH. Selon ces critères, les patients sont classés en trois catégories, bon pronostic, pronostic intermédiaire, ou défavorable (8).

Figure 1 : Calcul du score IMDC et groupes de risque. A. Ari Hakimi, IKCS 2022



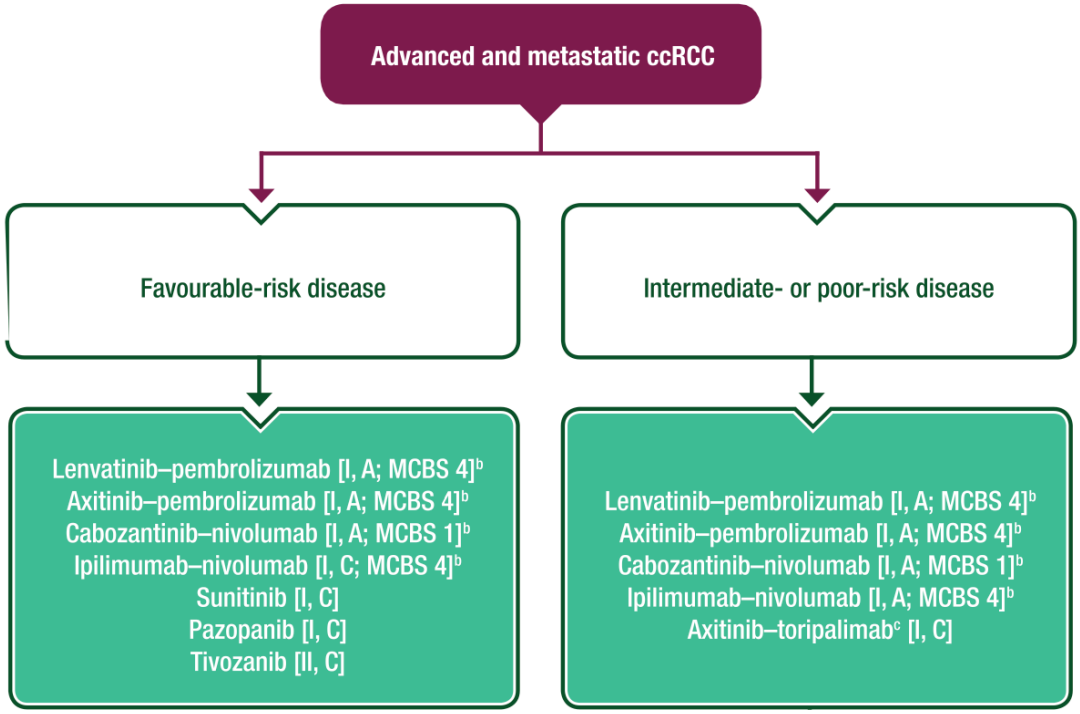
Dans la majorité des cas la présence d'une forte masse tumorale ou d'une maladie rapidement évolutive impose l'initiation de thérapies systémiques.

En raison de sa chimiorésistance, l'arsenal thérapeutique des cancers du rein métastatique est longtemps resté limité. Avant l'arrivée des ICI en première ligne métastatique, le traitement faisait appel aux inhibiteurs de tyrosine kinase anti-VEGF en monothérapie (Sunitinib et Pazopanib) (9).

L'immunothérapie par inhibiteur du point contrôle a d'abord fait son arrivée dans le cancer du rein métastatique avec le Nivolumab, après échec d'une ligne de TKI (10). Les premiers essais cliniques introduisant les ICI en association ou en monothérapie en première ligne métastatique ont vu le jour en 2017 avec la première AMM obtenue en 2019 pour l'association Nivolumab-Ipilimumab (11). Par la suite sont apparues des associations immunothérapie - TKI avec notamment l'association Pembrolizumab-Axitinib en 2019 (12).

Le score IMDC est nécessaire pour guider le choix parmi les options thérapeutiques **(Figure 2).**

Figure 2 : Algorithme de traitement en 1ère ligne du cancer rénal à cellules claires. ESMO guidelines.



1.2. Immunothérapie par inhibiteurs des points de contrôle

1.2.1. Réponse immunitaire anti-tumorale

L'émergence de l'immunothérapie par inhibiteurs de points de contrôle impose la compréhension des mécanismes de l'immunité anti-tumorale.

La reconnaissance des néoantigènes tumoraux est assurée par des effecteurs de l'immunité innée, les cellules présentatrices d'antigène (CPA). Les CPA exposent l'antigène tumoral au lymphocyte T par le biais du complexe majeur d'histocompatibilité (CMH), dans un ganglion lymphatique. Le lymphocyte T naïf, via son TCR spécifique, reconnait le complexe CMH-antigène tumoral, orientant la différenciation des lymphocytes et favorisant l'expansion clonale des lymphocytes T CD8+ cytotoxiques. Ces lymphocytes activés vont ensuite migrer jusqu'au site tumoral pour la phase effectrice de la réponse anti tumorale et ainsi reconnaitre et lyser les cellules cancéreuses.

Cette réponse immunitaire suivant la reconnaissance de l'antigène par le TCR est finement régulée par un équilibre entre signaux de co-stimulation, nécessaire à l'activation de la réponse anti tumorale, constituant la synapse immunologique, et signaux d'inhibition.

Parmi ces signaux d'inhibition, les points de contrôle immunitaires (IC) sont essentiels dans la tolérance du soi (anergie), évitant l'emballement du système immunitaire et les dommages collatéraux aux tissus sains. En situation physiologique, ces IC inhibent l'activation des lymphocytes autoréactifs naïfs en lymphocytes effecteurs dans la phase initiale de la réponse, et permettent également le retour à l'état de repos d'un lymphocyte ayant éliminé l'antigène (13) (14).

Ce mécanisme d'inhibition de la réponse immune est détourné par les cellules tumorales. En augmentant l'expression des IC, les cellules tumorales inhibent la réponse immunitaire anti-tumorale tant dans sa phase de priming que dans la phase effectrice. Ceci conduit un pool de lymphocytes T "exhausted" caracterisés par une expression persistante des recepteurs inhibiteurs et une perte des fonctions effectrices (ou mémoires) (15).

1.2.2. Mode d'action des ICI

Le blocage de ces points de contrôle immunitaire permet de restaurer l'immunité anti-tumorale. Deux points de contrôle sont la cible d'inhibiteurs développés en pratique clinique, PD-1 (programmed cell death protein 1) et CTLA-4 (cytotoxic T lymphocyte-associated Antigen). Ces points de contrôle sont principalement situés sur les cellules T : les lymphocytes Tregulateurs et les Teffecteurs après activation - pour CTLA-4 ; sur les cellules T activées, B, NK pour PD-1, son ligand PD-L1 ayant une expression tissulaire ubiquitaire. Leur expression s'intensifie dans le microenvironnement tumoral, constituant le mécanisme d'échappement à la réponse immuno-oncologique (14).

Les thérapies par ICI développées utilisent des anticorps monoclonaux pour bloquer les points de contrôle ou leurs ligands, réactivant les cellules T, alors en mesure d'exercer leurs fonctions cytotoxiques anti tumorales (**Figures 3 et 4**).

Dans certains types de cancers , il a été observé une meilleure efficacité des ICI lorsque les cellules T et les cellules tumorales expriment fortement les IC et leurs ligands, restreignants par fois leur prescription selon l'expression de PD L1 en immunohistochimie, comme pour le Pembrolizumab dans le cancer du poumon non à petites cellules (NSCLC) métastatique (13).

Figure 3 : Mécanisme d'action des anti-PD1. Waldman et al, 2020

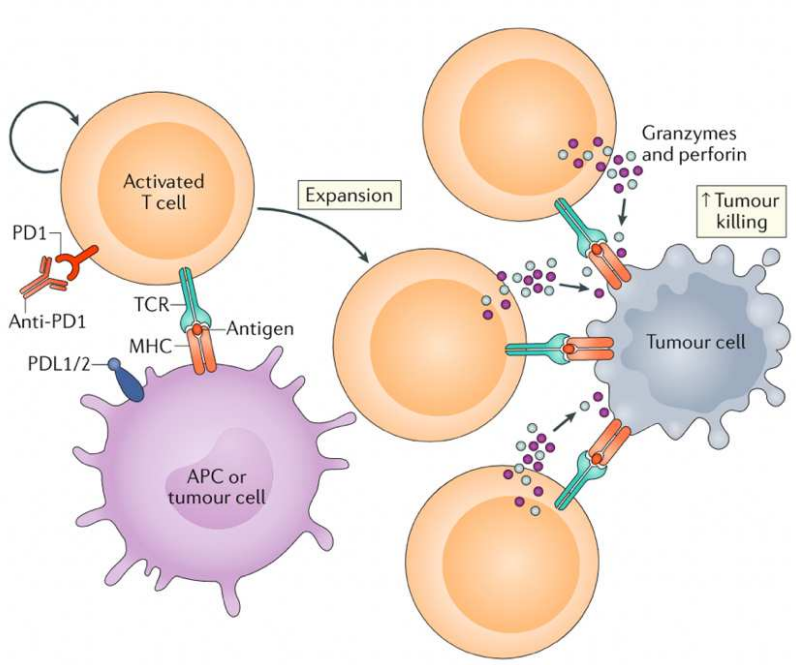
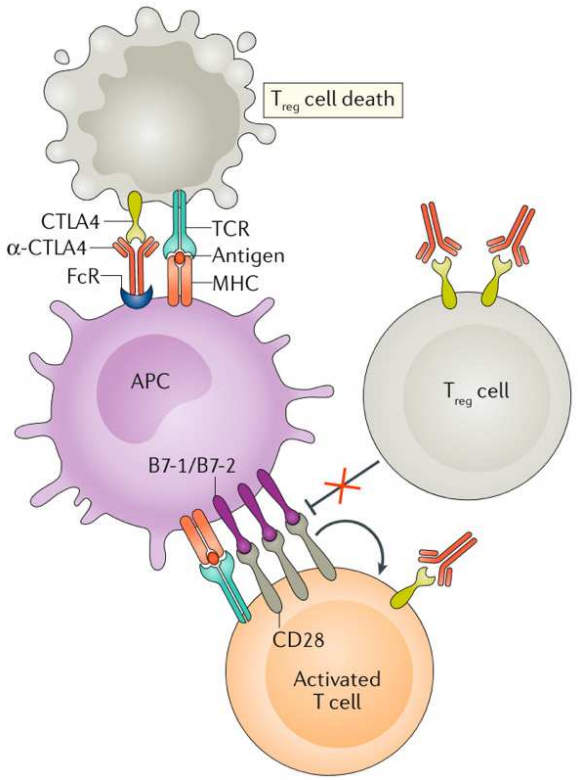


Figure 4 : Mécanisme d'action des anti-CTLA4. Waldman et al, 2020



1.2.3. Inhibiteurs de points de contrôle immunitaire en pratique clinique

Les inhibiteurs de points de contrôle immunitaire (ICI) ont d'abord démontré leur efficacité en situation métastatique dans les tumeurs les plus immunogènes (mélanome et NSCLC) (16) (17). Les indications se sont élargies au stade métastatique comme au stade adjuvant (18) ou néoadjuvant (19). Ces traitements ont considérablement modifié le pronostic de certains cancers avec toutefois des profils de réponse observés différents de ceux habituellement connus sous traitements conventionnels tels que la chimiothérapie ou les thérapies ciblés. Certains patients présentent une réponse prolongée alors que d'autres sont d'emblée résistants. Des cas de de pseudo-progression et d'hyper-progression sont également décrits (20).

De par leur mécanisme bloquant l'inhibition de la réponse lymphocytaire T, le profil de tolérance de ces molécules est particulier, caractérisé par un éventail très étendu d'effets indésirables d'ordre immunologique. Tous les organes peuvent être touchés indifféremment

bien que les toxicités cutanées, endocriniennes ou digestives soient les plus fréquemment décrites. Ces toxicités, parfois graves, peuvent conduire à une altération de la qualité de vie, à l'arrêt de l'immunothérapie, voire au décès (21).

L'enjeu est donc d'identifier parmi les patients, ceux qui bénéficieraient le plus de l'immunothérapie avec un profil de toxicité acceptable. Dans une revue de la littérature Hommes et al démontrent la difficulté à identifier des biomarqueurs cliniques pertinents. Malgré divers potentiels biomarqueurs étudiés, sanguins, microbiomiques ou immmunogéniques leurs reproductibilité et applicabilité en pratique clinique courante reste à définir (22).

Parmi les biomarqueurs pronostiques et prédictifs de la réponse à l'immunothérapie la sarcopénie a été un des premiers paramètres clinique étudié. En effet, la forte prévalence de la sarcopénie chez les patients au stade avancé de la maladie en fait un marqueur d'intérêt. Plusieurs études ont démontré le rôle pronostic défavorable de la sarcopénie dans le devenir des patients traités par immunothérapie (23,24).

A l'inverse, les effets de l'obésité sur la réponse à l'immunothérapie n'ont été étudiés que récemment. L'IMC est en effet une mesure standardisée, couramment utilisée en pratique clinique et d'intérêt en oncologie compte tenu de la forte prévalence à la fois de l'obésité et de la dénutrition chez les patients. Les auteurs ont alors démontré un « paradoxe de l'obésité ». Bien que facteur de risque connu de nombreux cancers, l'obésité apparaît être un facteur prédictif de survie chez les patients traités par ICI (25–27).

L'utilisation de l'IMC comme mesure de l'obésité a certaines limites. L'IMC ne permet pas de préciser les rôles respectifs que jouent la masse grasse et la masse musculaire, et de la même façon l'IMC ne distingue pas la masse grasse viscérale et la masse grasse sous-cutanée.

Pour mieux comprendre cette interaction, les auteurs ont alors développé des modèles cliniques plus précis définissant la composition corporelle.

1.3. La composition corporelle

1.3.1. Le paradoxe de l'obésité

1.3.1.1. Tissu adipeux sain

Au-delà de sa fonction de stockage, le tissu adipeux est capable de sécrétion d'hormones, de cytokines et d'adipokines. Ces molécules exercent un rôle de régulation du métabolisme systémique, agissant sur l'appétit, l'homéostasie du glucose, l'insulinémie, et les fonctions immunitaires. Le maintien de ses fonctions repose sur un équilibre dynamique entre les médiateurs et les cellules pro-inflammatoires et anti-inflammatoires.

