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Medicom Medical Publishers
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Contents

Influence of immunotherapy combinations on outcomes in sarcomatoid metastatic RCC: results from the UK Renal Oncology Collaborative

Authors

P. Roy[1], I. Irwin[1], R. Frazer[1], J. McGrane[2], A. Challapalli[3], A. Bahl[3], N. Charnley[1], J. Malik[1], C. Forde[4], E. Jones[1], A. Sharma[5], M. Elgendy[6], S-Y. Moorcraft[7], D. Parslow[8], A. Lydon[9], T. Geldart[10], V. Ford[11], I. Muazam[12], G.J. Melendez-Torres[13]

Affiliations

1. Velindre NHS Trust, UK; 2. Royal Cornwall Hospitals NHS Trust, UK; 3. University Hospitals Bristol NHS Foundation Trust, UK; 4. Leicestershire Partnership NHS Trust, UK; 5. East and North Herts NHS Foundation Trust, UK; 6. Birmingham Womens and Childrens NHS Foundation Trust, UK; 7. Royal Brompton and Harefield NHS Foundation Trust, UK; 8. University Hospitals Plymouth NHS Trust, UK; 9. Torbay and South Devon NHS Foundation Trust, UK; 10. University Hospitals Dorset NHS Trust, UK; 11. Leap Valley Medical Centre NHS Bristol, UK; 12. Hull University Teaching Hospital NHS Trust, UK; 13. Exeter NHS Trust, UK

Corresponding author

Ricky Frazer, Ricky.Frazer@wales.nhs.uk

ABSTRACT

Introduction: Sarcomatoid changes in renal cancer histology are recognised as having worse survival outcomes. Within renal oncology teams, it is thought they are more commonly poor-risk, immuno-oncology therapy (IO) responsive and should be treated with IO rather than with tyrosine kinase inhibitors (TKI). Subgroup analysis of Checkmate 214 has made ipilimumab and nivolumab (IO/IO) a standard of care. However, IO/TKI combinations may reduce the primary progression rate that can occur with IO/IO combination. We explored progression-free survival (PFS) and overall survival (OS) in sarcomatoid patients with metastatic renal cell cancer (mRCC) with different first-line treatments.

Methods: A multi-centre retrospective review of patients commencing systemic anti-cancer therapy for mRCC between 01/01/2018 and 30/06/2021 at 17 UK NHS trusts. Patient demographics, tumour histology and IMDC group were analysed. Survival data were compared using Kaplan-Meier curves for the statistical significance of differences in outcome between sarcomatoid and non-sarcomatoid groups. The treatment groups were assessed with the log-rank testing. Outcomes were analysed for sarcomatoid changes based on first-line treatment type.

Results: 1319 patients were included in the overall analysis. The median age was 64 years. 102 of the 1319 patients (7.7%) of patients had sarcomatoid changes in their histology. 7=fav, 60=int and 35=poor IMDC risk groups. 48 patients received IO/IO, 11 received IO/TKI and 43 received TKI therapy. Sarcomatoid patients had reduced OS versus non-sarcomatoid 21.7m vs 26.6m [Chi-square = 5.42, p=0.019]. Sarcomatoid patients also had worse PFS 8.7m vs 4.9m [Chi-square =10.1, p=0.002]. IOIO, IOTKI and TKI had median OS of 25m, NR, 16.8m respectively [Chi-square = 0.81, p=0.666]. IOIO, IOTKI and TKI had median PFS of 5.8m, 6.0m, 4.0m respectively [Chi-square =2, p=0.367].

Conclusions: This dataset confirms that sarcomatoid changes confer a worse prognosis compared to non-sarcomatoid patients. Immunotherapy-containing regimens improve survival outcomes compared to TKI. Allowing for the small number of IOTKI patients, IOIO seems to perform better for overall survival.

Introduction

Renal cancers are the fourteenth most common cancer type in the world according to incidence, accounting for 2.2% of all cancers recorded worldwide according to GLOBOCAN 2022.[1] However, in the United Kingdom, renal cancers account for 4% of all cancers with 13,834 cases between 2016 to 2018.[2] According to Cancer Research UK, the incidence of renal cancers in the United Kingdom has gone up by 88% since the 1990s, making the real-world practice regarding the management of renal cancers worth revisiting.[2]

Renal cancers can be histologically subdivided into various types. A large multicentre international study including more than 10,000 patients with mRCC showed that 92% of the patients had clear cell histology, followed by 7% of patients having papillary subtype and 2% having chromophobe subtype.[3] Sarcomatoid change is an uncommon differentiation that can be associated with most histological subtypes and is noted in about 4-5% of renal cancers.[4,5] However, this can go up to 20% in metastatic disease.[6] Patients with renal cancers having sarcomatoid differentiation on histology are recognised to have worse survival outcomes and the median overall survival according to various studies is generally under one year.[7-9] In fact, a higher proportion of sarcomatoid differentiation is associated with progressively worse outcomes.[5,10]

Management of advanced renal cancers can be categorised according to favourable, intermediate, or poor-risk disease depending on the presence of well-characterised clinical and laboratory risk factors.[11] These

categories of risk stratification use a validated model to assess prognosis that was developed by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC).[12,13] Renal cancer management relies heavily on this risk stratification model with survival outcomes being worse in poor risk group compared to favourable risk.[12,13]

The recommended first-line treatment for metastatic clear cell renal cancers according to the ESMO guidelines published in 2024 includes the following: pembrolizumab/axitinib, nivolumab/cabozantinib and pembrolizumab/lenvatinib, irrespective of risk stratification.[14] Ipilimumab–nivolumab is recommended as first-line treatment for IMDC intermediate- and poor-risk disease.[15] These recommendations are based on the outcomes of various pivotal trials, some of which have also looked into the outcomes in patients with sarcomatoid features on biopsy.[16-21] Subgroup analysis of Checkmate 214 has made ipilimumab and nivolumab (IOIO) a standard of care in renal cancers with sarcomatoid differentiation, however, IOTKI (immunotherapy and tyrosine kinase inhibitor) combinations may reduce the primary progression rate that can occur with IOIO combination.[16]

Management of advanced renal cancers has taken significant strides in the last decade. However, outcome data of renal cancers with sarcomatoid differentiation treated with these new protocols remains relatively sparse. Here, we report the results from our collaborative study which explored survival outcomes in sarcomatoid metastatic renal cancer patients with different first-line treatments in the real world.

Methods

A multi-centre retrospective review was conducted including patients commencing systemic anti-cancer therapy for mRCC between 01/01/2018-30/06/2021 at 17 UK NHS trusts. Inclusion criteria for this study were: patients aged 18 years or older, treatment-advanced renal cell carcinoma patients with histological confirmation of sarcomatoid differentiation and having received at least one line of treatment. The analysis of patients having sarcomatoid differentiation on histology was pre-planned. Participants were characterised according to IMDC risk stratification (favourable [score of 0], intermediate [score of 1 or 2], or poor [score of 3 to 6]). IMDC risk stratification was done based on the following clinical and laboratory parameters: a Karnofsky performance-status score of 70, a time from initial diagnosis to randomization of less than one year, a haemoglobin level below the lower limit of normal range, a corrected serum calcium concentration of more than 10 mg/dL (2.5 mmol/L), an absolute neutrophil count above the upper limit of the normal range, and a platelet count above the upper limit of the normal range.[12]

Outcomes and Assessments

Patient demographics, tumour histology, IMDC group, treatment choices in the first line and outcomes in the form of overall survival (OS) and progression-free survival (PFS) were analysed. Treatment options used in successive lines were also recorded. Overall survival was defined as the time from diagnosis of renal cancer to death from any cause. Progression-free survival (PFS) was defined as the time from initiation of treatment to the occurrence of disease progression or death. Reasons for discontinuation of treatment in the first line were also recorded.

Statistical Analysis

Outcomes were analysed for sarcomatoid changes based on first-line treatment type. Means were used to summarise quantitative data, whereas proportion/percentage was used to summarise qualitative data. Survival data was compared using Kaplan-Meier curves with 95% CIs between treatment arms for OS and PFS (sarcomatoid versus non-sarcomatoid histology). A stratified log-rank test at a two-sided 5% significance level was used to compare the distributions of OS and PFS between the different treatment groups (IMDC favourable, intermediate and poor risk).

Results

Demographics

A total of 1319 patients were included in the overall analysis of which 106 (8.04%) patients had sarcomatoid changes in their histology. The median age for the cohort was 62 years (IQR: 38-71 years) and the M:F ratio was 2.2:1. A majority of 73 (68.87%) patients had prior nephrectomies. Other baseline characteristics have been summarised in Table 1.

Table 1: Demographic characteristics of the cohort

Characteristics	n (%)
Predominant histological subtype	
Clear cell	85 (80.2%)
Sarcomatoid	10 (9.4%)
Papillary	5 (4.7%)
Undifferentiated	4 (3.8%)
Chromophobe	1 ((0.9%)
Not recorded	1 (0.9%)
IMDC risk group	
Favourable	8 (7.5%)
Intermediate	62 (58.5%)
Poor	35 (33.0%)
Not recorded	1 (0.9%)
IMDC scoring	
Time from initial diagnosis to systemic therapy <1 year	81 (76.4%)
Karnofsky Performance status <80%	13 (12.3%)
Haemoglobin less than lower limit of normal	48 (45.3%)
Corrected serum calcium more than upper limit of normal	19 (17.9%)
Neutrophilia	26 (24.5%)
Thrombocytosis	22 (20.8%)
Metastasis at presentation	
Lung	72 (67.9%)
Nodal	55 (51.9%)
Bone	26 24.5%)
Others	21 (19.8%)
Adrenal	16 (15.1%)
Liver	14 (13.2%)
Brain	6 (5.7%)
Pancreas	6 (5.7%)
Presentation of Brain metastasis	
<3 months from metastatic diagnosis	9 (8.5%)
>3 months from metastatic diagnosis	2 (1.9%)

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium

Treatment

The median number of lines of treatment received was two. Overall, 49 (46.2%) patients received IOIO combination in the first-line setting followed by TKI monotherapy in 44 (41.5%) patients and IOTKI in 12 (11.3%) patients. Treatment received, classified according to IMDC risk group, is depicted in Table 2. The most commonly used TKI for monotherapy in the first line was Sunitinib

Table 2: Treatment choices for different lines stratified according to IMDC risk classification.