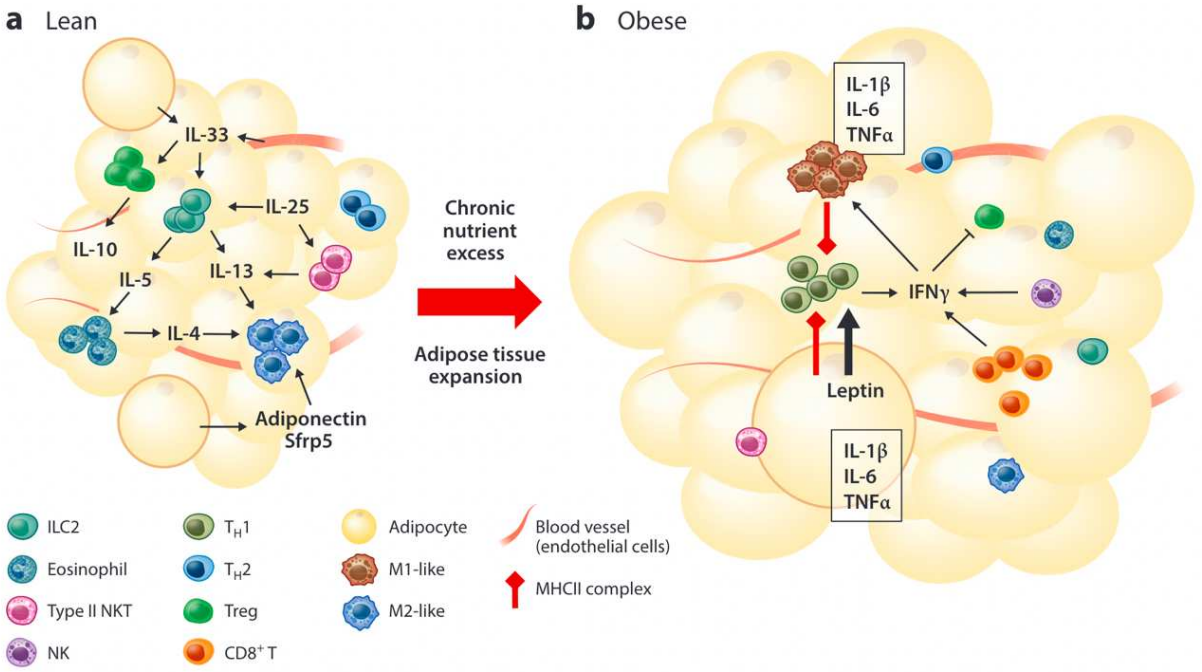
A l'état sain, le tissu adipeux présente une polarisation plutôt Th2, avec la présence de cellules T auxiliaires de type 2 (Th2), de cellules de profil anti inflammatoire comme les cellules T régulatrices (Tregs) et les macrophages de phénotype M2.
Cet équilibre résulte d'une cascade cytokinique initiée par l'interleukine 33. L'IL-33, produite par les adipocytes et les cellules endothéliales stimule l'activation, la prolifération et le recrutement des lymphocytes Treg. Sous l'effet de l'IL-33 les Treg produisent des cytokines anti-inflammatoires comme l'IL-10 (**Figure 5**).

Par ailleurs, l'IL-33 est un puissant activateur des cellules lymphoïdes innées de type II (ILC2s). Une fois activées ces dernières sécrètent l'IL-4, l'IL-5 et l'IL-13. Ces cytokines jouent un rôle essentiel dans la promotion de la réponse immunitaire de type Th2 et dans la polarisation des macrophages vers un phénotype M2 (28).

Parmi les autres régulateurs de l'homéostasie du tissu adipeux :
- Les cellules iNTK. Ces dernières exercent leurs propriétés anti-inflammatoires via la sécrétion des IL-5 et IL-13.

- Les lymphocytes T γδ sont d'autres lymphocytes T non conventionnels abondamment présents dans le tissu gras et jouant un rôle immunomodulateur.
- Les éosinophiles, via l'IL-5, infiltrant le tissu adipeux et soutenant les profils immunitaires Th2. (29)

Figure 5 : Régulation de l'inflammation du tissu adipeux, Deng et al., 2016



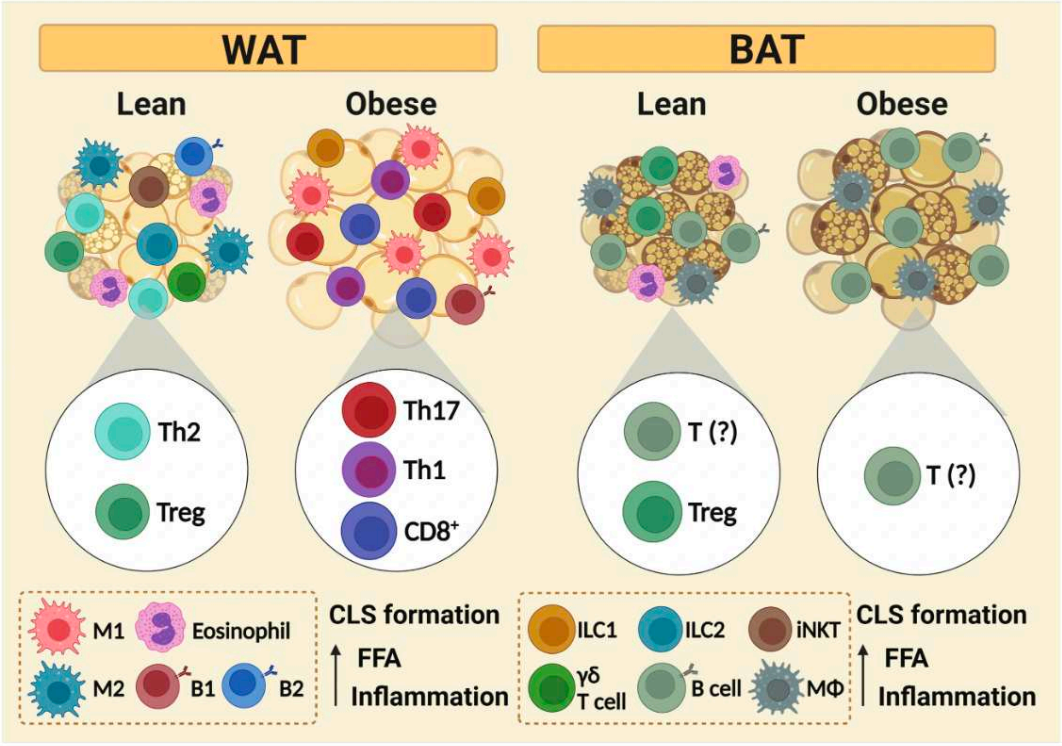
1.3.1.2. Tissu adipeux et obésité

L'excès de tissu adipeux est associé à un état inflammatoire chronique. L'hypertrophie et l'hyperplasie des adipocytes conduit à des formations histologiques appelées crown-like structures (CLS) où des macrophages M1 forment une disposition annulaire autour d'adipocytes apoptotiques (29). Ces structures sécrètent les cytokines pro-inflammatoires TNF-α, IL-1β, IL-6 (30) (**Figure 6**).

Au niveau tissulaire le tissu adipeux voit son phénotype modifié. La leptine orientant la réponse immunitaire vers un profil Th1. L'IFN-y sécrété par, les ILC1, les cellules Th1 activées, les cellules NK et les lymphocytes T CD8+ favorisent la polarisation des

macrophages de type M1 pro-inflammatoire. Les cytokines telles que l'IL-1b, l'IL-6 et le TNF-a entretiennent l'inflammation du tissu adipeux et diminuent les cellules Treg et Th2 (28). Par ailleurs les MAIT (mucosal-associated invariant T cells) résidant au sein du tissu adipeux seraient susceptibles d'entretenir les phénomènes inflammatoires en situation d'obésité via l'IL-17 (31).

Figure 6: Immune cells from BAT and WAT of lean and obese phenotypes. Pasquarelli-do-Nascimento et al. 2022

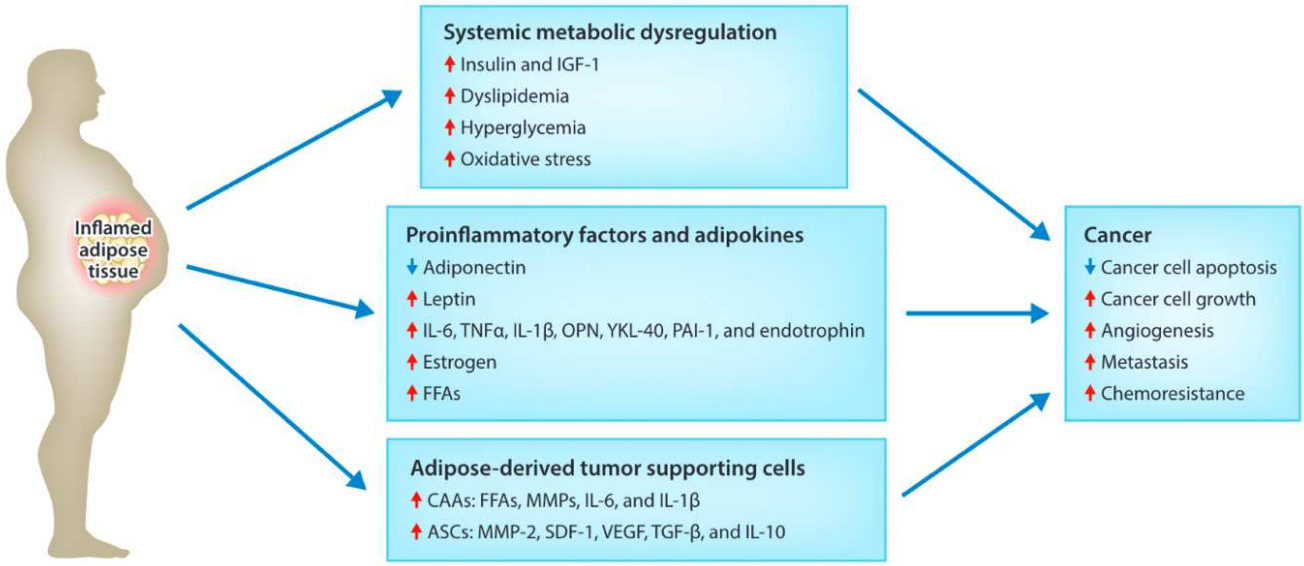


1.3.1.3. Obésité et microenvironnement tumoral

L'inflammation chronique associée à l'obésité créé un microenvironnement favorable à la croissance tumorale. Les cellules inflammatoires ainsi que leurs médiateurs sont retrouvées au sein du microenvironnement tumoral où ils exercent leurs fonctions de signalisation, de prolifération, de migration et d'angiogenèse selon plusieurs mécanismes (**Figure 7**) :

- L'inflammation exerce un rôle mutagène conduisant à la transformation des cellules malignes. L'inflammation active des voies de signalisation pro-tumorales par le biais de facteurs de transcription (NF-κB ; STAT3) (28).
- Au niveau cellulaire, certaines cellules issues du tissu adipeux (CAAs ; ASCs) peuvent infiltrer le microenvironnement tumoral et favoriser la croissance tumorale (32).
- Au niveau métabolique, l'insulinorésistance est responsable de la sécrétion accrue d'IGF-1, facteur de croissance tumorale (28).
- Le microenvironnement tumoral se caractérise également par une immunosuppression médiée par PD-1, dont l'expression serait augmentée par le TNF-α, l'IL-6, la leptine (33) ainsi que par l'activation de la voie de la glycolyse aérobie (34).

Figure 7 : Mechanisms linking obesity to cancer.T. Deng et al, 2016



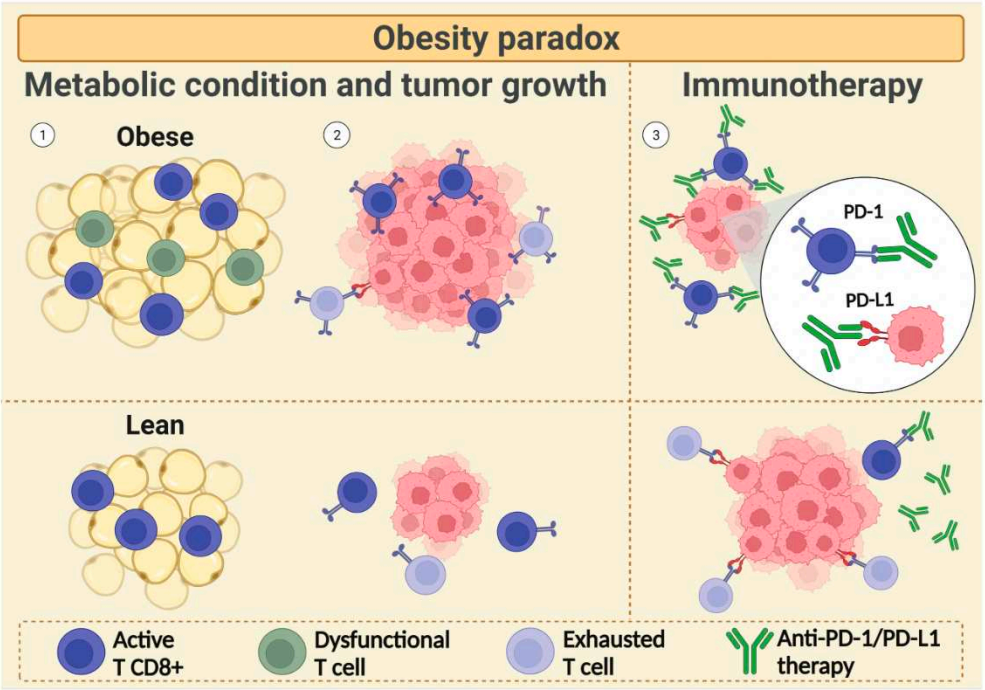
1.3.1.4. Obésité et inhibiteurs des points de contrôle immunitaires

L'hypothèse avancée pour expliquer le paradoxe de l'obésité est donc que : si l'interaction répétée entre PD-1 présent à la surface des cellules T et son ligand est responsable de l'état d'exhaustion des lymphocytes T, un microenvironnement tumoral riche en cellules T

CD8+ exprimant fortement PD-L1, « exhausted », est en revanche plus susceptible de répondre aux traitements ciblant l'axe PD-1/PD-L1 (29,35).

Ces traitements réactivant les cellules T épuisées, peuvent ainsi rétablir l'immunité anti tumorale (36) (**Figure 8**).

Figure 8 : The obesity paradox. Pasquarelli-do-Nascimento et al. 2022



1.3.2. Mesure de la composition corporelle par tomodensitométrie

Afin d'étudier ce paradoxe de l'obésité, les auteurs se sont intéressés à des mesures plus détaillées de la composition corporelle que ne l'était la seule mesure de l'IMC. Les travaux de Mourtzakis en 2008 ont comparé trois méthodes de mesure de la composition corporelle au sein d'une population de patients atteints de cancer, l'impédancemétrie bioélectrique (BIA), l'absorptiométrie biphotonique (DXA) et l'analyse des images de tomodensitométrie. Bien que simple et peu coûteuse, la BIA présente des limites de précision en comparaison à la DXA et ne permet pas de distinguer la masse musculaire de la masse maigre totale. La DXA constitue la méthode de référence, précise et non invasive pour estimer les masses musculaire et grasse totales (38). La tomodensitométrie a l'avantage d'être un examen

couramment réalisé à la fois au diagnostic et dans le suivi des patients atteints de cancer. Or, plusieurs études ont montré une corrélation entre les masses grasses et musculaires mesurés au niveau d'une coupe scanographique abdominale et les masses grasses et musculaires totales (37). Les travaux de Mourtazkis ont validé ce repère par comparaison aux performances de mesure de la DXA. La méthode utilisée pour mesurer et définir la composition corporelle selon les travaux et Mourtzakis et Martin est développée en **annexe 1** (38,39).

1.3.3. Principaux résultats des études sur la composition corporelle

De nombreuses études ont établi le rôle pronostic de la sarcopénie sur la survie globale (23,24,38,40). Dans la méta-analyse de Shachar plus de 11 seuils différents étaient utilisés pour définir la sarcopénie (23). Parmi ces études, celle publiait par Martin et al. en 2013 a démontré le rôle pronostique de la sarcopénie chez 1,473 patients atteints de cancer pulmonaires ou gastro-intestinaux tous stades confondus (39). Les seuils de SMI définis par Martin ont été significativement étudiés dans la littérature récente, appliqués à des localisations de primitif variées et aux patients traités par ICI (**Annexe 2**). Par exemple, dans l'étude de Martini sur 79 patients atteints d'un carcinome à cellules rénales traité par immunothérapie en première ligne, ces seuils de sarcopénie étaient significativement associés à la survie globale (41).