IMDC Risk Group	n (%)	First Line	Second Line	Third Line	Fourth Line
Favourable	IOIO	0	0	0	0
	TKI	2 (25.0%)	4 (66.7%)	2 (100%)	0
	IOTKI	6 (75.0%)	0	0	0
	IO	0	2 (33.3%)	0	0
	Other	0	0	0	0
	Total	**8 (100%)**	**6 (75%)**	**2 (25%)**	**0**
Intermediate	IOIO	33 (53.2%)	1 (3.33%)	0	0
	TKI	23 (37.1%)	20 (66.7%)	6 (54.5%)	1 (100%)
	IOTKI	6 (9.7%)	0	0	0
	IO	0	8 (26.7%)	2 (18.2%)	0
	Other	0	1 (3.33%)	3 (27.3%)	0
	Total	**62 (100%)**	**30 (48.4%)**	**11 (17.7%)**	**1 (1.6%)**
Poor	IOIO	16 (45.7%)	0	0	0
	TKI	15 (42.9%)	15 (88.2%)	6 (75.0%)	0
	IOTKI	4 (11.4%)	0	0	0
	IO	0	1 (5.9%)	2 (25.0%)	1 (50.0%)
	Other	0	1 (5.9%)	0	1 (50.0%)
	Total	**35 (100%)**	**17 (48.6%)**	**8 (22.9%)**	**2 (5.7%)**

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IOIO, Immunotherapy combination; IOTKI, Immunotherapy and Tyrosine Kinase Inhibitor combination; TKI, Tyrosine Kinase Inhibitor monotherapy

(16, 15.1%) and in subsequent lines was Cabozantinib (35, 33.0%). Avelumab-axitinib was the most commonly used IOTKI in any line in 7 (6.6%) patients. Lenvatinib-everolimus was the most commonly used combination not falling into any of the above categories in 4 (3.8%) patients.

Outcomes

Patients having sarcomatoid differentiation had a reduced median OS of 21.7 months (95% CI: 11.9-24.5 months) compared with patients lacking a sarcomatoid differentiation having a median OS of 26.6 months (95% CI: 24.1-28.7 months). This difference of about 4.9 months was statistically significant with a P value of 0.019 calculated by Chi-square test. (Figure 1) Patients having sarcomatoid differentiation also had a statistically significantly worse median PFS of 4.9 months (95% CI: 3.5-6.2 months) compared to 8.7 months (95% CI: 8.1-9.6 months) in patients lacking a sarcomatoid differentiation [p=0.002]. (Figure 1)

IOIO, IOTKI and TKI had a median OS of 25.0 months (95% CI: 12.7-30.9 months), NR (not reached) and 16.8 months (95% CI: 6.6-38.5 months) respectively [p= 0.666]. IOIO, IOTKI and TKI had a median PFS of 5.8 months (95% CI: 3.4-12.5 months), 6.0 months (95% CI: 3.0-17.5 months), 4.0 months (95% CI: 3.1-4.9 months) respectively [p= 0.367]. The OS and PFS stratified based on treatment received is depicted in Figure 2.

Figure 1: Figure showing that both the overall survival (left) and progression-free survival (right) were worse for patients with RCC with sarcomatoid differentiation versus those who lacked sarcomatoid differentiation (P value 0.019 and 0.002, respectively)

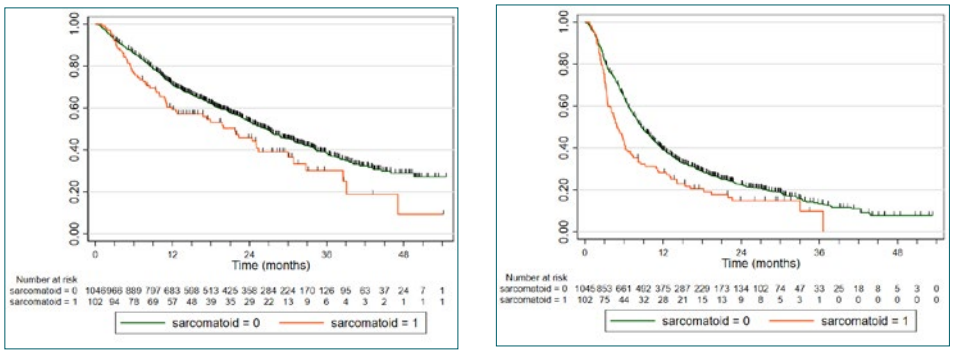
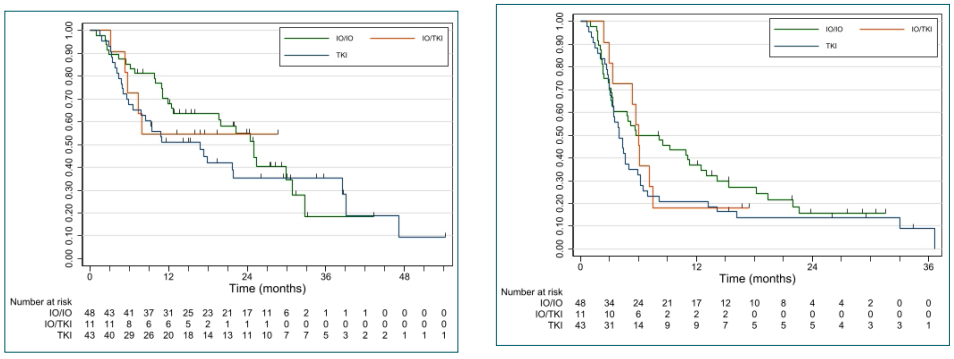


Figure 2: Figure showing overall survival (left) and progression-free survival (right) for patients with RCC with sarcomatoid differentiation based on first-line treatment received (P value 0.666 and 0.367, respectively)



IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IOIO, Immunotherapy combination; IOTKI, Immunotherapy and Tyrosine Kinase Inhibitor combination; TKI, Tyrosine Kinase Inhibitor monotherapy

Toxicities

Permanent discontinuation in first-line treatment due to toxicity was documented in 21

(20%) patients. Discontinuation IOIO, IOTKI and TKI in the first line were noted in 10 (9.5%), 10 (9.5%) and 1 (0.9%) patients, respectively.

Discussion

Historically, conventional treatment options have lacked efficacy in the management of mRCC with sarcomatoid features. The survival in most cases has been quite dismal and ranges between 6-13 months.[5,9,22,23] Recently, several trials have established the benefit of immune checkpoint inhibitors (ICI) in combination either with other ICI or tyrosine kinase inhibitors (TKI) as first-line options in the management of mRCC. Introduction of immunotherapy with PD-1/PD-L1/CTLA-4 inhibitors has produced significant clinical benefit for patients with renal cancers with sarcomatoid features as well with median overall survival now reaching over 20 months.[24]

Biologically, the benefit in overall survival with ICI in patients with mRCC with sarcomatoid differentiation could be attributed to increased programmed death ligand-1 (PD-L1) expression in this subgroup of tumours.[25] Genetic studies have also documented that renal cancers with sarcomatoid differentiation have heavily inflamed tumour microenvironments facilitating the action of ICI.[26] The biological spectrum of this subtype of renal cancers favouring the use of ICI in the first-line setting has been shown to translate into clinical benefit in various phase III and prospective phase II trials.[16-21] A comprehensive review of these practice-changing trials with respect to mRCC with sarcomatoid differentiation has been performed by Mario et. al.[24]

In the majority of the trials, sarcomatoid features have been documented in 5 to 15% of the study population, which is congruent to our subgroup of about 8% of patients.[16-21] However, the actual number of mRCC patients with sarcomatoid features in the trial arm in each of these studies has been well under 100. To the best of our knowledge, this study documents the outcomes of the largest group of patients with mRCC having sarcomatoid differentiation, treated with the current standard of care for mRCC, and their outcomes in the real-world setting. In the current study, ICI (in combination with another ICI or a TKI) was the preferred option in the first line in a majority of 61 (57.5%) patients. Throughout the course of their treatment 78 (73.6%) patients had received ICI, with 12 (11.3%) receiving ICI in the second line and 5 (4.7%) in further lines of treatment.

On progression with ICI, VEGFR-targeted therapies are an option as documented in various studies.[27-29] In the current study, out of a total of 53 patients who had received second-line treatment, 39 (73.6%) patients received TKI monotherapy in the second line. Cabozantinib was the most commonly used TKI in 24 (45.3%) patients in the second line, followed by Sunitinib in 7 (13.2%) patients. This is very similar to the findings of Hahn et. al. wherein Cabozantinib was the most preferred option as well. The median time on TKI in our study was 11 months which was more than the 6.1 months noted by Hahn et.al. in mRCC patients with sarcomatoid differentiation.[27]

The limitations of the current study include the fact that it is a retrospective study and prone to recall bias. The identification of specific toxicities and specifically the grading of toxicities was difficult to document. Also, some of the data collection was during the COVIS period which may have impacted decision making.

Conclusion

The current multi-institutional study represents the practice of the majority of the United Kingdom with respect to treatment choices in mRCC with sarcomatoid features. This dataset agrees with existing literature that sarcomatoid changes in patients with mRCC confer a worse prognosis compared with mRCC patients without sarcomatoid changes. Immunotherapy-containing regimens improve survival outcomes compared to TKI monotherapy alone in this group of patients. Allowing for the small number of patients receiving IOTKI, observed OS was longer for IOIO compared with TKI monotherapy. Based on this real-world data set, IOIO should remain the standard of care for mRCC patients with sarcomatoid change.

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Evaluation of bone response in metastatic renal cell carcinoma treated in first-line with immunotherapy-based combinations

Author

F. Moinard-Butot[1*], S. Nanninil, M. Pautasl, RL. Cazzato[2], G. Virbel[3], S. Martinl, L. Pierard[1], C. Schuster[1], I. Menoux[3], M. Burgy[1], G. Malouf[1], C. Roy[4], P. Barthélémy[1]

Affiliation

1. Service d'oncologie médicale, Institut de Cancérologie de Strasbourg Europe (ICANS), 67033 Strasbourg, France; 2. Service de radiologie interventionnelle, Hôpital universitaire de Strasbourg, 67096 Strasbourg, France; 3. Service de radiothérapie, Institut de Cancérologie de Strasbourg Europe (ICANS), 67033 Strasbourg, France; 4. Service de radiologie B, Hôpital universitaire de Strasbourg, 67096 Strasbourg, France.

***Corresponding author**

Fabien Moinard-Butot, f.moinard-butot@icans.eu

Abstract

Introduction: Immune Checkpoint Inhibitor (ICI) has revolutionised the management of metastatic renal cell carcinoma (mRCC). The presence of bone metastases (BM) is a poor prognostic factor. Few data are available on the response of ICI-based combinations to BM, and none take into account their location and numbers, which are prognostic factors. This retrospective study investigates the bone response to ICI-based treatments in first-line mRCC.