De la même façon, la myosteastose, caractérisée par l'infiltration de graisse dans les muscles squelettiques (42), a démontré son rôle pronostic sur la survie globale dans la population hétérogène d'étude de Martin (39). D'autres études récentes sur des patients traités par immunothérapies ont publiés des résultats discordants (24,43) L'essai de Chu et al sur 84 patients traités pour un mélanome retrouvait un impact négatif de la myosteatose sur la survie globale (43). En revanche, la méta-analyse réalisée par Takenada regroupant 2501 patients traités par ICI ne retrouvait pas d'association entre myosteatose et survie

globale, bien que la sarcopénie était associée à une survie globale diminuée (24). Cette étude ne comprend qu'une minorité de patients atteints d'un carcinome rénal à cellules claires.

À notre connaissance, peu d'études s'intéressant aux marqueurs adipeux ont démontré leur rôle prédictif sur l'efficacité et la toxicité de l'immunothérapie. Les travaux publiés, basés sur de faibles cohortes, rétrospectives ont révélé des associations inconstantes (**Annexe 2**).

Concernant les études s'intéressant spécifiquement à la population de patient présentant un cancer à cellules rénales au stade métastatique :

L'étude de Takei et al sur 60 patients traités en première ligne ne retrouvait aucune association entre les paramètres adipeux et la PFS ou l'OS (44).

L'étude de Martini portant sur 79 patients dont un tiers seulement en première ligne a montré une association entre un TFI élevé et une survie prolongée (41).

McManus en 2024 publiait une étude sur 99 patients traités par Nivolumab-Ipilimumab et ne retrouvait une association positive avec le SFI qu'en terme de PFS (45). L'étude la plus large est celle de Ged et al. rassemblant 205 patients, seulement 30% en première ligne, pour lesquels une association était retrouvée entre un faible SMI, un faible BMI et une survie globale prolongée. Cette association n'était toutefois plus significative dans le modèle multivariée (46).

L'incidence des toxicités immunomédiées et leur association aux paramètres de composition corporelle reste sous étudiée.

Bien que plusieurs méta-analyses aient retrouvé une incidence plus élevée d'irAEs chez les patients obèses ou en surpoids utilisant la mesure de l'IMC (40,47,48), le rôle prédictif de la sarcopénie et des paramètres d'adiposité montre des résultats discordants sur des populations d'études de faibles effectifs (49). L'étude de Hirsch retrouvait une association positive entre la sarcopénie et l'incidence des irAES dans un population de 92 patients

essentiellement traités pour un NSCLC (50). A l'inverse l'étude de Daly sur 84 patients atteints de mélanome métastatique ne retrouvait pas d'association significative entre sarcopénie et toxicité mais une association positive entre myosteatose et irAEs de grade III/IV (49). La méta analyse de Takenaka regroupant sept études dont ces deux dernières ne retrouvait finalement pas d'association en sarcopénie et irAEs. (24)

Ainsi, Les différentes populations des études publiées sont parfois hétérogènes en terme de primitif, ou discordante pour les études se focalisant sur les patients atteints d'un cancer à cellules rénales, et ne concerne pas toujours des patients de vie réelle, non sélectionnés. Nous proposons donc ici de nous concentrer sur la population de carcinome rénal à cellules claires, en France, pour laquelle les indications d'immunothérapie sont larges en première ligne, et les scanners avec coupes abdominales sont usuellement réalisés au diagnostic.

L'objectif de notre étude est d'explorer le lien entre la composition corporelle évaluée par la mesure scanographique du tissu adipeux, viscéral et sous-cutané et la survie globale du cancer du rein métastatique traité par immunothérapie seule ou en association en première ligne métastatique. La sarcopénie sera prise en compte dans l'analyse.
Les objectifs secondaires sont d'évaluer le lien entre la composition corporelle et les toxicités immunomédiées, ainsi que d'identifier l'apport d'une description détaillée de la composition corporelle par rapport à une mesure simple de l'IMC chez ces patients.

2. Introduction

Increasingly widespread use of immune checkpoint inhibitors (ICI) has revolutionized the prognostic of many cancers. Advanced clear cell renal cell carcinoma (ccRCC) was among the first to benefit from this treatment. In 2016 Nivolumab was approved as second-line treatment after prior anti-VEGF therapy failure (10). In 2019, results from the randomized phase III CHECKMATE-214 trial demonstrated Nivolumab-Ipilimumab combination overall survival superiority over Sunitinib (11). Thus, Nivolumab-Ipilimumab became the standard of care for the first-line treatment of patients with intermediate/poor-risk disease. Since 2020 and the KEYNOTE-426 publication results, Pembrolizumab-Axitinib has been approved by the EMA in treatment-naïve aRCC irrespective of IMDC risk (12). Then, CHECKMATE-9ER trial showed Nivolumab-Cabozantinib improved OS over Sunitinib (51). This combination has become an alternative therapy for the firstline treatment of advanced renal cell carcinoma (aRCC) in 2022. More recently CLEAR study demonstrated that Pembrolizumab-Lenvatinib was superior to sunitinib (52). These results led to the EMA approval of Pembrolizumab-Lenvatinib as a new treatment option in the first line setting.

The use of ICI demonstrated several patterns of response that differ from those seen with conventional therapies. While some patients benefit in a long duration of disease control, others experiment rapid progression. Similarly, these treatments result in various immune-related adverse events (irAEs). They occur at high frequency. For example, in the KEYNOTE-426 trial, 75.8% of patients reported grade ≥ 3 adverse events and 30.5% led to discontinuation of treatment (12). These toxicities can involve multiple organs and systems, sometimes life-threatening, and can alter quality of life (53,54). We lack predictive factors that can be used as everyday tools (52).

Whereas IMDC is still commonly use to classify patients in prognostic categories, we lack robust clinical biomarkers of response to ICI in aRCC (6). Cancer sarcopenia is known as

an independent prognostic factor in ICI-treated patients. Shachar et al. in 2016, studied the prognostic value of sarcopenia in a meta-analysis and systematic review of over 7,800 patients with solid tumors. They found an association between sarcopenia and poor OS among various tumors types and across disease stages (23). Among ICI-treated patients, the meta-analysis of 2,501 patients published by Takenaka et al. in 2021 demonstrated that sarcopenia was significantly associated with poor survival (24).

However, regarding BMI, studies show inconsistent results. The meta-analysis of 1,840 patients published in 2020 by Yoo et al. showed that higher BMI at baseline was associated with prolonged OS across 16 cancer types treated with ICI (27). As Yu Ann, in a pooled analysis of 13 studies comprising more than 5,000 patients treated with ICIs for NSCLC, melanoma or RCC, shows positive association between high BMI and improved OS. Among these 13 studies, three studies investigated association between BMI and irAEs in more than 2,600 patients. Incidence of irAEs did not differ between BMI category (26). Conversely, Zhang et al. conducted a cross-sectional analysis of 684 patients with advanced-stage cancer receiving ICI and found a high rate of irAEs among patients with higher BMI (47). In line with this study, Cortellini et al. conducted a multicenter analysis of 1,070 advanced cancer patients treated with ICI and showed that higher BMI was significantly related to any grade irAEs, G3/G4 irAES and irAE leading to discontinuation (48).

To explore beyond BMI and sarcopenia, authors have more recently tried to describe body-composition parameters. Therefore, they assessed radiographic markers of adiposity and muscle (39). Adipose tissue may have a role as prognostic biomarker highlighting a phenomenon called « obesity paradox ».

Although obesity is a well-known risk factor for increased incidence and aggressiveness of several cancers, such as aRCC (3) obese patients surprisingly seem to have better outcomes in ICI-based treatment (27). Mechanisms underlying this phenomenon are not well understood but involve obesity-related proinflammatory state and metabolic

dysregulations. Chronic inflammation induce an immune-suppressed phenotype characterized by T-cell dysfunction and exhaustion. These cells exhibit increased PD-1 which may enhance ICI effectiveness (29). Moreover, excess adiposity contributes to an imbalance secretion of adiponectin/leptin with increased circulating leptin blood levels. Leptin activity is mediated through the STAT3 pathway, which is involved in cell proliferation, survival and differentiation and potentially in PD-1 upregulation (55).

Previous publications studying adipose tissue markers have shown inconsistent associations between type of fat (either visceral or subcutaneous) and clinical outcomes: either OS, PFS or ORR, and some have failed to report any association. Moreover, these studies were retrospective design, small sample size or single-institutional that could not deny bias and validity (**Appendix 2**). For instance, Martini et al. in 2021 found an association between OS and TFI, however study population included only one-third treatment-naïve aRCC and various histologies (41). In contrast, Takei et al studied 60 ICI-treated aRCC patients in first line and did not found any association between OS and body composition parameters (44).

The largest study investigated 205 mRCC patients treated by ICI, but only 30% as first list. In this population Ged et al found that low SMI and low BMI were associated with poor survival (46). The most recent published study, included 99 aRCC treated by Nivolumab-Ipilimumab and found an association between high SFI and PFS but not with OS (45).

Therefore, the main objective of the current study was to investigate the association between adiposity assessed by the body composition on CT-scan and overall survival in an unselected ccRCC population treated in first line with ICI-based treatment regimens.

Secondary we assessed the relationship between body composition variables and immune-related toxicities. We described the body composition of our population, and the contribution of this assessment compared to BMI alone.

3. Patients and Methods

3.1. Patients

This study design was multicenter and retrospective. We included all metastatic ccRCC initiating ICB-based treatment between June 2017 and June 2022 at the following hospitals including oncology department in North of France:

1) Oscar Lambret Center (Lille comprehensive cancer care center)
2) Amiens-Picardie University Hospital
3) Boulogne-sur-Mer Hospital
4) Valenciennes Hospital
5) Roubaix Hospital.

These patients could be identified through the chemotherapy prescribing software (Chimioweb).

Patients were included if:

1. They were treated in the first-line therapy by Nivolumab-Ipilimumab, Pembrolizumab-Axitinib, Nivolumab alone or Nivolumab-Cabozantinib
2. They had an enhanced CT-scan covering L3 level
3. CT scan performed within 90 days of ICI initiation.

Exclusion criteria were:

1) Patients opposed to the use of their data according to the French legislation
2) Lack of available CT images in the appropriate time frame.

3.2. Clinical data

The following baseline characteristics were reviewed from medical records: gender, age at ICI first course, Eastern Cooperative Oncology Group performance status (ECOG), BMI defined by the World Health Organization, history of weight loss over the past six months and classified as malnutrition according to the Haute Autorité de Santé, IMDC prognostic score according to Heng publication, cardiovascular comorbidities (ie history of stroke,

coronary or peripheral artery disease, type 2 diabetes, hypertension or dyslipidemia) and active or past history autoimmune disease, smoking status. We also recorded sites of metastatic disease and their numbers at baseline. Other data collected included: prior nephrectomy at metastatic setting or at localized stage, history of metastasectomy or radiotherapy before initiation or throughout the duration of ICI therapy.

Plus, histopathological diagnosis on the nephrectomy specimen, when available, included pT stage, Furhman grade and sarcomatoid features were also recorded.

3.3. Biological data

At baseline, were recorded: serum albumin (g/L), C reactive protein (CRP) (mg/L), neutrophil-to-lymphocyte ratio (NLR).

3.4. Outcome, Treatment responses and Safety

Our primary endpoint was overall survival (OS) defined as time from treatment initiation to death or last follow-up. The cause of death was recorded as progression, toxicity, or intercurrent factor. Treatment duration was noticed with cessation causes classified as progression, toxicity of patient's choice. Considering the duration of follow-up some patients could be undergoing treatment at data cutoff date. Treatment-related adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) and reported by system organ class. irAEs management were noticed: systemic corticosteroids or immunosuppressive drugs use, ICB interruption or discontinuation. All grade ≥ 2 were recorded. We recorded AE related to immunotherapy, we did not record TKI related AE. Toxicity data were retrospectively and prospectively reviewed by the local center internist in Oscar Lambret Center.

3.5. Body composition assessment

Body composition parameters were evaluated by assessing muscle, adipose tissue areas and radiodensity on CT-scan images at the level of the third lumbar vertebra (L3). All

contrast-enhanced CT scans were obtained at the portal venous phase. The investigator performed all image analyses under supervision by one trained physician (A. Carnot) (56). The assessment was repeated on two consecutive CT-images. The average data obtained was use for the analyses. The level of L3 with both transverse processes visible was manually identified (**Appendix 2**). Selected CT-images were then uploaded on Slice-O-matic software (version 5.0; Tomovision) to differentiate components using Hounsfield Unit ranges references for each tissue (from -29 HU to 150 HU for muscle tissue ; -150 to -50HU for visceral fat and -190 HU to -30HU for subcutaneous fat tissue). Cross-sectional areas were normalized for height (m2) defining skeletal muscle index (SMI, cm2/m2), subcutaneous fat index (SFI, cm2/m2) and visceral fat index (VFI, cm2/m2). Total fat index (TFI) was defined as the sum of SFI and VFI. Average radiodensity (HU) for the entire cross sectional skeletal muscle area was reported defining SMD, which are inversely related to myosteatosis (42). Low SMD and CT-determined sarcopenia was defined according to previously established cut-offs by Martin et al. presented in **Appendix 2**, table 1.

3.6. Statistical analysis

Descriptives statistics for each variable were obtained. Continuous variables were reported as means and standard deviations or median and interquartile ranges. Categorical variables were reported as frequencies and percentages.

Patients characteristics were first described overall. Subsequently, two groups based on the TFI were performed. As no validated cut-off exists for TFI, they were classified into high and low median values similar to previous studies (44–46). Continuous variables were compared between groups using the Student t-test or Wilcoxon test. Categorical variables were compared using Fisher's test or $\chi 2$ test. Cox regression model was used to assess the association between OS and the following variables: TFI, SFI, VFI, BMI, sarcopenia, age, IMDC risk group, ECOG-PS, NRL, malnutrition and number of metastatic sites. For each

variable a hazard ratio (HR) and its 95% confidence interval (CI) were reported. Then, variables considered most clinically relevant were included in a multivariate model.

OS was calculated using the Kaplan-Meier method. Survival curves of patient with high versus low TFI were compared using the log-rank test. Toxicities were described in the whole population, then considering two groups, high versus low TFI. The two groups were compared using appropriate tests (Fisher's test or $\chi 2$ test).

All statistical analysis were performed using R version 4.4.1 (2024-06-14). Significance level was set to $P < 0.05$.

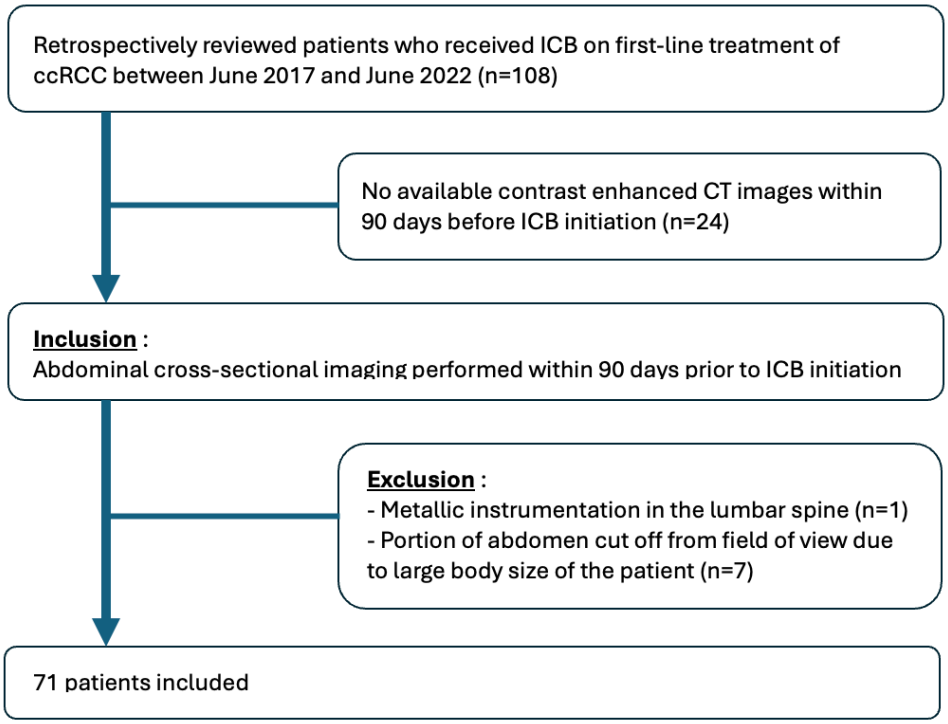
4. Results

4.1. Study Population

We reviewed 108 metastatic ccRCC patients treated with ICI-based treatment regimens in first line between June 2017 and June 2022 in the five sites.