Methods: We included all patients with BM mRCC treated at the Institut de Cancérologie Strasbourg Europe (ICANS), in first-line with ICI-based combinations. Bone radiological evolution according to RECIST v1.1, reviewed by an expert radiologist, as well as tissue osteolytic and/or osteocondensing character was assessed according to the site of bone involvement (spinal column, sacrum, long bones), number of BMs (1, 2-5, >5), and immunotherapy-based combination.

Results: Between May 2015 and November 2023, we identified 38 patients with bone

metastatic mRCC. The median age was 64 years old, and 26 patients (68%) were male. Nineteen patients (50%) received an ICI-ICI combination, 17 patients (45%) ICI-TKI and 2 (5%) patients ICI alone. Fifteen patients (39%) had 1 BM, 15 patients (39%) had 2-5 BMs and 8 patients (22%) had >5 BMs. Patients with spinal column metastases had disease control in 67%, compared with 70% for sacrum metastases and 65% for long bone metastases. Fourteen patients (93%) with 1 BMs had disease control, 12 patients (80%) with 2-5 BMs and 3 patients (37%) with >5 BMs. Eleven (29%) developed bone condensation and/or bone reconstruction, with a median time to onset of 4.3 months. With a median follow-up of 45.8 months, only one patient with bone condensation progressed on bone.

Conclusion: The bone response in mCRC treated with ICI-based therapy appears to be a response according to RECIST v1.1, but also the early appearance of condensation-type bone changes.

Introduction

The incidence of bone metastasis (BM) in renal cell carcinoma (RCC) is around 30%[1]. The most frequent locations are the spinal column, sacrum and proximal femur[2]. BMs are predominantly osteolytic leading to altered bone integrity and inducing significant morbidity for patients with high levels of skeletal-related events (SRE)[3]. SRE was defined as a pathological fracture, requirement for palliative radiotherapy or surgery to bone, hypercalcemia or spinal cord compression. In metastatic RCC (mRCC), 74-85% of patients experienced at least one SRE and impacted quality of life1.

BM is an independent poor prognostic factor for patients with mRCC[4]. In a study with 223 patients treated with sunitinib, progression-free survival and overall survival (OS) were significantly improved for patients without bone metastasis[5]. Ruatta et al. showed patients with less than 5 BM had a longer OS versus patients with >5 BM. Moreover, the location of BM had an impact on OS, with patients presenting BM located to long bones having better prognostic than patients with BM located to the spinal column or sacrum (28.6 months vs 19.7 months vs 17.6 months respectively, P < 0,0001)[6].

The treatment of RCC has been revolutionised by the advent of immunotherapy (ICI)-based combinations. ICI may be combined with either another ICI or a vascular endothelial growth factor pathway receptor (VEGFR) targeted therapy. These different combinations have shown benefits in terms of OS and overall response rate (ORR), compared with Sunitinib in several large randomised phase 3 trials[7–10].

Some data suggest that ICI-TKI combinations are particularly effective against bone metastases, notably subgroup analyses of the CLEAR and CheckMate 9ER studies[11,12]. The aim is to monitor the efficacy of immunotherapy-based combinations on bone metastases, depending on their location and numbers.

Materials and methods

We performed a single-centre retrospective study of patients treated for mRCC with BM in first-line treatment with ICI-based therapy, from May 2015 to May 2023 at the Institut de Cancérologie Strasbourg Europe. Eligible patients had histologically confirmed clear cell Renal Cell Carcinoma treated with an ICI-based therapy combined with either an ICI or anti-VEGFR tyrosine kinase inhibitor (TKI) according to the standard approved schedule. The used protocols included: ipilimumab and nivolumab, pembrolizumab and axitinib, nivolumab and cabozantinib, pembrolizumab and lenvatinib. Dose reduction for toxicity, based on the standard recommendations for all agents, was permitted at the investigator's discretion. No patient received specific bone-directed therapy like bisphosphonates or anti-RANKL therapy. The diagnosis and assessment of BMs were carried out on a CT scan. Exclusion criteria were non-clear cell carcinoma and patients treated with single-agent TKI.

Pre-treatment patient characteristics and laboratory data were collected. Demographic, clinical, and pathological data were also collected. Patients were characterised according to IMDC prognostic risk score[13].

Endpoints

The primary endpoint was bone disease control rate (DCR) according to BM location (spinal column, sacrum, long bones). Bone DCR was defined as the percentage of patients with partial or complete response or stable disease on bone over the study period. DCR was reviewed and confirmed by a medical oncologist and an expert GU radiologist (RLC). The secondary endpoints included bone DCR according to BM number (1, 2-5, >5), and assessment of bone modifications (reconstruction, condensation). All data were exclusively obtained retrospectively, with no procedure taken to recover unavailable data by contacting healthcare providers or patients.

Statistical analysis

Descriptive statistics were utilised to summarize patient demographics, clinical characteristics, and treatment patterns. Categorical variables were expressed as frequency and percentage, and continuous variables as mean and standard deviation or median and range.

Results

Between May 2015 and May 2023, we identified 38 patients with bone metastatic RCC. The median age was 64 years old (range 43-92), and 26 patients (68%) were male. The IMDC score distribution was: 2 favourable (6%), 18 intermediate (47%), and 18 poor (47%) risk patients. Nineteen patients (50%) received an ICI-ICI combination, 17 patients (45%) ICI-TKI and 2 patients (5%) IO alone. Twenty-seven pts (71%) had spinal column metastases, 20 pts (53%) had sacrum metastases and 17 pts (45%) had long bone metastases. Fifteen pts (39%) had 1 BM, 15 pts (39%) had 2-5 BMs and 8 pts (22%) had >5 BMs (Table 1). Sixteen patients (42%) received local treatment of at least one metastatic site. The most frequent was radiotherapy for 6 patients (38%) (Table 1). No patient received specific bone-directed therapy.

Table 1: Patient characteristics

Characteristics	Number of patients, n (%)
Median age, years (range)	64 (43-92)
Gender	
Male	26 (68)
Female	12 (32)
IMDC	
Favourable	2 (6)
Intermediate	18 (47)
Unfavorable	18 (47)
Other sites of metastasis	
Lymph node	20 (54)
Lung	19 (51)
Liver	7 (19)
Treatment	
ICI + ICI	19 (50)
ICI + TKI	17 (45)
ICI alone	2 (5)
Local therapy	16 (42%)
Radiotherapy	6 (38%)
Interventional radiology	5 (31%)
Surgery	4 (25%)

ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor

Overall efficacy

Overall, the DCR for systemic therapy was 68%. Among the 38 patients, 3 patients (8%) achieved a partial response, and 6 patients (16%) achieved a complete response. Nine patients (24%) had progressive disease, and 20 patients (52%) had stable disease as the best response. In total, the ORR was 24%. Regarding the ORR by type of combination, the bone objective response rate was 21% for patients treated with ICI-ICI and 24% for those treated with ICI-TKI.

Efficacy according to BM locations

Out of the 27 patients with spinal column metastases, 4 patients (15%) achieved a CR, 1 patient (4%) had a partial response (PR) and 13 patients (48%) had stable disease (SD). Overall, the DCR was 67% and the ORR was 19%. Out of the 20 patients with sacrum metastases, 3 patients (15%) had a complete response (CR), 2 patients (10%) had a PR and 9 patients (45%) had SD. Overall, the DCR was 70% and the ORR was 25%.

Out of the 17 patients with long bone metastases, 2 patients (12%) had a PR and 10 patients (59%) had SD. Overall, the DCR was 71% and the ORR was 12% (Table 2).

Table 2: Efficacy according to BM sites

	Spinal column N = 27	Sacrum N = 20	Long bones N = 17
CR, n (%)	4 (15)	3 (15)	0 (0)
PR, n (%)	1 (4)	2 (10)	2 (12)
SD, n (%)	13 (48)	9 (45)	10 (59)
PD, n (%)	9 (33)	6 (30)	5 (29)
DCR, n (%)	18 (67)	14 (70)	12 (71)

CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; DCR, disease control rate

Efficacy according to the number of BM

Out of the 15 patients with 1 BM, 4 patients (27%) achieved a CR, 1 patient (7%) had a PR and 9 patients (59%) had SD. Overall, the DCR was 93%.

Out of the 15 patients with 2-5 BMs, 2 patients (13%) had a CR, 2 patients (13%) had a PR and 8 patients (53%) had SD. Overall, the DCR was 80%.

Out of the 8 patients with >5 BMs, 3 patients (37%) had SD as the best response. Overall, the DCR was 37%.

Bone modifications

Eleven patients (29%) developed bone condensation and/or bone reconstruction with a median time to onset of 4.3 months. No patient with bone condensation failed to respond to immunotherapy. With a median follow-up of 45.8 months, only one patient with bone modifications progressed on bone.

Complete responders

A total of 6 patients had a complete bone response. The median age was 57 years (44-75). The IMDC score distribution was: 2 intermediate (33%) and 4 poor (67%) risk patients, respectively. Four patients (67%) received an ICI-ICI combination, 2 patients (33%) IO-TKI. Four patients (67%) had spinal column metastases, and 3 patients (50%) had sacrum metastases. Four patients (67%) had 1 BM, and 2 patients (33%) had 2-5 BMs (Table 3). Three patients (50%) received local treatment for at least one bone metastasis. The median duration of CR was 57 months (8-101). All patients had bone modifications.

Table 3: Complete responder characteristics

Characteristics	Number of patients, n (%)
Median age, years (range)	57 (44-75)
IMDC	
Favourable	0 (0)
Intermediate	2 (33)
Unfavorable	4 (67)
Sites of bone metastases	
Spinal column	4 (67)
Sacrum	3 (50)
Long bones	0 (0)
Treatment	
ICI + ICI	4 (67)
ICI + TKI	3 (33)
Local therapy	3 (50%)
Radiotherapy	1(17%)
Interventional radiology	1 (17%)
Surgery	1 (17%)

ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor

Discussion

BM in RCC

In the present study, we found that bone response in mCRC treated with ICI-based therapy appears to be a response according to RECIST v1.1. BMs occur in approximately one-third of mRCC patients1 and their prevalence is increasing with the advent of new treatments that prolong patients' outcomes. The presence of BM is associated with poor prognosis, particularly depending on the location and number of BM[6]. Understanding the efficacy of current treatments for BM in mRCC is crucial for improving patient outcomes.