Of these, 79 patients had available enhanced computed tomography (CT) scans within 90 days of ICI initiation. Due to: allergy to CT contrast agent, renal insufficiency or locale practice, 24 patients had disease staging performed by unenhanced CT scan, abdominal MRI or positron emission tomography. Three CT scans could not be retrieved from radiology department and two CT scan were performed beyond 90 days. After exclusion of one scan for excess artifact, and seven scans for unanalyzable field, 71 patients were included. (**Figure 9**). Median time between baseline scan and start of ICI treatment was 2.9 weeks (range 0.0 - 8.7).

Figure 9: Flow-chart of the study



Baseline demographic characteristics of the 71 patients included are presented **in table 1.** Overall, most patients were males (74,6%). Median age at start of treatment was 60,7 years. More than three quarters (77.5%) had an ECOG PS of 0-1. Most patients were primarily intermediate (61.4%) or poor-risk (34.3%) per IMDC criteria. Twenty-seven patients (38%) had a history of weight loss before start ICB treatment. Among them eleven patients (15.5%) reported a weight loss ≥ 15% compared to usual weight. Forty-four (62%) patients had cardiovascular comorbidities whereas only four (5.6%) patients had autoimmune comorbidities. Fourteen patients (20.6%) had an increased neutrophile to lymphocyte ratio. Around half of the patients (47.9%) had prior nephrectomy. Lung was the most common metastatic site (64.8%), followed by lymph node (52.1%) and bone (29.6%).

Regarding TFI high and low groups, baseline characteristics were similar in the two groups except of cardiovascular comorbidities: patients with high TFI had significantly more cardiovascular comorbidities than those with low TFI (p=0.022).

28 (39.4%) patients had a metachronous disease. Histopathological classification and grading based on the nephrectomy are presented in **appendix 3.**

Table 1 : Demographic and clinical characteristics at baseline, overall and by TFI.

Characteristic	Overall(N=71)	TFI		p
		Low (n=35, 49.3%)	High (n=36, 50.7%)	
Male sex, n (%)	53 (74.6)	26 (74.3)	27 (75.0)	0.94
Center, n (%)				0.029
Centre Oscar Lambret	45 (63.4)	17 (48.6)	28 (77.8)	
Amiens	19 (26.8)	14 (40.0)	5 (13.9)	
Other*	7 (9.9)	4 (11.4)	3 (8.3)	
Age, years, median (IQR)	60.7 (55.9—67.6)	57.6 (51.9—67.3)	63.2 (57.4—69.7)	0.082
Time from CT to treatment, month, median (range)§	0.8 (0.0—2.8)	0.9 (0.0—2.8)	0.8 (0.0—2.8)	0.58
ECOG-PS, n (%)				0.53
0-1	55 (77.5)	26 (74.3)	29 (80.6)	
≥2	16 (22.5)	9 (25.7)	7 (19.4)	
IMDC risk group, n (%)				0.78
Favorable	3 (4.3)	2 (5.9)	1 (2.8)	
Intermediate	43 (61.4)	20 (58.8)	23 (63.9)	
Poor	24 (34.3)	12 (35.3)	12 (33.3)	
Missing data	1	1	0	
Malnutrition, n (%)†				0.49
No	44 (62.0)	24 (68.6)	20 (55.6)	
Moderate	16 (22.5)	7 (20.0)	9 (25.0)	
Major	11 (15.5)	4 (11.4)	7 (19.4)	
Smoking status, n (%)				0.29
No	29 (42.6)	11 (33.3)	18 (51.4)	
Former	26 (38.2)	14 (42.4)	12 (34.3)	
Current	13 (19.1)	8 (24.2)	5 (14.3)	
Missing data	3	2	1	
Comorbidities				
Cardiovascular, n (%)	44 (62.0)	17 (48.6)	27 (75.0)	0.022
Autoimmune, n (%)	4 (5.6)	2 (5.7)	2 (5.6)	>0.99

Table 1 : Demographic and clinical characteristics at baseline, overall and by TFI – *(continued).*

Characteristic	Overall(N=71)	TFI		p
		Low (n=35, 49.3%)	High (n=36, 50.7%)	
Albumin, g/L, n (%)				0.93
≤30	10 (18.5)	5 (19.2)	5 (17.9)	
30-35	5 (9.3)	2 (7.7)	3 (10.7)	
>35	39 (72.2)	19 (73.1)	20 (71.4)	
Missing data	17	9	8	
CRP increased, n (%)	31 (62.0)	14 (56.0)	17 (68.0)	0.38
Missing data	21	10	11	
NLR increased, n (%)	14 (20.6)	6 (18.2)	8 (22.9)	0.63
Missing data	3	2	1	
No. of metastatic sites, median (IQR)	2 (2—3)	2 (1—3)	2 (2—3)	0.24
Lung, n (%)	46 (64.8)	22 (62.9)	24 (66.7)	0.74
Lymph node, n (%)	37 (52.1)	17 (48.6)	20 (55.6)	0.56
Bone, n (%)	21 (29.6)	10 (28.6)	11 (30.6)	0.85
Adrenal gland, n (%)	16 (22.5)	8 (22.9)	8 (22.2)	0.95
Liver, n (%)	12 (16.9)	4 (11.4)	8 (22.2)	0.23
Kidney, n (%)	8 (11.3)	5 (14.3)	3 (8.3)	0.68
Central nervous system, n (%)	7 (9.9)	2 (5.7)	5 (13.9)	0.45
Pancreas, n (%)	5 (7.0)	4 (11.4)	1 (2.8)	0.34
Other, n (%)[‡]	12 (16.9)	6 (17.1)	6 (16.7)	0.96

TFI: total fat index; ECOG-PS: Eastern Cooperative Oncology Group - Performance status; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; CRP: C-reactive protein; NLR: neutrophil to lymphocyte ratio; IQR: interquartile range.

[*]Roubaix [3]; Boulogne-sur-mer [2]; Valenciennes [2].

[†]Moderate malnutrition denotes a weight loss ≥ 5% in 1 month OR ≥ 10% in 6 months OR ≥ 10% compared to usual weight. Major malnutrition denotes a weight loss ≥ 10% in 1 month OR ≥ 15% in 6 months OR ≥ 15% compared to usual weight.

[‡]Locoregional recurrence [4]; peritoneal carcinosis [4]; muscle [2]; pulmonary pleura [2]; colon [1]; parotid gland [1].

Treatment characteristics are summarized in **table 3**. The majority (78.9%) of patients were treated with Nivolumab-Ipilimumab combination. Nine (12,7%) patients received Pembrolizumab-Axitinib combination. Six (8,5%) patients were treated with Nivolumab monotherapy and no patient received Nivolumab-Cabozantinib combination. More than one third of patients did not completed the four cycles of Ipilimumab because of disease progression (17.9%) or toxicity (17.9%).

At the data cutoff date, six (8.5%) patients were still undergoing anti-PD-1 treatment whereas eleven (15.5%) patients completed the planned 2-years treatment.

Median time of treatment duration was six months (IQR: 2.1—23.3).

Table 3 : Treatment characteristics, overall and by TFI.

Characteristic	Overall (N=71)	TFI		p
		Low (n=35, 49.3%)	High (n=36, 50.7%)	
Systemic treatment, n (%)				0.92
AntiPD1 + AntiCTLA4	56 (78.9)	27 (77.1)	29 (80.6)	
AntiPD1 + Axitinib	9 (12.7)	5 (14.3)	4 (11.1)	
AntiPD1	6 (8.5)	3 (8.6)	3 (8.3)	
AntiPD1 cycle completion, n (%)*				0.82
Completed	11 (15.5)	4 (11.4)	7 (19.4)	
Discontinued for toxicity	9 (12.7)	4 (11.4)	5 (13.9)	
Discontinued for progression	44 (62.0)	23 (65.7)	21 (58.3)	
Discontinued for personal choice	1 (1.4)	1 (2.9)	0 (0.0)	
Ongoing treatment	6 (8.5)	3 (8.6)	3 (8.3)	
AntiCTLA4 cycle completion, n (%)†				0.85
Completed	36 (64.3)	18 (66.7)	18 (62.1)	
Discontinued for toxicity	10 (17.9)	4 (14.8)	6 (20.7)	
Discontinued for progression	10 (17.9)	5 (18.5)	5 (17.2)	
Treatment duration, months, median (IQR)	6.0 (2.1—23.3)	6.0 (2.1—17.2)	6.8 (1.7—23.8)	0.77
Metastasis surgery, n (%)	13 (18.3)	6 (17.1)	7 (19.4)	0.80
Radiotherapy, n (%)	29 (40.8)	11 (31.4)	18 (50.0)	0.11

TFI: total fat index; CT: computed tomography scan; IQR: interquartile range.

*Among patients under any systemic treatment.

†Among patients under AntiPD1 + AntiCTLA4 systemic treatment.

‡Time between prior nephrectomy at localized stage and start of systemic treatment.

§1 observation was missing.

4.2. Baseline Body Composition Parameters

Median BMI was 25.2 kg/m2 (IQR 22.8-28.1) in the overall population. More than half (56.6%) men were overweight or obese, whereas 38.9% of women were overweight. No women were obese (**table 4**).

Slightly more women than men were sarcopenic, but not significantly, 66.7% and 47.2% respectively. 41.5% of men and 50.0% of women had myosteatosis according to Martin established cut offs. Men and women had a similarly median TFI value, 107.7cm2/m2 and 108.6cm2/m2 respectively. Median VFI values were significantly different between men and

women, with men having a higher VFI value compared to women (56.1cm2/m2 versus 26.5cm2/m2; p=0.004). Women trend to have a highest median SFI compared to men, but the difference was not significant (73.4cm2/m2 versus 47.7cm2/m2; p=0,010).

Table 4 : Body composition parameters, overall and by TFI

Characteristic	Overall(N=71)	Sex		p
		Male (n=53, 74.6%)	Female (n=18, 25.4%)	
BMI, kg/m2, median (IQR)	25.2 (22.8—28.1)	25.5 (23.6—28.1)	23.5 (22.1—26.9)	0.13
BMI, kg/m2, n (%)				0.16
18.5-24.9	34 (47.9)	23 (43.4)	11 (61.1)	
25-29.9	29 (40.8)	22 (41.5)	7 (38.9)	
≥30	8 (11.3)	8 (15.1)	0	
SMI, cm2/m2, median (IQR)	45.2 (39.0—52.6)	49.2 (42.4—54.0)	38.1 (34.4—42.0)	<0.001
Sarcopenia, n (%)	37 (52.1)	25 (47.2)	12 (66.7)	0.15
Low muscle attenuation, n (%)[†]	31 (43.7)	22 (41.5)	9 (50.0)	0.53
SFI, cm2/m2, median (IQR)	56.1 (43.3—86.9)	47.7 (40.7—70.3)	73.4 (62.7—89.5)	0.010
VFI, cm2/m2, median (IQR)	46.4 (27.8—69.9)	56.1 (34.8—70.8)	26.5 (15.5—54.4)	0.004
TFI, cm2/m2, median (IQR)	107.7 (81.3—136.9)	107.7 (81.3—141.6)	108.6 (87.5—132.0)	0.99

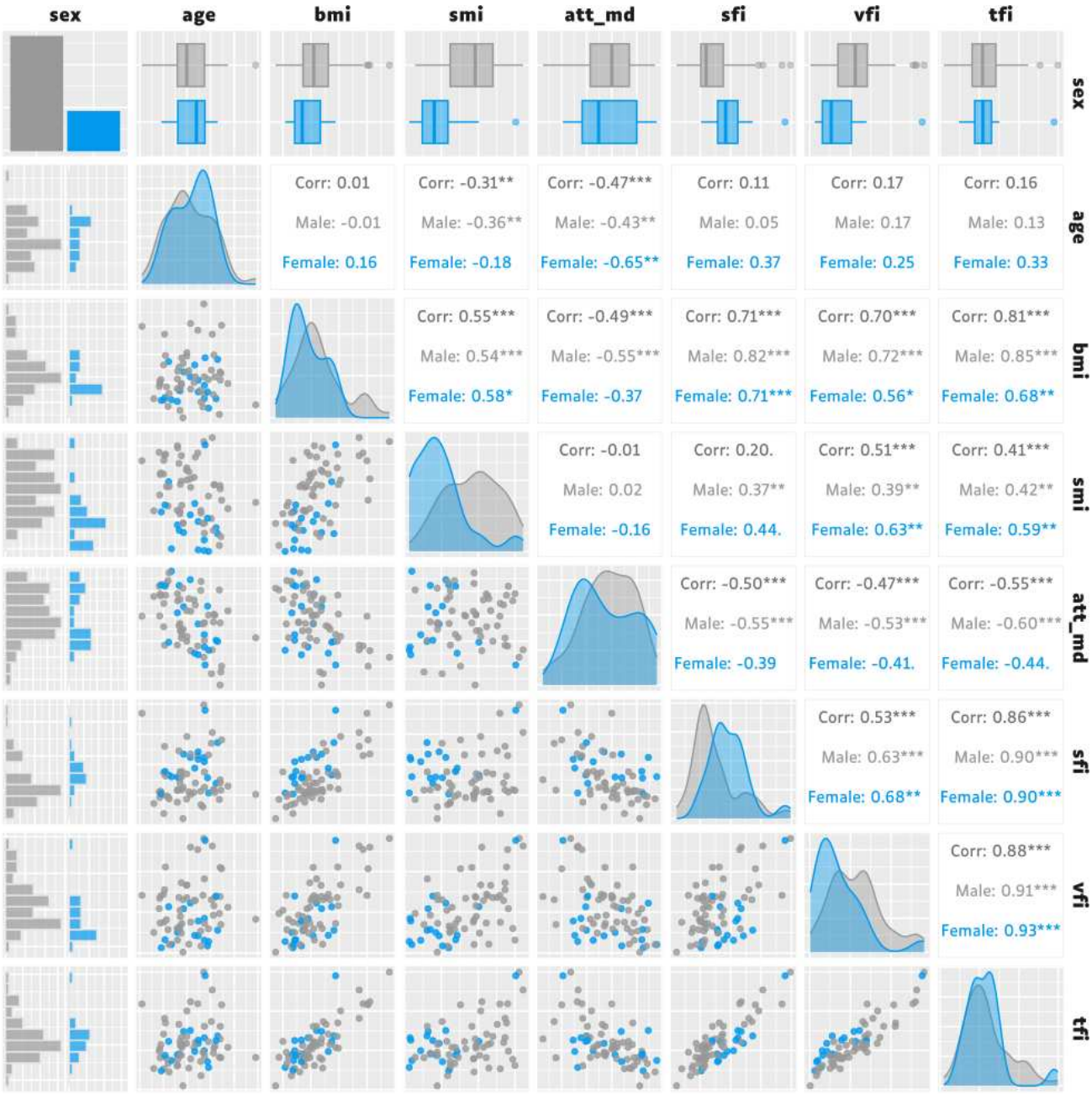
BMI: body mass index; SMI: skeletal muscle index; SFI: subcutaneous fat index; VFI: visceral fat index; TFI: total fat index; IQR: interquartile range.
[†]Myosteatosis, denotes an attenuated muscle depletion < 33 Hounsfield units and BMI ≥ 25 kg/m2 OR an attenuated muscle depletion < 41 Hounsfield units and BMI < 25 kg/m2.