Immune microenvironment and BM

Understanding the bone immune microenvironment is essential for enhancing the efficacy of tumour immunotherapy. As highlighted by Jiang et al., the immune microenvironment significantly influences the response to immunotherapies. By thoroughly understanding these interactions, we can develop more precise and effective therapeutic strategies, overcoming current challenges related to treatment resistance and variable clinical responses[14].

Effectiveness of systemic treatment on BM

During the TKI era, a retrospective study

of 188 patients suggested a poor prognosis for patients with BM compared to those without BM. Currently, the first-line treatment for advanced ccRCC is based on anti-PD1 combinations[7–10]. The CheckMate 9ER study assessed Nivolumab and Cabozantinib, showing improved overall survival with a hazard ratio (HR) of 0.64 (95% CI 0.39-1.06) in patients with BM 12. Similarly, the CLEAR study demonstrated the benefit of Pembrolizumab and Lenvatinib in first-line treatment, with a sub-group analysis showing improved outcomes for patients with bone metastases[11]. In our study, there was no significant difference in the overall response rate between ICI-ICI and ICI-TKI combinations, though the sample size was small.

Specific bone-directed therapy

In our study, no patient received specific bone-directed therapy. BTAs have prospectively shown survival benefits and reduced skeletal-related events (SREs) in several cancer types[15–17]. However, in mRCC, available data on BTAs are based on retrospective studies from the antiangiogenic TKI era, which reported an increased risk of adverse events, particularly osteonecrosis of the jaw (ONJ), without a benefit on overall survival (OS)[18,19]. Few data are available in the immunotherapy era. The Phase II NIVOREN study investigating nivolumab and post-anti-angiogenic TKI failure suggested that the combination of BTAs with ICI may decrease the incidence of SREs without increasing the risk of ONJ[20].

Bone modifications

Our data suggest that early bone modification seems to correlate with a sustained bone response. Nakata et al. reported in lung cancer that osteosclerotic changes were associated with a favourable prognosis[21]. This finding highlights the potential importance of early bone response in predicting long-term outcomes.

The main limitations of our study are its single-centre, retrospective design and the small number of patients, which precluded survival analyses.

Conclusion

The bone response in mRCC treated with immune checkpoint inhibitors (ICI) appears to align with RECIST v1.1 criteria and is influenced by the number of bone metastases at baseline. Furthermore, the early appearance of sclerotic bone changes seems to correlate with a favourable bone response. Prospective studies are necessary to confirm these findings and to further elucidate the mechanisms behind bone response in mRCC patients undergoing ICI treatment.

Conflict of interest

Fabien Moinard-Butot certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: F. Moinard-Butot has served in advisory roles for BMS. RL. Cazzato has received travel and accommodation expenses from Medtronic, Ipsen and QUANTUM SURGICAL. L. Pierard has received travel and accommodation expenses from Ipsen, Johnson & Johnson, Pfizer, Eli lilly and company, MUNDI PHARMA. M. Burgy has served in advisory roles for Lilly; reports speaker services for BMS and MSD; has received travel and accommodation expenses from Pfizer, Ipsen and MUNDIPHARMA. G. Malouf has served in advisory roles for BMS, MSD and Ipsen; has received travel and accommodation expenses from MSD, Ipsen and BMS. P. Barthélémy has served in advisory roles for Amgen, Astellas, Bayer, BMS, Ipsen, Janssen Cilag, Merck, MSD, Novartis, Gilead Sciences and Pfizer and reports speaker services for AstraZeneca and Seagen. S. Nannini, M. Pautas, G. Virbel, I. Menoux, C. Schuster, C. Roy, P. Boudier have any conflicts of interest.

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Real-world experience of adjuvant pembrolizumab in resected renal cancer

Author

L. James[1], K. Thompson[2], G. Clements[2], A. Clayton[2], S. Slater[1], B. Venugopal[1,3], C. Forde[2], M. Randhawa[1]

Affiliation

1. Beatson West Of Scotland Cancer Centre, G120YN, Glasgow; UK. 2. Northern Ireland Cancer Centre, Belfast City Hospital, BT97AB, Belfast, UK; 3. University Of Glasgow, G128QQ, Glasgow, UK

Corresponding author

Liao James, lijo.james@nhs.scot

Abstract

Introduction: Pembrolizumab is the only adjuvant treatment demonstrating improvements in disease-free and overall survival in patients post-nephrectomy for clear cell renal cell carcinoma. We assess the real-world experience in the Beatson West of Scotland Cancer Centre and Northern Ireland Cancer Centre, since its approval in October 2022 by SMC and NICE.

Methods: Electronic medical records of eligible patients were reviewed between October 2022 and December 2023. Data on patient demographics, pathology, multidisciplinary team meeting (MDT) discussion, rates and reasons for declining treatment and toxicity was collected.

Results: 166 patients were identified at MDT as being eligible for adjuvant pembrolizumab based on pathology as per Keynote-564 inclusion criteria. 92.6% were intermediate-high risk with 7.9% having sarcomatoid features. 149 patients (89.8%) were reviewed in the oncology clinic, with 17 not referred, mainly due to co-morbidities felt to preclude adjuvant immunotherapy. 80 patients (48.1%) proceeded to adjuvant treatment (69 on pembrolizumab and 11 on a clinical trial). Reasons for the 67 pts not proceeding, included patient choice (n=27), co-morbidities (n=29) and metastatic disease on postoperative imaging (n=13). Immune-related adverse events (irAE) of any grade have occurred in 59 patients (85.5%) with grade 3 or 4 events occurring in 5 (7.2%). Steroids have been required in 13 patients (18.8%) and 6 (8.6%) have required hospitalisation for irAE. Treatment discontinuation due to adverse events has occurred in 13 patients (18.8%). 51 patients continue on pembrolizumab with 5 to date having completed the one-year course.

Conclusion: Our real-world experience demonstrates the majority of patients eligible for adjuvant pembrolizumab based on pathology are reviewed by an oncologist for discussion. Approximately half of patients proceed with adjuvant treatment. The adverse event profile, steroid use and discontinuation rates are comparable to date with the Keynote-564 data.

Introduction

Pembrolizumab is an immune checkpoint inhibitor used to treat various malignancies. It is a selective monoclonal antibody that inhibits programmed cell death (PD-1) and activates the T cell response. In the setting of renal cancer, pembrolizumab was first used in combination with axitinib as the standard first-line treatment for metastatic or advanced renal cancer.

The KeyNote 426 trial showed significant improvements in progression-free and overall survival.[2] More recently, the Keynote 564 trial has demonstrated its use in the adjuvant setting. This landmark phase 3 trial randomised patients to pembrolizumab 200 mg 3 weekly intravenously or placebo and showed that adjuvant pembrolizumab improved disease-free and overall survival in patients with renal cancer.[1,7]

Pembrolizumab is the only adjuvant immune checkpoint inhibitor recommended for post-nephrectomy patients who fit the inclusion criteria. The inclusion criteria for the Keynote 564 trial were age 18 years or above, histologically confirmed clear cell locoregional renal cell cancer, nephrectomy, and high risk of recurrence. A high risk of recurrence is defined as a stage 2

tumour with nuclear grade 4 or sarcomatoid differentiation or stage 3 tumour or higher, regional lymph node metastasis, or stage M1 with NED, whereas M1 NED (No Evidence of Disease on postoperative scans) is defined as resection of primary tumour and solid, isolated, and soft tissue metastasis.[1,7]

We assessed the real-world experience at the Beatson West of Scotland and Northern Ireland Cancer Centre, since approval in October 2022 by both the Scottish Medicines Consortium and the National Institute for Health and Care Excellence. The main study objective was to assess our experience with adjuvant pembrolizumab in resected renal cancer as there is a paucity of real-world evidence of adjuvant pembrolizumab given the recent approval.

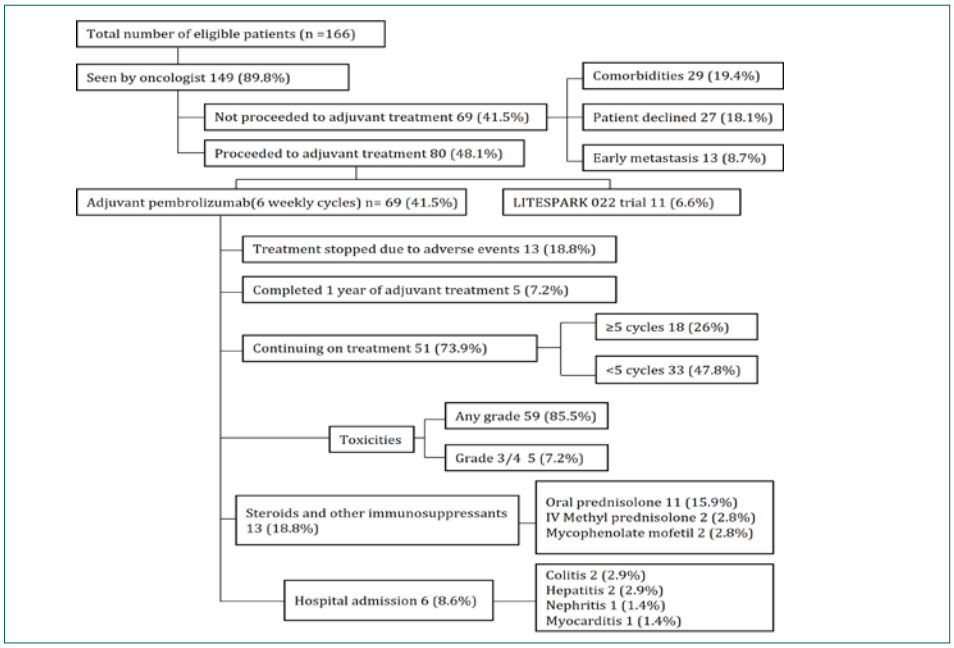
Methods

The electronic medical records of eligible patients were reviewed between October 2022 and December 2023. All patients were discussed at the multidisciplinary team (MDT) meeting, and those deemed eligible based on histopathological results according to the inclusion criteria of the KeyNote 564 trial were included. Data on demographic characteristics, pathology, reasons for not proceeding to treatment and toxicity were collected. Patients in adjuvant trials were excluded from the review. Since this is a retrospective audit, informed consent was not obtained and does not require an IRB review of the protocol.