4.3. Correlations between BC-Parameters

Correlation matrix and box plot are presented in **figure 10**. Each BC related variable was represented by sex. Box plot shows SFI, VFI and TFI distribution according to sex. While TFI distribution appears similar in both male and female, males show greater VFI and lower SFI compared to females. All BC-parameters were significantly correlated with BMI. BMI was most highly correlated with TFI (r = 0.81), compared with VFI (r = 0.70) and SFI (r = 0.71). The weakest correlations were between BMI and SMI (correlation coefficient 0.55). In men, BMI was negatively correlated with the mean muscle radiation attenuation (r = -0.55). To identify myosteatosis, the cut-point for muscle attenuation of < 41 HU and BMI < 25 kg/m2 or muscle attenuation < 33 HU and BMI ≥ 25 kg/m2 is usually used. Therefore, BMI is well correlate with myosteasosis.

SFI and VFI were well correlated (r = 0,53). Muscle radiodensity and TFI were negatively correlated (r = -0,55).

Figure 10 : Correlation matrix between BMI and BC parameters by gender



BMI: body mass index; SMI: skeletal muscle index; at_md: attenuated muscle depletion; SFI: subcutaneous fat index; VFI: visceral fat index; TFI: total fat index; IQR: interquartile range. Corr: Pearson's correlation coefficient; ***: p<0.001; **: p<0.01; *: p<0.05. On the left, first column contains histograms reflecting the distribution of continuous variables by absolute frequency and by sex. On the top, first line shows Box plot. Blue box plot indicates women data and grey box plot indicates men data. The box represents interquartile range. The vertical line dividing the box represents the median. Whiskers are the horizontals lines that extend from the box and shows the data's range excluding outliers. The outliers are individuals points outside the whiskers that show unusually high or low value compared to the rest of the data. The upper diagonal indicates the Spearman coefficient, from -1 to 1, in black for whole population, in grey for women and in blue for men. The left-lower diagonal shows the scatterplot which illustrates the intersection of two continuous variables, with distinction between men and women. The diagonal represents the relative frequency densities between men and women.

4.4. Association between TFI and Survival Outcomes

During follow-up (median, 33 months) 31 patients died. Cause of deaths are presented in table 5. Almost all patients (27) died of disease progression. No toxic death was observed.

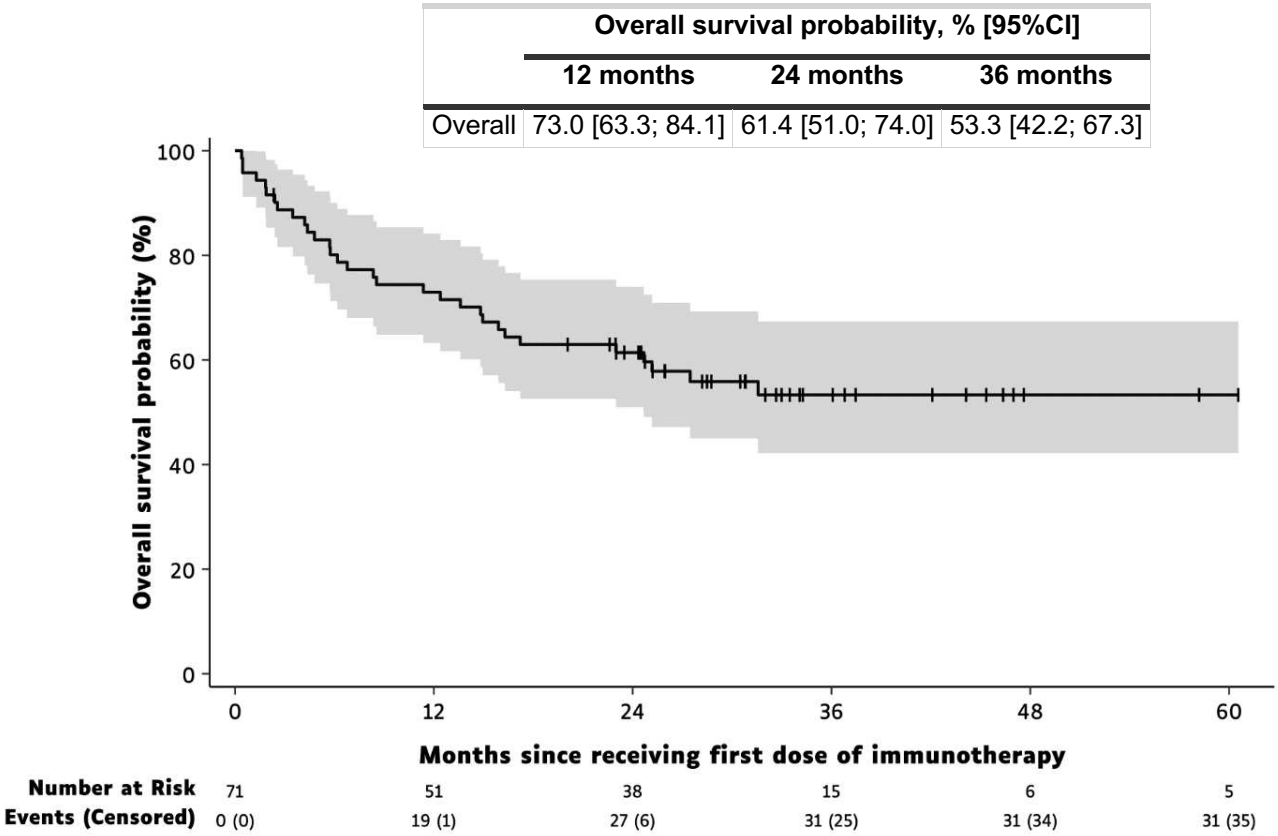
Table 5 : Clinical outcomes

Characteristic	Overall(N=71)	TFI	
		Low (n=35, 49.3%)	High (n=36, 50.7%)
Death from any cause, n	31	17	14
Cause of death, n			
Immune-related AE	0	0	0
Progression	27	14	13
Other*	3	2	1
Missing data	1	1	0

TFI: total fat index; AE: adverse event.

*Sepsis [2]; lung cancer [1].

Figure 11 : Overall survival in overall population



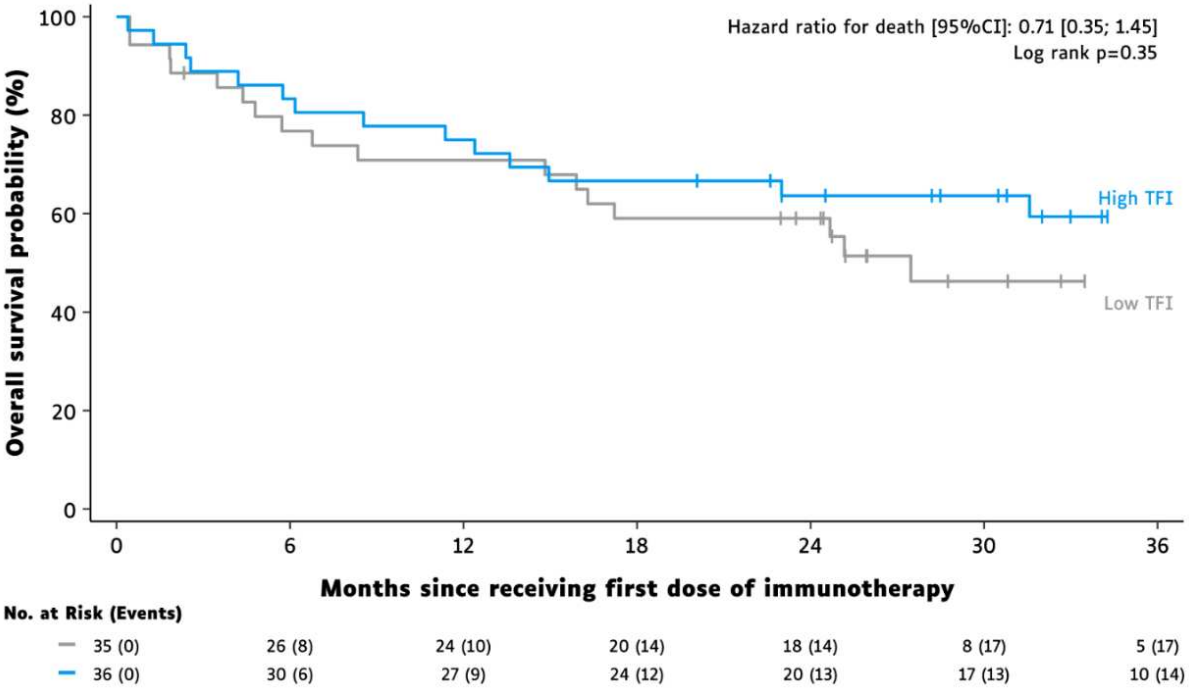
Events and censoring are presented as cumulative counts over time.

Kaplan–Meier curve for overall survival is presented in **figure 11**. In the whole population 73% of patients were alive at 12 months and 53.3% at 36 months. The overall survival probability at 12 months did not differ in high TFI compared to low TFI : 75.0% (95% CI, 62.1 to 90.6) and 70.9% (95% CI, 57.2 to 87.8), respectively. The corresponding estimates for 36 months were 59.4% (95% CI, 44.8 to 78.8) and 46.3% (95% CI, 31.1 to 68.8) for high and low TFI respectively. Hazard ratio for overall survival was 0.71 (95% CI, 0.35 to 1.45; P=0.35). The median overall survival was not reached in either group (**Figure 12**).

Figure 12 : Overall survival according to TFI

	Overall survival probability, % [95%CI]		
	12 months	24 months	36 months
Low TFI	70.9 [57.2; 87.8]	59.0 [44.6; 78.1]	46.3 [31.1; 68.8]
High TFI	75.0 [62.1; 90.6]	63.6 [49.6; 81.6]	59.4 [44.8; 78.8]

TFI: total fat index.



Events and censoring are presented as cumulative counts over time.

A multivariable model was built to assess the association of baseline characteristics, including body composition parameters, with all-cause mortality (**Table 6**). Baseline characteristics were first analyzed individually in the univariable model. In the univariate

analysis, we observed a significant negative prognostic effect on overall survival of ECOG-PS ≥ 2 (HR, 2.73; p=0.012). Poor-IMDC risk group compared to intermediate showed a trend toward shorter OS (HR, 1.73; p=0.052) as increased NLR (HR, 2.06; p=0.087). When incorporate in multivariate analysis increased NLR did not have significant association with OS. In univariate analysis, age, TFI, SFI, VFI, BMI, malnutrition, sarcopenia and the number of metastatic sites were not associated with OS.
In multivariate model, TFI hazard ratio for overall survival did not differ from univariate analysis (0.70 [0.33; 1.48]).

Table 6 : Univariable and multivariable Cox regression model for overall survival.

	Univariable analysis			Multivariable analysis*	
Characteristic	**Events/Obs**	**HR [95%CI]**	**p**	**aHR [95%CI]**	**p**
TFI (binary)			0.35		0.35
Low	17/35	-		-	
High	14/36	0.71 [0.35; 1.45]		0.70 [0.33; 1.48]	
TFI (considering quartiles)			0.68		
[9.7,81.3]	9/18	-			
(81.3,108]	9/18	1.22 [0.48; 3.07]			
(108,136]	6/17	0.69 [0.24; 1.94]			
(136,299]	7/18	0.75 [0.28; 2.02]			
SFI (binary)			0.89		
Low	15/35	-			
High	16/36	1.05 [0.52; 2.12]			
SFI (considering quartiles)			0.59		
[8.9,43.5]	9/18	-			
(43.5,56.1]	6/18	0.62 [0.22; 1.74]			
(56.1,85.4]	9/17	1.16 [0.46; 2.94]			
(85.4,159]	7/18	0.71 [0.27; 1.92]			
VFI (binary)			0.49		
Low	17/36	-			
High	14/35	0.78 [0.38; 1.58]			
VFI (considering quartiles)			0.23		
[0.8,28.1]	6/18	-			
(28.1,46.4]	11/18	2.61 [0.96; 7.09]			
(46.4,69.6]	7/17	1.31 [0.44; 3.90]			
(69.6,141]	7/18	1.28 [0.43; 3.80]			
BMI, kg/m2			0.73		
18.5-24.9	16/34	-			
25-29.9	12/29	0.80 [0.38; 1.70]			
≥30	3/8	0.66 [0.19; 2.26]			
Age, years (5-year increment)	31/71	1.07 [0.86; 1.31]	0.55		
Martin sarcopenia index			0.29		
No	17/34	-			
Yes	14/37	0.68 [0.34; 1.38]			
IMDC risk group			0.052		0.11
Intermediate	18/43	-		-	
Poor	13/24	1.73 [0.85; 3.55]		1.53 [0.71; 3.30]	
Favorable	0/3				

Table 6 : Univariable and multivariable Cox regression model for overall survival – *(continued)*

	Univariable analysis			Multivariable analysis*	
Characteristic	**Events/Obs**	**HR [95%CI]**	**p**	**aHR [95%CI]**	**p**
ECOG-PS			0.012		
0-1	20/55	-			
≥2	11/16	2.73 [1.30; 5.71]			
NLR increased			0.087		0.20
No	20/54	-		Reference	
Yes	9/14	2.06 [0.94; 4.53]		1.72 [0.77; 3.85]	
Malnutrition			0.39		
No	19/44	-			
Moderate	6/16	0.72 [0.29; 1.81]			
Major	6/11	1.61 [0.64; 4.05]			
No. of metastatic sites			0.36		
1	6/15	1.26 [0.47; 3.35]			
2	12/32	-			
3 or more	13/24	1.77 [0.81; 3.89]			

HR: hazard ratio; aHR: adjusted hazard ratio; TFI: total fat index; SFI: subcutaneous fat index; VFI: visceral fat index; BMI: body mass index; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; ECOG-PS: Eastern Cooperative Oncology Group - Performance status; NLR: neutrophil-lymphocyte ratio.

Because of a non-monotonic relationship with the outcome, continuous variables TFI, SFI and VFI were included as dichotomous variables and considering quartiles.

*Multivariable Cox regression model included 29 events for 67 complete observations (4 observations deleted due to missing values).

4.5. Association between TFI and Immune-related Adverse Events

Incidence, grading and consequences of immune-related adverse toxicities are summarized in **table 7**. Thirty-seven (52%) patients experienced at least one any grade irAE and twenty-two (31%) had grade III-IV. Fourteen patients (37.8%) had an irAEs leading to treatment interruption whereas eight patients (21.6%) discontinuated the treatment. Among the Nivolumab-Ipilimumab population three patients switch to Nivolumab monotherapy due to an irAE. 35% of patients who experienced irAEs received corticosteroids to manage toxicity while 13% were treated with immunosuppressive agents.
Most commons severe adverse events involved the digestive system and the hepatics functions. Eleven (15.5%) patients experienced a gastrointestinal or digestive irAE with 9 (12.7%) patients had grade III/IV. Following, hepatic irAEs affected 10% of patients, with

8.5% experiencing grade III/IV toxicity. Endocrine irAEs were the most frequents, 29.6% of patients, with only 7.0 % grade III/IV.

Regarding skin irAES, five (7.0%) patients were concerned, as rheumatic irAEs. One patient had a flare-up of pre-existing rheumatoid arthritis, and another had a flare-up of rheumatic paraneoplastic syndrome. (**Table 8**)

No significant differences were observed between high TFI group versus low TFI group.

Table 7 : Immuno-mediated adverse events, overall and by TFI

Characteristic	Overall (N=71)	TFI		p
		Low (n=35, 49.3%)	High (n=36, 50.7%)	
Maximum AE grade, n (%)				0.32
No toxicity or grade I	34 (47.9)	15 (42.9)	19 (52.8)	
Grade II	15 (21.1)	10 (28.6)	5 (13.9)	
Grade III-IV	22 (31.0)	10 (28.6)	12 (33.3)	
No. of AE, n (%)				0.59
0	34 (47.9)	15 (42.9)	19 (52.8)	
1	20 (28.2)	10 (28.6)	10 (27.8)	
2	14 (19.7)	9 (25.7)	5 (13.9)	
3	3 (4.2)	1 (2.9)	2 (5.6)	
Time to AE, months, median (IQR)*	2.3 (1.3—3.7)	2.8 (1.7—4.1)	2.1 (1.2—2.6)	0.085
Consequence in treatment, n (%)*				0.75
None	12 (32.4)	7 (35.0)	5 (29.4)	
Switch to AntiPD1 monotherapy†	3 (8.1)	2 (10.0)	1 (5.9)	
Treatment discontinuation	8 (21.6)	3 (15.0)	5 (29.4)	
Treatment interruption	14 (37.8)	8 (40.0)	6 (35.3)	
Additional treatment*				
Systemic corticosteroid, n (%)	13 (35.1)	9 (45.0)	4 (23.5)	0.17
Immunosuppressant, n (%)	5 (13.5)	3 (15.0)	2 (11.8)	>0.99

Table 8 : Immuno-mediated adverse events system organ class, overall and by TFI

System organ class*	Overall (N=71)	Low TFI (n=35)		High TFI (n=36)	
		Any grade	Grade III-IV	Any grade	Grade III-IV
Endocrine	21 (39.6)	8 (22.9)	0	13 (36.1)	5 (13.9)
Gastrointestinal	11 (15.7)	7(10.0)	5 (7.0)	4 (11.1)	4 (11.1)
Hepatic	7 (10.0)	4 (11.4)	3 (4.3)	3 (4.3)	3 (4.3)
Rheumatic	5 (7.0)	2 (5.7)	0	3 (8.3)	2 (5.6)
Skin	5 (7.0)	4 (11.4)	1 (2.9)	1 (2.8)	0
Lung	3 (4.2)	1 (2.9)	0	2 (5.6)	1 (2.8)
Cardiac	1 (2.8)	0	0	1 (2.8)	1 (2.8)
Nervous system	1 (2.8)	1 (2.9)	1 (2.9)	0	0
Immune system	1 (1.4)	0	0	1 (2.8)	0
Renal	1 (1.4)	1 (2.9)	0	0	0

TFI: total fat index.

*According to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

5. Discussion

The main objective of our study was to evaluate the association between adiposity markers and overall survival in patients with metastatic ccRCC treated by ICI in first line.

Our main results are:

1/ Our ccRCC population treated by ICI has: a median BMI of 25.2kg/m2, a median TFI of 107.7cm2/m2, a median VFI of 46.4cm2/m2, a median SFI of 56.1 cm2/m2, and a median SMI of 45.2cm2/m2 witch classified 37% of patients as sarcopenic. Men and women are similar in median BMI and TFI values but differ regarding sarcopenic frequency (47.2% vs 66.7%), median SFI value (cm2/m2) (47.7 vs 73.3 respectively), and median VFI value (cm2/m2) (56.1 vs 26.5). 38% of patients had moderate of major malnutrition at baseline.

2/ We did not find any association between TFI and OS, either in univariate or multivariate analysis. Hazard ratio for overall survival was 0.71 [0.35; 1.45] in TFI high group in univariate, and 0.70 (CI 95% = [0.33; 1.48]) in the multivariate analysis.

3/ We did not find any association between TFI and irAEs. 31.4% of patients experienced a grade III/IV irAEs. 21.6% of patients had to discontinue ICI.

First of all, we focused on the assessment of body fat in these patients. Overweight and obese men patients represented 56.6% which is similar to the prevalence observed in our region among adults' men (53.5%) (data from regional health agency). Adiposity was also estimated by TFI variable. We found that in our population, TFI value had a non-monotonic relationship with the outcome, so high TFI population was defined using median TFI value (107.7cm2/m2). We showed that high TFI population did not differ from low TFI population in baseline characteristics, including malnutrition definition. This may be attributed to a memory bias. TFI was an accurate reflection of subcutaneous and visceral adiposity given that the Pearson correlation coefficients with SFI and VFI were 0.86 and 0.88, respectively (both $p<0.001$). Similarly, BMI was a good reflection of TFI ($r = 0,81$) ($p<0.001$). SFI and VFI showed a weak correlation ($r = 0.53$).

Ours results regarding body composition and BMI correlation are consistent with previous studies, such as Young publication who studied a metastatic melanoma population treated by ICI (57). He found a correlation coefficient of 0.88 between BMI and TFI, 0.83 between TFI and SFI and 0.83 between TFI and VFI. Similarly to our study BMI and SMI had a weak correlation ($r = 0.49$) as SFI and VFI ($r = 0.38$).

It is to note that compared to the pivotal studies CHECKMATE-214 and KEYNOTE-426, we observe a more severe cohort. In our study poor-IMDC risk group represented 34% of patients while they were 21% and 13% in Motzer and Rini publications respectively (58,59) This is inherent to real-life studies. The 12-months overall survival rate in our study and those of Motzer and Rini were 73%, 80% and 89.5% respectively. This confirms the poor prognostic cohort of our study.

In this study, we failed to demonstrate any association between TFI at baseline and survival in ICI-based treatment. Conversely, Martini et al, found a significant association between low TFI and shorter OS (HR: 2.72, $p=0.002$) (41). The population included 79 metastatic RCC patients treated by ICI. Our patients were relatively similar in terms of age, sex, ECOG-

PS, IMDC-risk group, baseline BMI (median 25.2 vs 26.2 kg/m2), and TFI (cm2/m2) (M: 107.7 vs 98.7 and F: 108.6 vs 94.3), SFI (cm2/m2) (M: 47.7 vs 51.4 and F: 73.4 vs 69.8) and SMI (cm2/m2) (M: 49.2 vs 44.0 and F: 38.1 vs 39.2). However, Martini population included all patients who received at least one dose of ICI regardless of histology subtype or line of therapy. Morevoer the patients were divided as high or low TFI by applying gender-specific optimal cut points using OS as the primary outcome, without validation cohort.

Lee et al study (60), based on a Korean populations of 102 patients treated in first line, showed a benefit of high SFI on survival. Ours populations were similar in terms of age, gender, IMDC-risk group but differed in terms of BMI and BC-parameters. They had only 30.4% of overweight/obese patients. 29.4% of patients were sarcopenic using Asian specific cut-off (SMI < 34.9cm2/m2 for women and < 40.8 for men). Adipose values were dichotomized base on sex-specific medians as follows: VFI (men: 37.0 cm2/m2, women: 53.4 cm2/m2), SFI (men: 32.8 cm2/m2, women: 17.6 cm2/m2), and TFI (men: 69.9 cm2/m2, women: 74.3 cm2/m2). The SFI value was particularly inconsistent with our population, making the extrapolation of these results to our Caucasian population particularly difficult. It is interesting to note that, as in our study and Young study, no association was found between SMI and BMI (57). These results highlight the contribution of a reliable measurement tool for estimating sarcopenia, such as CT-based measurements.

Similar conclusions can be drawn from Ged et al study, which, despite finding an association between survival and BMI, did not find any significant association between survival and SMI (46). Moreover, as our study, Ged et al did not find any association between adiposity-related BC variables and survival. Therefore, they evaluated the associations of SMI and VATI in relation to OS. Subgroups comparisons suggested worst OS for SMI low/VATI low group, where estimated 2-year OS was 45% (vs. 73% in SMI high/VATI high). Ged et al was the largest published study to investigate BC-variable with OS in aRCC. They included 205

patients regardless of the line of treatment and had a high proportion of overweight/obese patients (71%).

In line with our study, McManus in a retrospective study of 99 aRCC treated by Nivolumab-Ipilimumab did not found any association between BC-variables and survival (45). We noticed that SATI and VATI increased with BMI, whereas SMI increased to a much lesser extent in overweight and obese patients compared to normal weight patients.

Latest authors studying BC-variables in aRCC, Takei et al, did not found any association between adipose markers and OS in 60 Japan patients treated as first line (44). His population differs from ours with older patients, 26% of overweight patients and no obese. 70% were sarcopenic according to Martin cut-off.

All these discrepancies between study populations, BC-parameters cut off, highlights the great heterogeneity in the proportion and distribution of adipose and muscle mass. The interest in precise assessing of the body composition parameters could be to define patterns of the relative proportions of skeletal muscle, subcutaneous fat, and visceral fat identifying clusters of patient that are most likely to benefit from treatment.

Regarding toxicities, the safety profile was consistent with what has been previously reported in earlier studies. We observed after a 33-month median follow-up, similarly rates of grade III/IV gastrointestinal, hepatic and endocrine irAEs than reported in Motzer (58) and Rini (59) publications (32.4- and 30.6-months median follow-up respectively). Skin toxicities were less recorded in our study potentially due to measurement bias (grade 1 was not recorded). irAEs management by corticosteroids us was comparable in our cohort and those of Motzer (35.1% vs 29% respectively). Treatment-related adverse events leading to discontinuation of ICI were similar in our population compared to those of Motzer and Rini (21.6%, 22% and 21% respectively). To our knowledge no study has found an association between CT-measurement adiposity and irAEs with few studies published, whereas BMI

studies have inconsistent results. McManus reviewed number of induction cycles of Ipilimumab + Nivolumab according to BMI (dichotomized as < or ≥ 30kg/m2) , SFI and VFI (dichotomized using median value) and did not find any correlation (45). Takei et al investigated all grades irAEs, ≥ grade 2 irAEs and irAEs leading to treatment discontinuation. No association was found with sarcopenia (Martin cut-off), BMI (< ou ≥ 25kg/m2) or TFI (dichotomized using median value) (44)

Regarding SMI, a meta-analysis of larger sample (519 patients) with various tumors treated by ICI was performed. No association with irAEs was found between sarcopenic and no sarcopenic patients OR 0.97 (95% CI: 0.62–1.53) (61). Given the high rate of treatment discontinuation due to irAEs and their impact on quality of life, it may be valuable to investigate the predictive role of body composition parameters in large prospective cohort.

The strengths of our study was: an unselected real-life population cohort. To our knowledge, our study is the first French cohort to investigate association between body composition variable and overall survival of aRCC tread by ICI. Another quality of our study to highlight is the use of the same reported gold standard method to measure CT-scan BC-parameters, despite the different body composition measurement software used in previous studies. Plus, we had few missing data, and a review to assess irAEs.

The main limitation of our study is its lack of power. Small sample size did not permit to observe significant association between TFI and overall survival. Moreover, we could not perform subgroup analysis by sex and by visceral and subcutaneous fat due to small sample size. OS assessment was limited by duration of follow-up and the number of OS events. Excluded patients who did not undergo enhanced CT scans or whose CT scans were not analyzable may result in selection bias. A potential bias in our study is the time between baseline CT scans and the initiation of immune checkpoint inhibitors (ICI), which could have been up to 90 days. This extended frame time is inherent to real life study. Body composition may have changed during this period, especially in the context of advanced disease. Owing

to the exploratory nature of this study, multiple statistical tests increased the risk of type 1 errors.

To conclude, we described a reel life population of naïve metastatic aRCC treated by ICI. This population appears to be more severe than previous cohort investigated. Body composition appears to be similar with others Caucasian populations, with high rates of overweight, a known risk factor for aRCC. As several previous studies, we failed to find an association between TFI and overall survival. We described a safety profile according to previously reported data. Only few data were missing. We demonstrated the strong correlation between TFI and BMI. Therefore, BMI remains a useful and easily applicable measure in clinical practice reflecting adiposity. By contrast, sarcopenia definition lack of clinical practicability, and often only muscle strength is assessed. Thus, CT-based measurement of sarcopenia should be further studied. In conclusion, whether excess adiposity would predict ICI-treatment regimens outcomes remains unclear, further large sample studies with prospective design are needed to investigate sex-linked differences obesity and subcutaneous and visceral fat compartments. The distribution of fat tissue rather than the absolute value should be further studied. Validation cohorts may be conducted to determine prognostic and predictive SFI, VFI and TFI cut-offs that steel remain unclear. This are mandatory to harmonize future studies to help us understand the impact of the obesity paradox on the response to immunotherapy.

6. Conclusion

Notre étude s'intéressant à une population de vie réelle de patients traités par ICI seul ou en combinaison, en première ligne, n'a pas permis de mettre en évidence une association entre la composition corporelle évaluée par le TFI et la survie globale dans le cancer du rein métastatique. Nous avons confirmé la force prévalence du surpoids dans cette population malgré une maladie traitée au stade avancé. Cela confirme la nécessité de poursuivre l'exploration du rôle potentiel des masses grasses dans le devenir des patients.

Nous avons montré que l'IMC était fortement corrélé à la mesure de la masse grasse totale confirmant ainsi l'importance de cette mesure usuellement réalisée en pratique clinique. L'IMC ne doit toutefois pas faire oublier la forte prévalence de la dénutrition dans ces populations, dont celle de notre étude, malgré l'absence de patients avec un IMC < 18,5 kg/m2, définissant la maigreur. Notre pratique doit s'attacher à rechercher toute perte de poids souvent négligée par les patients alors même que son impact sur la qualité de vie et la fatigue est connu. L'IMC et le TFI ne permettent pas d'évaluer la variabilité de distribution des masses grasses sous cutanée et viscéral qui ne peut être objectivée qu'après l'analyse des coupes de tomodensitométrie. Bien que leur rôle prédictif n'ait pas été démontré dans notre étude ou dans la littérature leurs phénotype et fonctions physiopathologiques s'avèrent différentes et bien connus dans les maladies cardiovasculaires et métaboliques. Nous savons par ailleurs que ces tissus sont immunologiquement actifs, ainsi l'étude de leur caractère pronostic et prédictif reste d'intérêt à l'heure où l'obésité atteint des proportions endémiques.

Références bibliographiques

1. Defossez, G., Le Guyader-Peyron, S., Estimations nationales de l'incidence et de la mortalité par cancer en France métropolitaine entre 1990 et 2018 - Volume 1 : Tumeurs solides : Étude à partir des registres des cancers du réseau Francim. 2019, Santé Publique France.

2. Bukavina L, Bensalah K, Bray F, et al. Epidemiology of renal cell car- cinoma: 2022 update. Eur Urol. 2022;82(5):529-542.

3. Huang J, Leung DKW, Chan EOT, Lok V, Leung S, Wong I, et al. A Global Trend Analysis of Kidney Cancer Incidence and Mortality and Their Associations with Smoking, Alcohol Consumption, and Metabolic Syndrome. Eur Urol Focus. janv 2022;8(1):200-9.