Results

The data cutoff was December 19, 2023, for the final analysis and the median follow-up was 5.5 months. A total of 166 patients were identified as eligible for adjuvant pembrolizumab. Of these, 151 had intermediate-to-high-risk disease (92.6%), (5.4%) had high-risk disease, and 1.8% had M1NED. Sarcomatoid features were present in 7.9% of the cohort. 44% of patients with high-risk disease proceeded to adjuvant treatment or clinical trials, whereas 49% of intermediate-high-risk patients proceeded to adjuvant treatment including clinical trials.149 patients (89.8%) were reviewed in the oncology clinic, with 17 patients not being referred from the MDT, mainly due to comorbidities felt to preclude adjuvant immunotherapy by the clinicians present in the MDT. 80/166 patients (48.1%) proceeded to adjuvant treatment (69 on pembrolizumab and 11 on a clinical trial). 69 patients who were reviewed and did not proceed with adjuvant pembrolizumab, reasons included patient choice (n=27), comorbidities (n=29), and metastatic disease on postoperative imaging (n=13) (Figure).

Figure. Consort Diagram[1,7]



The median age of patients proceeding to adjuvant pembrolizumab (n=69) was 61 years, and the male-to-female ratio was 2:1 (46 male and 23 female patients). In the patients who proceeded to adjuvant pembrolizumab, 63 (91.3%) had intermediate-high-risk disease, 4 (5.7%) had high-risk disease, and 2 (2.8%) had M1NED (Table 1).

Eight (11.5%) patients had sacramatoid features in the tumour pathology.

Table 1. Studies assessing Sars-Cov-2 vaccine immunogenicity in patients with chronic plaque psoriasis.

Patient Characteristics	Patients who proceeded to adjuvant pembrolizumab treatment (n=69)	Patients who did not receive any or pembrolizumab adjuvant treatment including clinical trials (n=86)
Median age, years	61	68
≥65, n (%)	27 (39.1)	54 (62.7)
Male sex, n (%)	46 (66.6)	52 (60.4)
Female sex, n (%)	23 (33.3)	34 (39.5)
Sarcomatoid features, n (%)	8 (11.6)	3 (3.4)
Disease risk category, n (%)		
M0, intermediate-to-high risk	63 (91.3)	80 (93)
M0, high risk	4 (5.7)	5 (5.8)
M1 NED	2 (2.8)	1 (1.1)
T stage, n (%)		
pT2	none	2 (2.3)
pT3	67 (97.1)	84 (97.6)
pT4	2 (2.8)	none

Immune-related adverse events (irAEs) of any grade occurred in 59 patients (85.5%) with grade 3 or 4 events occurring in 5 (7.2%) (Table 2). High-dose steroids were required in 13 patients (18.8%), and 6 (8.6%) patients required hospitalisation for immune-related adverse events. Treatment discontinuation due to adverse events occurred in 13 patients (18.8%). 51 patients continue on pembrolizumab, with five to date having completed 12 months of treatment. None of the patients had disease progression while on treatment or shortly after discontinuation.

Table 2. Adverse events in patients treated with adjuvant pembrolizumab[1,7]

Immune related AEs, n (%)	
Any grade	59 (85.5%)
Grade 3 or 4	5 (7.2%)
Common irAEs (Any grade), n (%)	
Fatigue	30 (43.4%)
Thyroid dysfunction	19 (27.5%)
Pruritus	13 (18.8%)
Rash	12 (17.4%)
Arthralgia	12 (17.4%)
Diarrhoea	12 (17.4%)
Nephritis	3 (4.3%)
Increase in blood creatinine level	3 (4.3%)
Colitis	2 (2.9%)
Hepatitis	2 (2.9%)
Constipation	2 (2.9%)
Pneumonitis	1 (1.4%)
Myocarditis	1 (1.4%)
Polymyalgia rheumatica	1 (1.4%)

AE, adverse event; irAE, immune-related adverse event

Discussion

The Keynote 426 trial showed that patients with resected renal cancer benefit from adjuvant pembrolizumab. There are a few other trials in this setting, including CheckMate 914, IMmotion010, and PROSPER does not show any survival benefits and none of these trials met its primary endpoint. Checkmate 914 assessed the role of a combination of ipilimumab and nivolumab in an adjuvant setting in patients with localised renal cell carcinoma and it did not reach its primary endpoint of disease-free survival.[5] In the IMmotion010 trial, adjuvant atezolizumab also showed no improvement in disease-free survival when compared with placebo whereas in the PROSPER trial which compared the outcomes of nephrectomy versus giving a single dose of nivolumab before surgery and nine doses after surgery with observation. This trial also showed no disease-free survival benefit at interim analysis.[4,6]

In the KeyNote 564 trial, a total of 496 patients were randomly assigned to receive adjuvant pembrolizumab and 498 patients to receive placebo. Pembrolizumab was administered at a dose of 200mg every 3 weeks for up to 17 cycles (approximately 1 year).[1,7] In our real-world data only 69 patients received adjuvant pembrolizumab and this was given at a dose of 400mg every 6 weeks for a total of 9 cycles.

The reason we adopted 6 weekly dosing is that studies have shown similar safety and efficacy as three weekly dosing.[3] It is easier for patients to have 9 cycles versus 17 in terms of travel and parking at oncology departments, clinic visits, and local blood tests. In terms of dealing with a lack of capacity and staffing issues within most UK oncology departments, 6 weekly infusions are hugely advantageous and have made the clinical workload of absorbing adjuvant pembrolizumab manageable.

In our study, only half of the patients discussed at MDT proceeded to adjuvant pembrolizumab and therefore, as numbers are likely to increase in future as patient groups become more aware and accepting of adjuvant pembrolizumab, oncology teams will need to adapt to this increased workload. For example, they may need to consider separating adjuvant and metastatic patients such as adjuvant NMP (non-medical prescribing) clinics.

There is a 12-week window from nephrectomy to starting adjuvant pembrolizumab. During this time patient cases need MDT discussion of pathology and post-surgery CT. Due to the delays in getting CT scans, some patients met the oncologists to discuss adjuvant pembrolizumab prior to getting their CT results. Our data show that 18.8 % of patients had already progressed on CT scans prior to starting adjuvant pembrolizumab. We know this is an incredibly stressful time for patients and is made worse by discussing the likelihood of adjuvant pembrolizumab and then being told they will be starting palliative SACT (systemic anti-cancer treatment) instead. Therefore, it is essential that the adjuvant pathway is streamlined from MDT meetings so that the post-operative CT scan is done before the first oncology appointment. However, we recognise that radiology departments are under huge pressure and this is not always possible. Furthermore, with the advent of clinical trials looking at mRNA vaccines for adjuvant renal patients the strict timelines will become even more crucial and therefore, maximum effort will need to be made to streamline the MDT meeting process and adjuvant service. Therefore, an adjuvant lead oncologist may need to be considered in future.

In our cohort, patients were selected for adjuvant pembrolizumab according to KeyNote 564 inclusion criteria and the patient demographics including median age and M:F (male to female ratio) were comparable. In the phase 3 trial, 86.1% of patients had M0, an intermediate-to-high-risk pathology compared to 92.6% in our cohort. There were fewer patients with high-risk disease or in the M1NED group compared to the trial population. A total of 1,406 patients were screened for the phase 3 trial with 412 patients being excluded. The most common reason was the presence of baseline disease at the time of screening (37.9%).[1,7] From our data the most common reason for not proceeding with adjuvant treatment was patient choice and the main reason behind this was concerns about toxicities of treatment. The next common reason for exclusion from treatment was comorbidities. The most common comorbidity that precluded treatment was poor renal function.

As adjuvant treatment is a new concept in renal cancer, oncologists would not have previously met patients with renal cancer at this stage in their treatment and it would be their surgeons explaining their risk of recurrence. Anecdotally, it was noted that some patients meeting the oncologists to discuss adjuvant pembrolizumab were not aware of their percentage of risk of recurrence after nephrectomy and they were expecting a lower risk of recurrence. In future studies, we are interested in investigating patients' understanding of the high and intermediate risk of renal cancer, how surgical teams discuss this with patients

and whether the risk of recurrence is one of the main determining factors in accepting adjuvant systemic anti-cancer treatment. Furthermore, whether the arrival of adjuvant immunotherapy has changed the discussions between surgeons and patients about the risk of renal cancer recurrence.

In the Keynote 564 trial, the most common toxicity was fatigue (29.75) followed by diarrhoea (25.4%).[1,7] Our data also showed fatigue as the common side effect which was reported by 43.4% of patients, followed by thyroid dysfunction (27.5%). Twelve (17.3%) patients were started on levothyroxine. Pruritis (18.8%) and rash (17.4%) were also common toxicity in our cohort, which is comparable to trial data where 22.7% and 20.1% respectively.[1,7] Treatment-related adverse events of any grade in patients who received adjuvant pembrolizumab as assessed by the investigator in the trial was 79.1% and Grade 3 to 5 was 18.9%.[1,7] Our data showed that 85.5% of patients had experienced toxicities of any grade and grade 3 or 4 toxicities occurred in 7.2% of patients. Discontinuation of pembrolizumab due to adverse events occurred in 7.6% of patients in the trial whereas 18.8% in our patients.

Our data showed that a majority of patients are continuing on treatment and only five patients had completed a year of adjuvant treatment. The median follow-up was also only 5.5 months which was short and a longer duration of median follow-up is needed for accurate comparison. We know that immunotherapy side effects can occur late in treatment so we accept that our toxicity data is premature and will continue to collect this data. We will also collect data on not only steroid usage and type of toxicity but also medical speciality referrals, as we continue to learn that immunotherapy can result in multi-system toxicities that often involve medical expertise. Furthermore, toxicities can be lifelong for example endocrine abnormalities, which is an essential consideration when consenting adjuvant patients for immunotherapy.

Nearly a fifth of our cohort of patients did not complete their 9 cycles of pembrolizumab and therefore, we will have to consider guidelines for when we refer these patients back for surgical surveillance. While patients are on pembrolizumab under oncology surveillance the frequency of CT scans tends to be every 3-4 months whereas, surgical surveillance is routinely every 6 months. For patients completing 9 cycles, they are referred back to the surgical follow-up within 6 weeks of the last infusion. It is recognised that patients with significant immunotherapy toxicity may require more clinical reviews than surgical surveillance and are likely to stay under oncology review for longer. Most large cancer centres are developing immunotherapy toxicity clinics and MDT meetings, and all centres will likely need to consider developing these.