4. Urofrance | Recommandations du comité de cancérologie de l'Association Française d'Urologie - actualisation 2022-2024 : prise en charge du cancer du rein - Urofrance [Internet]. [cité 14 août 2024]. Disponible sur: https://www.urofrance.org/recommandation/recommandations-du-comite-de-cancerologie-de-lassociation-francaise-durologie-actualisation-2022-2024-prise-en-charge-du-cancer-du-rein/#10

5. Escudier B, Porta C, Schmidinger M, Rioux-Leclercq N, Bex A, Khoo V, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. mai 2019;30(5):706-20.

6. Powles T, Albiges L, Bex A, Grünwald V, Porta C, Procopio G, et al. ESMO Clinical Practice Guideline update on the use of immunotherapy in early stage and advanced renal cell carcinoma. Ann Oncol. déc 2021;32(12):1511-9.

7. Dabestani S, Marconi L, Hofmann F, et al. Local treatments for metastases of renal cell carcinoma: a systematic review. Lancet Oncol. 2014;15(12):e549-e561.

8. Ko JJ, Xie W, Kroeger N, Lee J lyun, Rini BI, Knox JJ, et al. The International Metastatic Renal Cell Carcinoma Database Consortium model as a prognostic tool in patients with metastatic renal cell carcinoma previously treated with first-line targeted therapy: a population-based study. Lancet Oncol. mars 2015;16(3):293-300.

9. Waring R. Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma. N Engl J Med. 2007;

10. Motzer RJ, Escudier B, George S, Hammers HJ, Srinivas S, Tykodi SS, et al. Nivolumab versus everolimus in patients with advanced renal cell carcinoma: Updated results with long-term follow-up of the randomized, open-label, phase 3 CheckMate 025 trial. Cancer. 15 sept 2020;126(18):4156-67.

11. Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 5 avr 2018;378(14):1277-90.

12. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl

J Med. 21 mars 2019;380(12):1116-27.

13. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. avr 2012;12(4):252-64.

14. Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immunotherapy: from T cell basic science to clinical practice. Nat Rev Immunol. nov 2020;20(11):651-68.

15. Wherry EJ. T cell exhaustion. Nat Immunol. juin 2011;12(6):492-9.

16. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 5 oct 2017;377(14):1345-56.

17. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer. N Engl J Med. 9 juill 2015;373(2):123-35.

18. Bajorin DF, Witjes JA, Gschwend JE, Schenker M, Valderrama BP, Tomita Y, et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. N Engl J Med. 3 juin 2021;384(22):2102-14.

19. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, et al. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 27 févr 2020;382(9):810-21.

20. Champiat S, Ferrara R, Massard C, Besse B, Marabelle A, Soria JC, et al. Hyperprogressive disease: recognizing a novel pattern to improve patient management. Nat Rev Clin Oncol. déc 2018;15(12):748-62.

21. Michot JM, Bigenwald C, Champiat S, Collins M, Carbonnel F, Postel-Vinay S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer. févr 2016;54:139-48.

22. Hommes JW, Verheijden RJ, Suijkerbuijk KPM, Hamann D. Biomarkers of Checkpoint Inhibitor Induced Immune-Related Adverse Events—A Comprehensive Review. Front Oncol. 11 févr 2021;10:585311.

23. Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. Eur J Cancer. avr 2016;57:58-67.

24. Takenaka Y, Oya R, Takemoto N, Inohara H. Predictive impact of sarcopenia in solid cancers treated with immune checkpoint inhibitors: a meta-analysis. J Cachexia Sarcopenia Muscle. oct 2021;12(5):1122-35.

25. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. 2008;371:10.

26. An Y, Wu Z, Wang N, Yang Z, Li Y, Xu B, et al. Association between body mass index and survival outcomes for cancer patients treated with immune checkpoint inhibitors:

a systematic review and meta-analysis. J Transl Med. 12 juin 2020;18(1):235.

27. Yoo SK, Chowell D, Valero C, Morris LGT, Chan TA. Outcomes Among Patients With or Without Obesity and With Cancer Following Treatment With Immune Checkpoint Blockade. JAMA Netw Open. 28 févr 2022;5(2):e220448.

28. Deng T, Lyon CJ, Bergin S, Caligiuri MA, Hsueh WA. Obesity, Inflammation, and Cancer. Annu Rev Pathol. 23 mai 2016;11:421-49.

29. Pasquarelli-do-Nascimento G, Machado SA, De Carvalho JMA, Magalhães KG. Obesity and adipose tissue impact on T-cell response and cancer immune checkpoint blockade therapy. Immunother Adv. 1 janv 2022;2(1):ltac015.

30. McNelis JC, Olefsky JM. Macrophages, Immunity, and Metabolic Disease. Immunity. juill 2014;41(1):36-48.

31. Zakaroff-Girard A, Belles C, Umuhoza F, Fontaine J, Bouloumié A. Les cellules immunes résidentes du tissu adipeux. Médecine Mal Métaboliques. juin 2019;13(4):331-4.

32. Eljaafari A, Pestel J, Le Magueresse-Battistoni B, Chanon S, Watson J, Robert M, et al. Adipose-Tissue-Derived Mesenchymal Stem Cells Mediate PD-L1 Overexpression in the White Adipose Tissue of Obese Individuals, Resulting in T Cell Dysfunction. Cells. 3 oct 2021;10(10):2645.

33. Li Z, Zhang C, Du JX, Zhao J, Shi MT, Jin MW, et al. Adipocytes promote tumor progression and induce PD-L1 expression via TNF-α/IL-6 signaling. Cancer Cell Int. déc 2020;20(1):179.

34. Jiang Z, Liu Z, Li M, Chen C, Wang X. Increased glycolysis correlates with elevated immune activity in tumor immune microenvironment. EBioMedicine. avr 2019;42:431-42.

35. Zhang Z, Liu S, Zhang B, Qiao L, Zhang Y, Zhang Y. T Cell Dysfunction and Exhaustion in Cancer. Front Cell Dev Biol. 11 févr 2020;8:17.

36. Kim TK, Vandsemb EN, Herbst RS, Chen L. Adaptive immune resistance at the tumour site: mechanisms and therapeutic opportunities. Nat Rev Drug Discov. juill 2022;21(7):529-40.

37. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol Bethesda Md 1985. déc 2004;97(6):2333-8.

38. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab Physiol Appl Nutr Metab. oct 2008;33(5):997-1006.

39. Martin L, Birdsell L, MacDonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer Cachexia in the Age of Obesity: Skeletal Muscle Depletion Is a Powerful Prognostic Factor, Independent of Body Mass Index. J Clin Oncol. 20 avr 2013;31(12):1539-47.

40. Guzman-Prado Y, Ben Shimol J, Samson O. Body mass index and immune-related adverse events in patients on immune checkpoint inhibitor therapies: a systematic review and meta-analysis. Cancer Immunol Immunother. janv 2021;70(1):89-100.

41. Martini DJ, Olsen TA, Goyal S, Liu Y, Evans ST, Magod B, et al. Body Composition Variables as Radiographic Biomarkers of Clinical Outcomes in Metastatic Renal Cell Carcinoma Patients Receiving Immune Checkpoint Inhibitors. Front Oncol. 9 juill 2021;11:707050.

42. Aubrey J, Esfandiari N, Baracos VE, Buteau FA, Frenette J, Putman CT, et al. Measurement of skeletal muscle radiation attenuation and basis of its biological variation. Acta Physiol Oxf Engl. mars 2014;210(3):489-97.

43. Chu MP, Li Y, Ghosh S, Sass S, Smylie M, Walker J, et al. Body composition is prognostic and predictive of ipilimumab activity in metastatic melanoma. J Cachexia Sarcopenia Muscle. juin 2020;11(3):748-55.

44. Takei K, Kijima T, Okubo N, Kurashina R, Kokubun H, Uematsu T, et al. Association between Immune Checkpoint Inhibitor Treatment Outcomes and Body Composition Factors in Metastatic Renal Cell Carcinoma Patients. Cancers. 26 nov 2023;15(23):5591.

45. McManus HD, Zhang D, Schwartz FR, Wu Y, Infield J, Ho E, et al. Relationship Between Pretreatment Body Composition and Clinical Outcomes in Patients With Metastatic Renal Cell Carcinoma Receiving First-Line Ipilimumab Plus Nivolumab. Clin Genitourin Cancer. déc 2023;21(6):e429-e437.e2.

46. Ged Y, Sanchez A, Patil S, Knezevic A, Stein E, Petruzella S, et al. Associations between Pretreatment Body Composition Features and Clinical Outcomes among Patients with Metastatic Clear Cell Renal Cell Carcinoma Treated with Immune Checkpoint Blockade. Clin Cancer Res. 1 déc 2022;28(23):5180-9.

47. Zhang D, Shah N, Cook M, Blackburn M, Serzan M, Advani S, et al. Association between Body Mass Index and Immune-Related Adverse Events (irAEs) among Advanced-Stage Cancer Patients Receiving Immune Checkpoint Inhibitors: A Pan-Cancer Analysis. Cancers. 3 déc 2021;13(23):6109.

48. Cortellini A, Bozzetti F, Palumbo P, Brocco D, Di Marino P, Tinari N, et al. Weighing the role of skeletal muscle mass and muscle density in cancer patients receiving PD-1/PD-L1 checkpoint inhibitors: a multicenter real-life study. Sci Rep. déc 2020;10(1):1456.

49. Daly LE, Power DG, O'Reilly Á, Donnellan P, Cushen SJ, O'Sullivan K, et al. The impact of body composition parameters on ipilimumab toxicity and survival in patients with metastatic melanoma. Br J Cancer. janv 2017;116(3):310-7.

50. Hirsch L, Bellesoeur A, Boudou-Rouquette P, Arrondeau J, Thomas-Schoemann A, Kirchgesner J, et al. The impact of body composition parameters on severe toxicity of nivolumab. Eur J Cancer. janv 2020;124:170-7.

51. Choueiri TK, Powles T, Burotto M, Escudier B, Bourlon MT, Zurawski B, et al. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 4 mars 2021;384(9):829-41.

52. Motzer R, Alekseev B, Rha SY, Porta C, Eto M, Powles T, et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. N Engl J Med. 8 avr 2021;384(14):1289-300.

53. Calabrese LH, Calabrese C, Cappelli LC. Rheumatic immune-related adverse events from cancer immunotherapy. Nat Rev Rheumatol. oct 2018;14(10):569-79.

54. Haanen J, Obeid M, Spain L, Carbonnel F, Wang Y, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. déc 2022;33(12):1217-38.

55. Wang Z, Aguilar EG, Luna JI, Dunai C, Khuat LT, Le CT, et al. Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade. Nat Med. janv 2019;25(1):141-51.

56. Carnot A. Mesure des variations de masse maigre et de masse grasse chez les patients atteints de sarcomes métastatiques et recevant du regorafenib ou un placebo. Une étude ancillaire du protocole REGOSARC [thèse]. Lille : Université Lille 2 Droit et Santé ; 2016.

57. Young AC, Quach HT, Song H, Davis EJ, Moslehi JJ, Ye F, et al. Impact of body composition on outcomes from anti-PD1 +/− anti-CTLA-4 treatment in melanoma. J Immunother Cancer. juill 2020;8(2):e000821.

58. Motzer RJ, Rini BI, McDermott DF, Arén Frontera O, Hammers HJ, Carducci MA, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncol. oct 2019;20(10):1370-85.

59. Powles T, Plimack ER, Soulières D, Waddell T, Stus V, Gafanov R, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. Lancet Oncol. déc 2020;21(12):1563-73.

60. Lee S, Kim JH, Song W, Sung HH, Jeon HG, Jeong BC, et al. Prognostic Role of Pre-Treatment Body Composition Parameters in Patients Undergoing First-Line Immunotherapy for Metastatic Renal Cell Carcinoma. Cancer Manag Res. août 2024;Volume 16:1091-101.

61. Li S, Wang T, Lai W, Zhang M, Cheng B, Wang S, et al. Prognostic impact of sarcopenia on immune-related adverse events in malignancies received immune checkpoint inhibitors: a systematic review and meta-analysis. Transl Cancer Res. déc 2021;10(12):5150-8.

Annexes

Appendix 1 : Assessment of CT-based BC-parameters

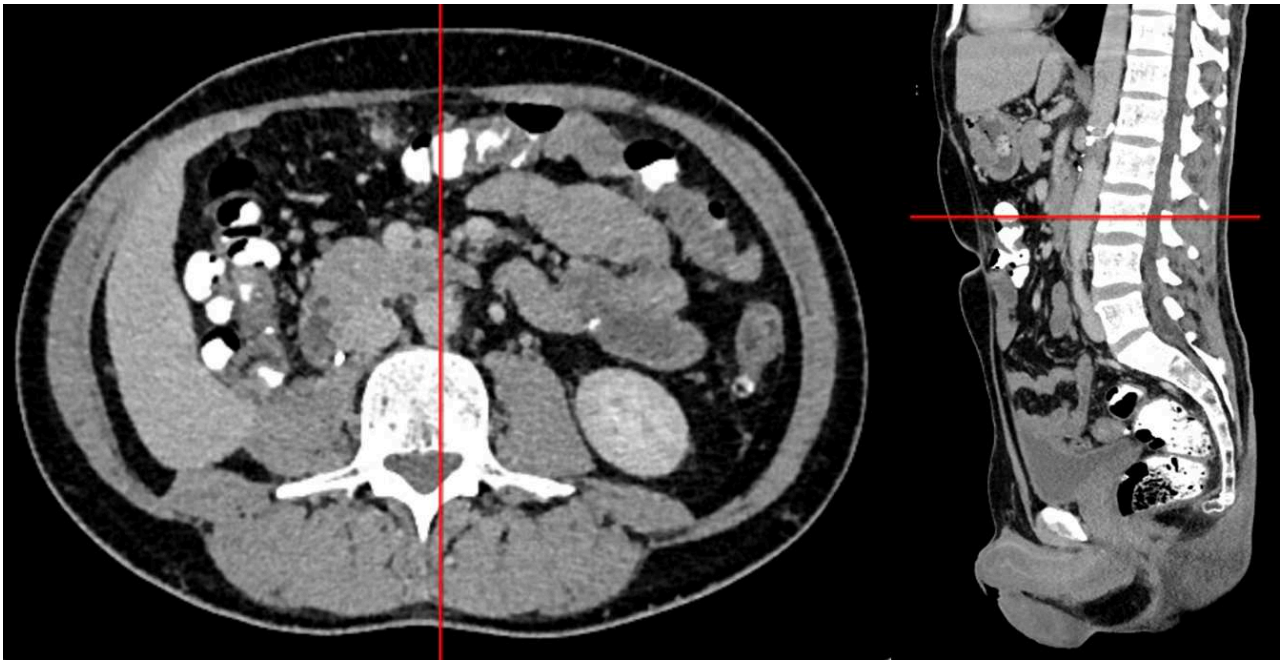


Figure 1 : Initial acquisition at the middle of the third lumbar vertebra (L3) on axial and coronal CT images

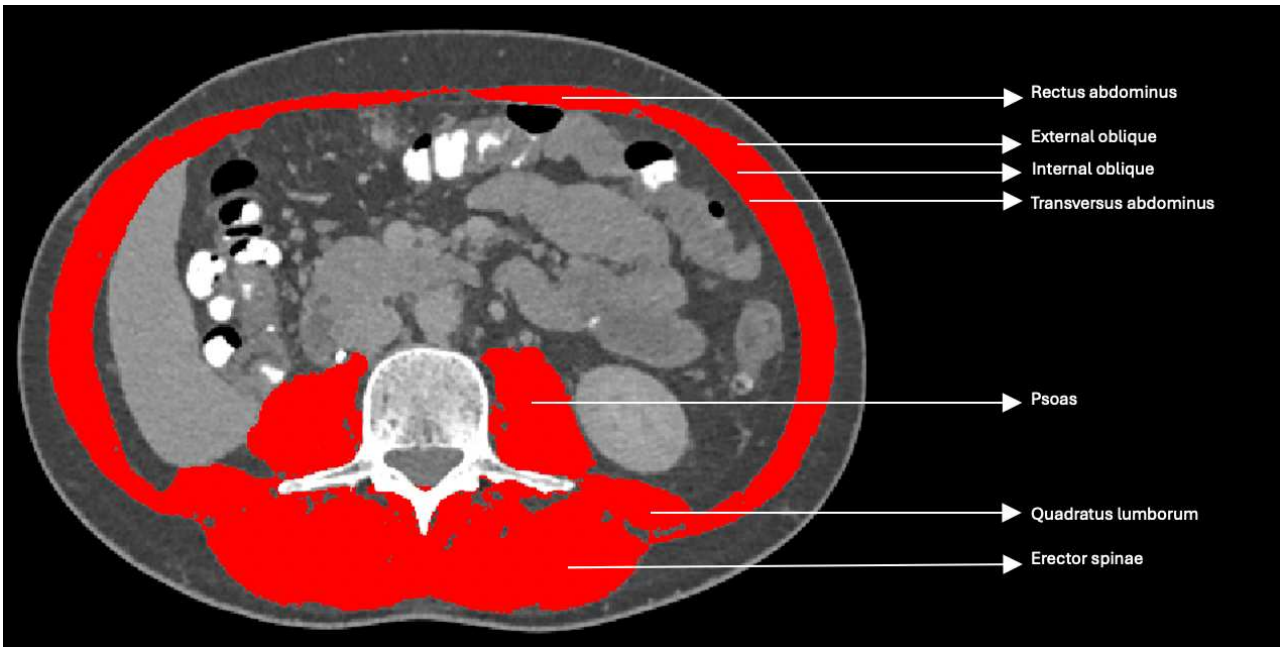


Figure 2 : Skeletal muscle segmentation on cross-sectional CT image at L3 level.