Conclusion

Our real-world experience demonstrates that the majority of patients eligible for adjuvant pembrolizumab based on pathology are reviewed by an oncologist for discussion. Approximately 50% of patients proceed with adjuvant treatment. The early adverse event profile, steroid use, and discontinuation rates are comparable to date with the Keynote-564 data. The majority of patients are still undergoing treatment, and the data is premature so further follow-up is required. The advent of adjuvant treatment for renal cancer is an exciting time to learn invaluable lessons about streamlining MDT decision-making and treatment pathways especially when considering mRNA vaccine trials are now underway. While our real-world experience of adjuvant pembrolizumab mirrors the KEYNOTE-564 trial, there are constraints in this study including a limited sample size, a shorter follow-up period, and a small number of patients finishing the treatment. Further follow-up is necessary.

Conflict of interest

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Fumarate hydratase-deficient renal cell carcinoma

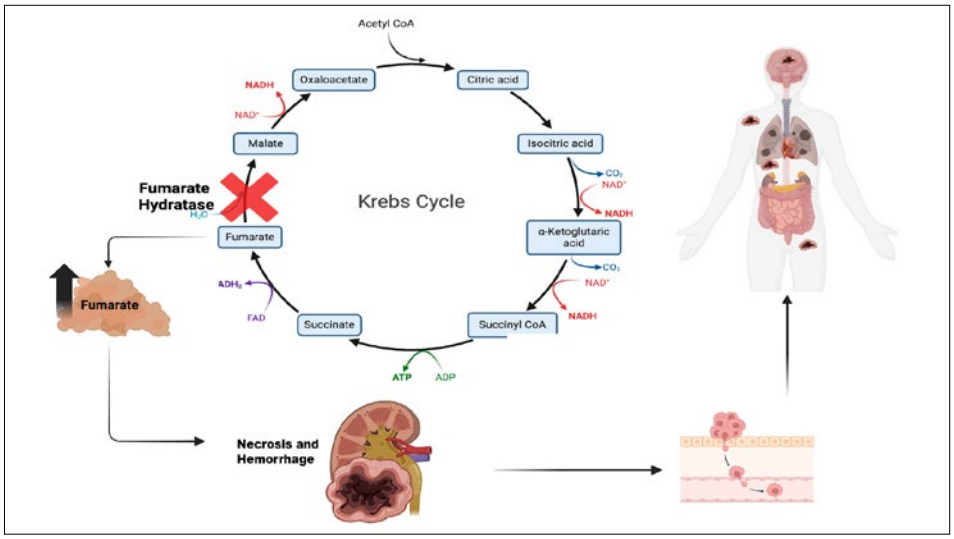
Author
Y. Ürün
Affiliation
Ankara University School of Medicine, Department of Medical Oncology; Cebeci Hospital, TR-06590, Dikimevi, Ankara, Türkiye
Corresponding author
Yüksel Ürün, MD, yuksel.urun@ankara.edu.tr

Abstract
Fumarate Hydratase (FH)-deficient renal cell carcinoma (RCC) is a rare, aggressive subtype linked to hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome. It predominantly affects middle-aged adults, with a higher prevalence in males. Patients often present with advanced disease, showing symptoms such as flank pain, hematuria, and abdominal pain. Radiologically, these tumours are large, unilateral, and cystic. Pathologically, they display varied architectural patterns and prominent eosinophilic nucleoli. FH-deficient RCC is driven by FH gene mutations leading to fumarate accumulation, promoting tumorigenesis through metabolic reprogramming and epigenetic changes. Management includes radical nephrectomy for localised disease and combination therapies like bevacizumab and erlotinib for metastatic cases. Further research is needed to develop effective treatments and improve early detection through genetic screening.

Highlights
1. FH-deficient RCC is an aggressive renal cancer subtype linked to HLRCC syndrome and FH gene mutations.
2. Common symptoms include flank pain, hematuria, and abdominal pain, often presenting with advanced disease.
3. Radiological features include large, unilateral, cystic tumors with infiltrative margins.
4. Pathological characteristics involve varied patterns and prominent eosinophilic nucleoli, driven by fumarate accumulation.
5. Treatment includes radical nephrectomy for localised cases and combination therapies like bevacizumab and erlotinib for metastatic disease.

Introduction
Renal cell carcinoma (RCC) is the most common type of kidney cancer. It makes up about 90% of all kidney cancers. There are three main types: clear cell RCC (ccRCC), which is about more than 70-75% of cases; papillary RCC (pRCC), which is 10-15%; and chromophobe RCC (chRCC), which is around 5%. RCC cases are increasing globally, with an estimated 434,000 new cases and 155,000 deaths in 2022[1]. This rise is mostly due to more people getting abdominal scans, which can find small kidney tumours early. Risk factors include obesity, smoking, and high blood pressure. Genetic research has found many mutations linked to RCC, helping us understand its development and find new treatments[2].
Fumarate hydratase (FH) deficiency is very important in a rare and aggressive type of RCC called FH-deficient RCC. It is related to hereditary leiomyomatosis, and renal cell carcinoma (HLRCC) syndrome caused by FH gene mutations. The FH enzyme is essential in the Krebs cycle. Without it, fumarate builds up in the body, which can lead to cancer through changes in genes and metabolism. FH-deficient RCC often shows up with advanced disease. Common symptoms are abdominal or flank pain, blood in the urine, and a palpable mass. This type of RCC usually affects younger adults, around 40-50 years old, and compared with women, it is slightly more prevalent in men[3–5]. This review aims to provide a complete overview of FH-deficient RCC, focusing on its genetic, clinical, and pathological features to improve understanding and patient care.

Figure 1. Pathogenesis of FH-deficient RCC



Epidemiology

FH-deficient RCC commonly presents in middle-aged adults. In a study of 32 patients, the median age at presentation was 43 years, ranging from 18 to 69. The male-to-female ratio was approximately 2.2:1, indicating a higher prevalence in males. Specific data on the ethnic distribution of FH-deficient RCC is limited due to its rarity. However, as with many rare genetic syndromes, it is likely underreported across various populations. The hereditary nature suggests it can affect diverse ethnic groups without a clear predisposition[6].

Clinical Presentation

FH-deficient RCC often presents with advanced or metastatic disease at diagnosis. Common symptoms include flank pain, hematuria, and abdominal pain. Patients may also have a personal or family history of uterine or cutaneous leiomyomas. This cancer subtype is aggressive, frequently showing a mix of histologic growth patterns and often presenting symptoms related to metastasis rather than a localised renal mass. Early and comprehensive diagnostic evaluation is crucial for effective management[4,6]. Despite the aggressive nature and late presentation of FH-deficient RCC, there is a growing interest in identifying biomarkers for early diagnosis. One promising candidate is S-(2-succinyl)cysteine (2SC), which accumulates due to FH deficiency and can be detected through immunohistochemistry. However, the application of 2SC as a routine diagnostic marker requires further validation. Additionally, circulating tumour DNA (ctDNA) and metabolomic profiling are being explored as non-invasive tools for early detection, though these approaches are still in the experimental stages.

Radiological Features

FH-deficient RCC exhibits aggressive radiological features. On computed tomography (CT) and magnetic resonance imaging (MRI), these tumours are typically unilateral, large, and have infiltrative margins. In many cases, they frequently contain significant cystic components, constituting more than 75% of the tumour volume. Contrast-enhanced imaging reveals heterogeneous enhancement patterns, while MRI shows heterogeneous T2 signals and diffusion restriction in solid components, indicating high cellularity.

Commonly, these tumours invade the renal sinus fat and the hilar collecting system with renal vein thrombus. F-18-Fluorodeoxyglucosepositron emission tomography (FDG PET)/CT scans demonstrate high metabolic activity, reflecting the tumour's dependence on glycolysis, a distinguishing feature from other RCC subtypes. These detailed imaging characteristics aid in the early identification and aggressive management of FH-deficient RCC[7,8].

Pathological Features

FH-deficient RCC typically displays a variety of architectural patterns, including papillary, tubular, solid, and microcystic formations. The tumours are generally unilateral and solitary, presenting with a gross appearance that ranges from light brown to whitish. Commonly, these tumours show infiltrative margins and often invade surrounding structures such as the renal sinus and perinephric fat. In some cases, sarcomatoid changes and rhabdoid features are present, contributing to the aggressive nature of the disease. A hallmark cytological feature is the presence of prominent, eosinophilic nucleoli surrounded by a clear halo resembling cytomegaloviral (CMV) inclusions.

FH-deficient RCC is associated with HLRCC syndrome, characterised by mutations in the FH gene. These mutations lead to an accumulation of fumarate, which acts as an oncometabolite, promoting tumorigenesis. The tumours often present at an advanced stage, frequently with metastases to organs such as bones, lungs, liver, and lymph nodes. Microscopically, the tumours display a range of growth patterns, often mixed within the same tumour, and commonly exhibit necrosis and haemorrhage.

Immunohistochemistry (IHC) plays a critical role in diagnosing FH-deficient RCC. Tumours typically show a loss of FH protein expression, confirmed by negative staining for FH on IHC. Additionally, detecting succinate proteins (S-(2-succinyl) cysteine, 2SC) using specific antibodies can be a robust biomarker for FH deficiency. These succinate proteins accumulate due to the loss of FH activity, and their presence is highly specific to FH-deficient tissues. IHC for 2SC has proven to be a sensitive and specific method for identifying FH-deficient RCC, even without direct genetic testing[6,9–17]. These detailed morphological, pathological, and immunohistochemical features are crucial for accurately diagnosing and managing FH-deficient RCC, distinguishing it from other RCC subtypes.

Genomic and Molecular Features

FH-deficient RCC is characterised by mutations in the FH gene, which encodes the Krebs cycle enzyme fumarate hydratase. These mutations can be germline, leading to HLRCC syndrome, or somatic in sporadic cases. Germline FH mutations are found in approximately 70-90% of individuals with HLRCC, including missense, nonsense, frameshift, and splicing variants. Notably, FH mutations result in the loss of enzymatic activity, leading to the accumulation of fumarate, an oncometabolite that promotes tumorigenesis through various pathways. The inactivation of FH in tumour cells results in a pseudohypoxic state by stabilising hypoxia-inducible factor 1-alpha (HIF-1α), which drives the transcription of genes involved in angiogenesis, glycolysis, and other pathways that support tumour growth. This metabolic shift is known as the Warburg effect, where cells rely heavily on glycolysis for energy production, even in the presence of oxygen. Accumulated fumarate can inhibit α-ketoglutarate-dependent dioxygenases, including those involved in histone and DNA demethylation, leading to epigenetic modifications that further drive cancer progression.

Molecular diagnostics for FH-deficient RCC include genetic testing for FH mutations and IHC staining for FH protein. Loss of FH protein expression in tumours is indicative of FH deficiency. Additionally, S-(2-succinyl) cysteine (2SC), a byproduct of fumarate accumulation, is a specific biomarker for FH-deficient tumours. These diagnostic tools are critical for identifying patients with FH-deficient RCC and guiding appropriate treatment strategies[11,18–24].

Recent studies have also shown that

FH-deficient tumours exhibit upregulation of antioxidant response genes and suppression of the homologous recombination DNA repair pathway, making these cells vulnerable to specific therapeutic strategies, such as poly (ADP-ribose) polymerase (PARP) inhibitors.

FH-deficient RCC is characterised by a low somatic mutation burden but frequent somatic copy number alterations (SCNAs). Key SCNAs include losses at 1p, 8q, and 10p, and gains at 4p and 7q. FH mutations lead to epigenetic reprogramming, including a CpG island methylator phenotype (CIMP), contributing to tumorigenesis. These epigenetic alterations affect genes related to tumour suppression and DNA repair, offering potential therapeutic targets, such as immune checkpoint inhibitors and demethylating agents[12].

In summary, the genomic and molecular features of FH-deficient RCC underscore its unique pathogenesis driven by metabolic reprogramming and epigenetic alterations, providing distinct diagnostic and therapeutic opportunities.

Management of FH-Deficient RCC

The management of FH-deficient RCC often involves a multimodal approach, with radical nephrectomy being the standard for localised tumours due to their aggressive nature. Systemic therapies, including VEGF inhibitors and mTOR inhibitors, have shown varying degrees of efficacy in metastatic cases. Retrospective studies have demonstrated the potential benefit of anti-angiogenic agents. Building on these findings, current prospective trials are exploring combinations of targeted therapies and immunotherapies, offering hope for more effective treatment strategies in the future.

For localised HLRCC-associated renal tumours, the National Comprehensive Cancer Network (NCCN) guidelines recommend total radical nephrectomy due to the aggressive nature of these tumours. Surveillance of renal tumours is generally not recommended. Patients with confirmed HLRCC should undergo annual MRI or CT scans of the abdomen with and without IV contrast starting at ages 8-10 years.

Srinivasan et al. conducted a phase II study investigating the combination of bevacizumab and erlotinib in patients with advanced HLRCC or sporadic pRCC. The study included subjects with histologically confirmed advanced HLRCC or sporadic pRCC, with a median age of 44 years. Participants were treated with bevacizumab (10 mg/kg every two weeks) and erlotinib (150 mg/day). The rationale for this combination is based on their complementary mechanisms: bevacizumab inhibits vascular endothelial growth factor (VEGF), thereby reducing tumour blood supply, while erlotinib targets epidermal growth factor receptor (EGFR), inhibiting tumour cell proliferation. The study reported an objective response rate (ORR) of 72% and a median progression-free survival (PFS) of 21.1 months, with the median overall survival (OS) not reached at the time of analysis. In this study, the ORR was specifically reported for patients with FH-deficient RCC. For the HLRCC group, the ORR was 72.1% (95% CI 57.2–83.4), whereas the sporadic group exhibited an ORR of 35% (95% CI 22.1–50.6). This distinction emphasizes the varying response rates between hereditary and sporadic forms of this rare cancer subtype. Treatment-related adverse events (AEs) included hypertension (64%), proteinuria (36%), diarrhoea (34%), and rash (30%), with manageable grade 3-4 toxicities. This study, presented at the 2020 ASCO Annual Meeting, demonstrates the efficacy and manageable safety profile of the bevacizumab and erlotinib combination in treating advanced HLRCC[25].

Building on the promising results from the Srinivasan et al. (ASCO 2020) study[25], a new phase II trial is evaluating the combination of bevacizumab, erlotinib, and atezolizumab in patients with advanced HLRCC-associated RCC or sporadic pRCC. This open-label, multicenter study includes adult and paediatric patients with histologically confirmed advanced HLRCC-associated or sporadic pRCC, aged ≥12 years, with an ECOG performance status ≤2. Patients with up to two prior VEGF-targeted therapies and no previous PD-1 or PD-L1 inhibitor treatment are eligible. The primary endpoint assesses the complete response rate according to RECIST 1.1, with secondary endpoints including safety, ORR, disease control rate (DCR), PFS, and OS. Key exploratory endpoints involve evaluating immunologic modulation[26]. This study is currently ongoing (NCT04981509).

A retrospective study by Choi et al. analyzed the efficacy and safety of bevacizumab plus erlotinib in Korean patients with HLRCC-associated RCC[27]. The study included 10 patients with confirmed FH germline mutations treated at three academic hospitals. The median age at diagnosis was 41 years, and the majority of patients had locally advanced or metastatic disease. Bevacizumab was administered at 10 mg/kg every two weeks and erlotinib at 150 mg/day. The ORR was 50%, with a median PFS of 13.3 months and a median OS of 14.1 months. AEs were generally manageable, though one patient experienced fatal gastrointestinal bleeding[27].

Also, there are case reports about the combination of bevacizumab and erlotinib. In one case report by Tomar et al., a 42-year-old female with FH-deficient RCC achieved extended remission using this combination. The patient, who presented with a large renal mass and multiple distant metastases, received 46 cycles of treatment over 23 months. Despite experiencing grade 3 acneiform rash and an episode of acute calculous cholecystitis, the patient's tumour showed significant regression on follow-up CT scans, and she maintained stable disease until the last follow-up[28].

Lucia Carril-Ajuria et al. conducted a retrospective study to evaluate the efficacy of different systemic therapies in patients with FH-deficient RCC[29]. The study included 24 patients from multiple centres in France and Spain, with 21 patients receiving systemic therapy. The therapies evaluated included cabozantinib, sunitinib, other antiangiogenics (sorafenib, pazopanib, and axitinib), erlotinib-bevacizumab (E-B), mTOR inhibitors (mTORi), and immune checkpoint blockers (ICBs). The ORR were 50% for cabozantinib, 43% for sunitinib, 63% for other antiangiogenics, 30% for E-B, 0% for mTOR inhibitors, and 18% for ICBs. The median time-to-treatment failure (TTF) was significantly higher for antiangiogenics (11.6 months) compared to mTOR inhibitors (4.4

months) and ICBs (2.7 months). The study concluded that antiangiogenics might be superior to ICBs and mTOR inhibitors in treating FH-deficient RCC, suggesting a preference for these therapies in managing this aggressive cancer subtype[29].

In a study by Gleeson et al., the therapeutic responses of 32 patients with FH-deficient RCC were evaluated. The mTOR and VEGF inhibitor combination demonstrated the highest efficacy, with an ORR of 44% and a DCR of 77%. Monotherapies with VEGF and mTORi had lower ORRs of 20% and 0%, respectively, and ICBs had an ORR of 0% and a DCR of 38%. Among 27 evaluable patients, the median PFS was 8.7 months, with the mTORi/VEGF combination achieving the longest median PFS at 10.7 months. For OS, 28 patients were included, showing a median OS of 21.9 months. The mTORi/VEGF combination also led to the longest median OS of 33.0 months, compared to 30.0 months for ICBs, 13.2 months for VEGF monotherapy, and 8.2 months for mTORi monotherapy. These findings highlight the mTORi/VEGF combination as an effective treatment in extending PFS and OS for patients with FH-deficient RCC[30].

Sotés et al. published another case report discussing the combination of pembrolizumab and axitinib in a patient with HLRCC. The patient, an 18-year-old male with advanced RCC, demonstrated a significant partial response after two months of therapy, with a reduction in the size of the retroperitoneal node and resolution of other metastatic lesions. This combination therapy resulted in an OS of 20 months and disease-free survival of 15 months, highlighting the potential efficacy of pembrolizumab and axitinib in managing this rare and aggressive cancer subtype[31].

A recent phase II trial led by Ritesh R. Kotecha et al. evaluated the efficacy of talazoparib and avelumab in patients with genomically defined metastatic kidney cancer, specifically including those with FH-deficient RCC. The study included eight patients in the cohort for FH- or succinate dehydrogenase (SDH)-deficient RCC, four of whom had FH-deficient RCC. These patients had previously received at least one ICB or a VEGF inhibitor. The primary endpoint was the ORR by Immune Response Evaluation Criteria in Solid Tumors at four months. No objective responses were observed in the FH-deficient RCC cohort. Two patients achieved stable disease (SD) as the best response, with a median PFS of 1.2 months and a median OS of 8.6 months. The most common treatment-related AEs included fatigue (61%), anaemia (28%), and nausea (22%). Grade 3-4 AEs were reported, but no grade 5 events occurred[18]. This study highlights the challenges in treating FH-deficient RCC, indicating that while the combination of talazoparib and avelumab is tolerable, it does not provide significant clinical benefits in this patient population.

Conclusion and discussion

This review has highlighted key aspects of FH-deficient RCC, an aggressive and rare subtype linked to HLRCC syndrome. The comprehensive analysis included epidemiological data, clinical presentation, radiological and pathological features, genomic and molecular characteristics, and various treatment responses. Significant findings include the unique metabolic reprogramming and epigenetic alterations due to FH deficiency, which drive the pathogenesis of this aggressive cancer.

FH deficiency results in the accumulation of fumarate, an oncometabolite, leading to metabolic and epigenetic changes that promote tumorigenesis. This unique pathogenic mechanism underscores the aggressive nature of FH-deficient RCC and its tendency to present at an advanced stage with a poor prognosis. Stabilising hypoxia-inducible factor 1-alpha (HIF-1α) due to FH inactivation leads to increased angiogenesis and glycolysis, highlighting potential therapeutic targets.

For localised HLRCC-associated renal tumours, the NCCN guidelines recommend total radical nephrectomy due to the aggressive nature of these tumours. Surveillance of renal tumours is generally not recommended. The combination of bevacizumab and erlotinib has shown promising results for metastatic disease. Other treatment strategies, such as mTOR/VEGF combinations, have also demonstrated efficacy, with a median OS of 33.0 months in evaluable patients. However, monotherapies and checkpoint inhibitors have shown limited success, underscoring the need for more effective treatment strategies.

Patients with confirmed HLRCC should undergo annual MRI or CT scans of the abdomen with and without IV contrast starting at ages 8-10 years. Follow-up for relapsed or stage IV disease includes physical exams every 6-16 weeks, laboratory evaluations per therapeutic requirements, and imaging every 6-16 weeks, adjusted based on disease progression and patient status.