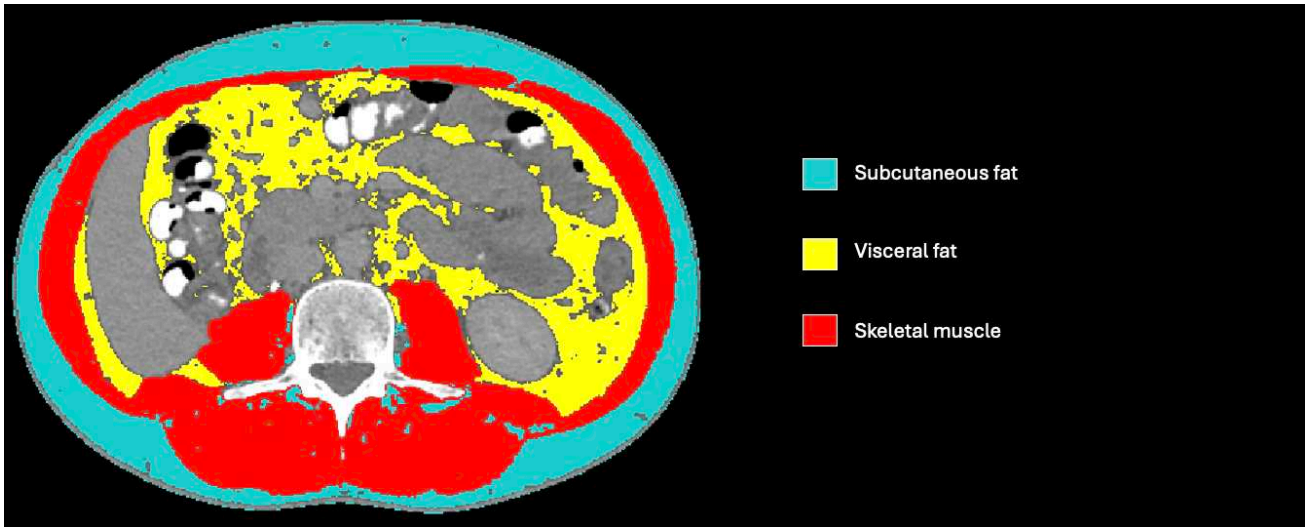


Figure 3 : Representative computed tomography images of a patient with high SMI and low VFI and SFI.

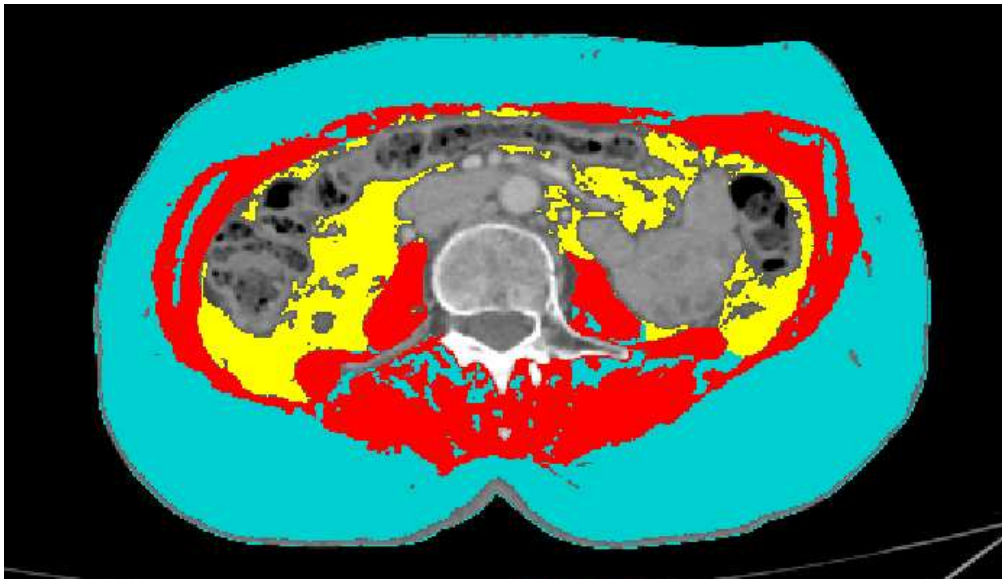


Figure 4 : Representative computed tomography image of a patient with high SFI and low VFI and SFI.

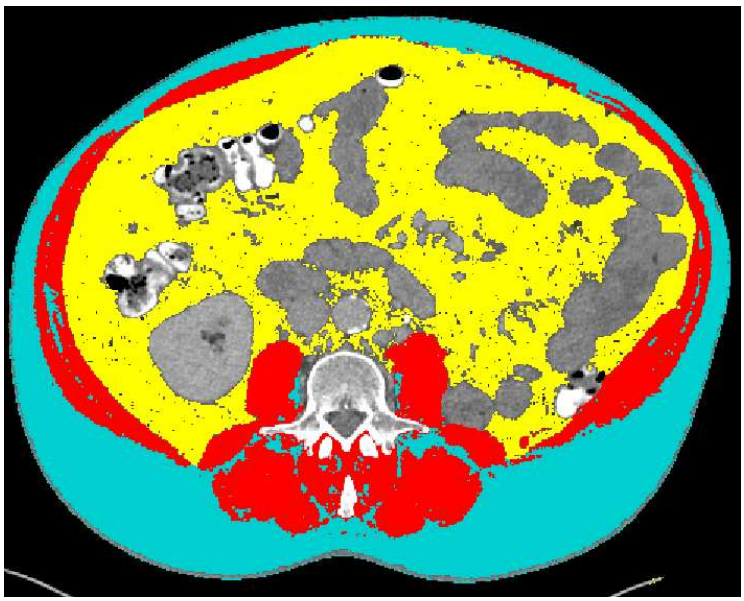


Figure 5 : Representative computed tomography images of a patient with high TFI and low SMI and SFI.

BMI category	SMI (cm2/m2)		SMD (HU)
	Male	Female	
Overweight (≥ 25)	53	41	33
Non-overweight (< 25)	43	41	41

Table 1 : Previously established cut-offs by Martin et al. defining sarcopenia and myosteasosis according to sex and BMI.

Appendix 2 : Reviews of studies investigating association between fat composition and ICI treatment efficiency.

Studies	Tumor	Results
Chu 2020	97 pre-treated melanoma : Locally advanced, unresectable disease 11.3% Dstant metastatic disease 88.7%	OS was significantly lower in low vs. high SMD patients (median 5.4 vs. 17.5 months, 2 year 0 vs. 33.9%, HR 2.47, 95%CI 1.84-6.02, P = 0.001)
Martini 2020	Phase I clinical trials Melanoma 33% GI 22% Lung or H&N 20% Others 24% ≥ 2 prior systemic therapies 69%	Low-risk patients (**SFI** ≥73) had longer OS (HR: 0.20, P < .001) and PFS (HR: 0.38, P = .003) compared with patients at intermediate risk (SFI <73 and IFI <3.4) and poor risk (SFI <73 and IFI ≥3.4) VFI did not appear to have a significant impact on outcomes
Minami 2020	74 pre-treated NSCLC	No significant difference in OS and PFS according to PMI, IMAC, VSR and VFA.
Young 2020	287 metastatic melanoma 1st line treatment 49,5%	High TATI was associated with decreased response rate (OR: 0.18, p=0.02). and PFS (HR: 1.71, p=0.04) among women.
Martini 2021	70 pts Urothélial 1st line treatment 19%	High-risk pts had significantly shorter OS (HR: 6.72, p < .001), PFS (HR: 5.82 p < .001), and lower chance of CB (OR: 0.02, p = .003) compared with the low-risk group. Risk score was SMI + 2 x attenuated SM mean + VFI
Martini 2021	79 mRCC ccRCC histology 74,3% 1st line treatment 35,4%	Low TFI had significantly shorter OS (HR: 2.72, p=0.002), PFS (HR: 1.91, p=0.025), and lower chance of CB (OR: 0.25, p=0.008) compared to high TFI
Xiao 2022	172 primary liver cancer	Sarcopenia (HR: 5.39; p=0.004) and TATI were significant predictors of OS.

Appendix 2 : Reviews of studies investigating association between fat composition and ICI treatment efficiency – *(continued)*

Studies	Tumor	Results
J. E. Park 2022	136 NSCLC 1st line treatment and beyond	Patients with a VFI in Q2-4 had prolonged OS (OS, Q1 vs. Q2-4: 5.6 months vs. 16.3 months, p = 0.004)
Ged 2022	205 patients mRCC 1st line : 30%	High BMI patients had longer OS than normal weight patients (unadjusted HR 0.66; p=0.035). High SMI was associated with longer OS (unadjusted HR: 1.65 (95% CI: 1.13–2.43); p=0.009). However, this OS association became non-significant after adjusting for IMDC score and line of therapy.
Takei 2023	First line 60 mRCC	No association was found between the subcutaneous, visceral, and total fat indices and the therapeutic effect of ICI-based therapy. Patients with sarcopenia had a significantly shorter median OS (21 months vs. not reached, p = 0.0023).
Ged 2022	205 patients mRCC 1st line : 30%	High BMI patients had longer OS than normal weight patients (unadjusted HR 0.66; p=0.035). High SMI was associated with longer OS (unadjusted HR: 1.65 (95% CI: 1.13–2.43); p=0.009). However, this OS association became non-significant after adjusting for IMDC score and line of therapy.
McManus 2023	99 mRCC treated in 1st line by Nivolumab Ipilimumab	High vs. low SMI (HR=2.433, P=.0017), high vs. low SATI (HR=1.641, P=.0398), and obese vs. normal/overweight BMI (HR=1.859, P=.0105) were significantly associated with PFS.
Lee 2024	110 mRCC treated in 1st line 87.3% : clear cell histology CT scan performed within 120 days before the initiation of systemic therapy	High SFI exhibited a significant association with improved OS (adjusted HR: 0.37; p = 0.029).

Appendix 3 : Nephrectomy histology for metachronous disease in overall population.

Characteristic	Overall(N=71)
Metachronous diagnosis, n (%)	28 (39.4)
pT stage, n (%)	
pT1	4 (16.0)
pT2	6 (24.0)
pT3	15 (60.0)
Missing data	3
Furhman grade, n (%)	
1-2	4 (16.0)
3-4	21 (84.0)
Missing data	3
Sarcomatoid faetures, n (%)	5 (20.0)
Missing data	3
Time to treatment, months, median (range)[†]	5.5 (0.7—44.1)

[†]Time between prior nephrectomy at localized stage and start of systemic treatment.

AUTEUR : Nom : BOUGET **Prénom : Tanguy**

Date de soutenance : 8 octobre 2024

Titre de la thèse : Association entre composition corporelle et survie globale chez les patients atteints d'un carcinome rénal à cellules claires traités par immunothérapie.

Thèse - Médecine - Lille 2024

Cadre de classement : *Médecine*

DES + spécialité : *Oncologie Médicale*

Mots-clés : Immunothérapie, Cancer du rein à cellules rénales, Biomarqueurs, IMC, composition corporelle, toxicités immunomédiées, relecture scanner

Résumé : Introduction : Les inhibiteurs de point contrôle immunitaire (ICI) sont largement prescrits en première ligne métastatique du carcinome rénal à cellules claires (CRCC), seuls ou en association. Les ICI peuvent entrainer des profils de réponses hétérogènes et des toxicités immunomédiées variées, parfois sévères, et imprévisibles. Au-delà du score IMDC, nous manquons de biomarqueurs prédictifs de réponse et de toxicité. Quelques auteurs qui se sont intéressés à l'IMC comme biomarqueur mettent en évidence le « paradoxe de l'obésité » : une meilleure efficacité des ICI est observée chez les patients obèses, pourtant facteur de risque de cancer. Pour mieux étudier ce paradoxe, les auteurs ont étudiés la composition corporelle (répartition des tissus graisseux et muscle squelettique) sur les scanners à l'initiation de l'ICI. Alors qu'une altération du muscle squelettique est associée à une moins bonne survie, les résultats concernant les compartiments du tissu adipeux sont disparates. Ainsi l'objectif ici était d'étudier le lien entre les paramètres scanographiques de composition corporelle, incluant la graisse sous cutanée et viscérale, et la survie globale (OS) chez les patients traités en 1ere ligne par ICI pour un CRCC métastatique, seul ou en association ; l'association avec les toxicités immunomédiées, et la description de la composition corporelle de ces patients, **Patients et méthodes :** Cette étude rétrospective et multicentrique a inclut des patients traités par ICI pour un CRCC entre juin 2017 et juin 2022 avec un TDM disponible dans les 90 jours précédents le début du traitement. Les paramètres de la composition corporelle, TFI, VFI, SFI et SMI était mesurés sur deux coupes à hauteur de L3 à l'aide d'un logiciel de quantification semi-automatique (Slice O Matic ®) indexés sur la taille au carré. **Résultats** : Notre étude a inclus 71 patients et n'a pas retrouvé d'association significative entre un TFI élevé et la survie globale (HR multivarié 0,70, 95 %CI = [0,33 ; 1,48]), ni de lien avec les toxicités. Le TFI et le BMI étaient corrélés (r=0.81) alors que la corrélation mesurée entre le SFI et VFI était faible. **Conclusion** : D'autres études prospectives de grands effectifs seraient nécessaires pour valider les seuils de parametres de composition corporelle ainsi mieux évaluer le rôle prédictif du tissu gras viscéral et sous cutanée.

<u>Composition du Jury</u> :

Président : Monsieur le Professeur Nicolas PENEL
Assesseurs : Monsieur le docteur Aurélien Carnot
Monsieur le docteur Gautier MARCQ
Directrice de thèse : Madame le Docteur Alexandra FORESTIER