While significant progress has been made in understanding and treating FH-deficient RCC, ongoing research and clinical trials are crucial to developing more effective and targeted therapies to improve patient outcomes. The rarity of this condition poses challenges in conducting large-scale clinical trials, highlighting the need for collaborative research efforts. Improving early detection through genetic screening and regular follow-up can potentially improve outcomes for patients with HLRCC.

Potential Areas for Future Research

- Exploring novel therapeutic targets that exploit the metabolic vulnerabilities of FH-deficient tumours.
- Developing and testing combination therapies that can effectively manage this aggressive cancer subtype.
- Conducting large-scale, multicentre trials to validate the efficacy of promising treatments and improve patient outcomes.
- Further understanding of the molecular pathways involved in FH deficiency to identify additional biomarkers for early detection and targeted therapy.

Conflict of interest

Advisory boards: Yüksel Ürün has served on the advisory board for Abdi-İbrahim, Astellas, AstraZeneca, Bristol Myers-Squibb, Deva, Eczacıbaşı, Gen ilaç, Gilead, GSK, Janssen, Merck, MSD, Novartis, Pfizer, Roche.
Travel, honoraria or consultation fees: Yüksel Ürün received honoraria or has served as a consultant for Abdi-İbrahim, Astellas, Bristol Myers-Squibb, Deva,

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Treatment of residual RCC following first-line systemic therapy

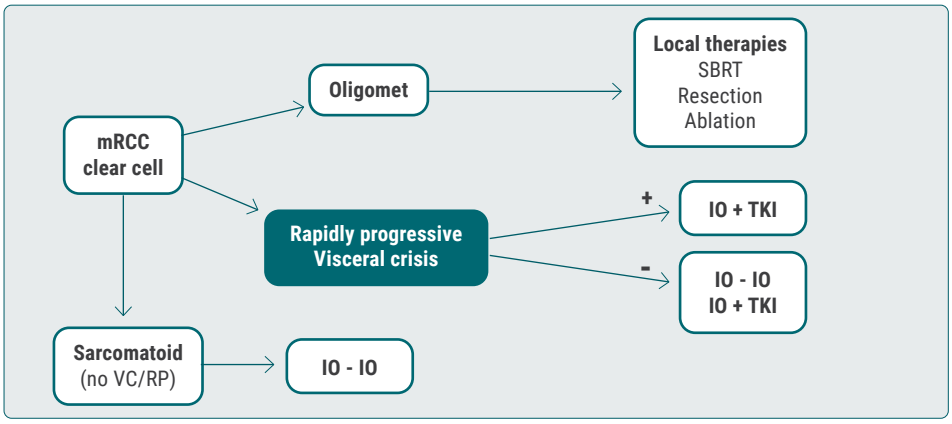
Author
Y. Ürün
Affiliation
Ankara University School of Medicine, Department of Medical Oncology; Cebeci Hospital, TR-06590, Dikimevi, Ankara, Türkiye
Corresponding author
Yüksel Ürün, MD, yuksel.urun@ankara.edu.tr

Abstract
Renal cell carcinoma (RCC) remains challenging despite advancements in VEGF TKIs and ICIs, as many patients develop residual disease after initial treatment. This review examines strategies for managing residual RCC, emphasizing the importance of addressing tumour heterogeneity and treatment resistance. Effective approaches include surgical interventions like metastasectomy and nephrectomy, and local ablative therapies such as SBRT, which have shown promising results in improving survival and quality of life. Combining these methods with systemic therapies offers the potential for long-term disease control. Addressing residual disease is crucial for optimizing patient outcomes in RCC management.

Highlights
1. Renal cell carcinoma (RCC) often leaves residual disease post-treatment.
2. Tumor heterogeneity complicates RCC management and treatment resistance.
3. Effective strategies include metastasectomy, nephrectomy, and SBRT.
4. Combining surgical, local ablative, and systemic therapies can improve outcomes.
5. Addressing residual disease is crucial for long-term control and survival.

Introduction
Renal cell carcinoma (RCC) represents approximately 90% of kidney cancer cases, making it the most common type of kidney cancer. The primary subtypes of RCC are clear cell RCC (ccRCC), papillary RCC (pRCC), and chromophobe RCC (chRCC), with ccRCC being the predominant subtype, accounting for about 75% of cases. The remaining subtypes are relatively rare[1,2].
Globally, the incidence of RCC has been rising, with an estimated 431,288 new cases in 2020. RCC is the 14th most common cancer worldwide, with higher incidence rates observed in developed regions such as Europe and North America. Men are approximately twice as likely to develop RCC as women, and the incidence increases with age[1,2].
Several risk factors contribute to the development of RCC. The most significant modifiable risk factors include smoking, obesity, and hypertension. Additionally, chronic kidney disease (CKD) and end-stage renal disease (ESRD) are known to increase the risk of RCC. Genetic predispositions, such as von Hippel-Lindau (VHL) syndrome and hereditary leiomyomatosis and RCC (HLRCC), also play a crucial role in the development of this cancer[1,3].
Advances in imaging techniques have led to an increase in the incidental detection of RCC, often before the onset of symptoms. Traditional symptoms, such as hematuria, flank pain, and a palpable mass, are now very seldom observed, occurring in less than 1% of cases, due to early detection through cross-sectional imaging[1].
Prior to 2005, cytokine therapies offered limited benefit for mRCC. The introduction of VEGF TKIs and then ICIs revolutionised treatment, leading to improved survival. Current regimens often combine ICIs, but disease progression remains common, necessitating further research for managing mRCC. Despite the effectiveness of these treatments, a significant number of patients develop residual disease, necessitating further therapeutic strategies. Understanding the biological mechanisms underlying treatment resistance and the management of residual disease is critical for improving patient outcomes[4].
The objective of this review is to provide a comprehensive analysis of the treatment options and outcomes for residual renal cell carcinoma (RCC) following first-line systemic therapy.

Figure 1. Treatment paradigm for Frontline ccRCC



Tumour heterogeneity and importance of residual disease

Tumour heterogeneity, characterised by diverse genetic and phenotypic variations within a single tumour, significantly impacts the treatment of RCC. This intratumor heterogeneity fosters tumour adaptation and resistance to therapies, complicating personalised medicine approaches that often rely on single biopsy samples. Residual disease following first-line systemic therapy presents a substantial clinical challenge, as it is frequently comprised of resistant tumour cell subpopulations. These cells can drive disease progression and metastasis, underscoring the necessity of developing effective therapeutic strategies to manage residual RCC and improve patient outcomes[5,6].

The evolution of clear cell RCC is predominantly characterised by the early loss of chromosome 3p, leading to the inactivation of key tumour suppressor genes such as VHL, PBRM1, SETD2, and BAP1. Distinct evolutionary trajectories have been identified: linear evolution with few driver events, branched evolution with high intratumor heterogeneity (ITH), and punctuated evolution with bursts of multiple mutations. Tumours with low ITH and low genomic instability exhibit low metastatic potential, whereas those with low ITH but high somatic copy-number alterations (SCNAs) show rapid, widespread metastasis[6].

A decade ago, the study by Gerlinger et al. highlighted the importance of tumour heterogeneity in RCC[5]. Intratumor heterogeneity can lead to underestimation of the tumour genomics landscape portrayed from single tumour-biopsy samples and may present major challenges to personalised medicine and biomarker development. Intratumor heterogeneity, associated with heterogeneous protein function, may foster tumour adaptation and therapeutic failure through Darwinian selection. The study also revealed "branching evolutionary tumour growth, with 63 to 69% of all somatic mutations not detectable across every tumour region, emphasizing the complexity of treating RCC due to its genetic diversity[5].

First-line systemic therapies for RCC

The NCCN guidelines for metastatic renal cell carcinoma (RCC) recommend a multifaceted approach, including cytoreductive nephrectomy for select patients and systemic therapy as primary treatment[7]. For clear cell histology, preferred first-line regimens include combinations such as axitinib with pembrolizumab, cabozantinib with nivolumab, and lenvatinib with pembrolizumab. Ipilimumab combined with nivolumab is also highly recommended. In cases where tumours are unresectable, systemic therapy options are prioritised. Best supportive care, including palliative radiation therapy and bisphosphonates or RANK ligand inhibitors for bony metastases, is essential for managing symptoms and improving quality of life[7]. (Table 1)

Residual disease in mRCC represents a critical challenge in the management of this malignancy, particularly following initial systemic therapies. Despite advancements in immunotherapy-based combinations that have significantly improved

Table 1. First-line combination Phase III trial

	CheckMate 214 Nivo-Ipi vs SUN n=550 vs n=546	KEYNOTE-426 Pembro-Axi vs SUN n=432 vs n=429	CM-9ER Nivo-Cabo vs SUN n=323 vs n=328	CLEAR Pembro-Lenva vs SUN n=355 vs n=357
Reference	Tannir NM et al[8]	Rini BI et al.[9]	Bourlon MT et al.[10]	Motzer RJ et al.[11]
Med flu, months	96	67	55	48
OS HR	0.72	0.84	0.77	0.79
mOS, months	52.7 vs 37.8	47.2 vs 40.8	46.5 vs 36.0	53.7 vs 54.3
Landmark OS	70% at 24 months	63% at 3 years	59% at 3 years	66% at 3 years
	35% at 90 months	42% at 5 years	49% at 4 years	
PFS HR	0.88	0.69	0.58	0.47
mPFS, months	12.4 vs 12.3	15.7 vs 11.1	16.4 vs 8.4	23.9 vs 9.2
Landmark PFS	37% at 24 months 23% at 90 months	29% at 3 years 18% at 5 years	23% at 3 years	37% at 3 years
ORR, %	39 vs 32	61 vs 40	56 vs 28	71 vs 37
CR, %	12 vs 3	2 vs 4	13.6 vs 4.6	18 vs 4
Primary PD, %	18 vs 14	12 vs 17	6.5 vs 13.7	5 vs 14
Favourable, OS, HR	0.82	1.1	1.10	0.94
Favourable, PFS, HR	1.76	0.76	0.69	0.50
Sarcomatoid, OS, HR	0.46 (0.29-0.71)	0.58 (0.21-1.59)	0.36 (0.17-0.79)	
Sarcomatoid, PFS, HR	0.50	0.54	0.42	

CR, complete response; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PD, partial disease; PFS, progression-free survival.

response rates, a considerable proportion of patients still exhibit residual disease post-treatment. This residual disease can be a source of ongoing morbidity and potential mortality, highlighting the necessity for additional therapeutic strategies aimed at achieving complete response[12].

Addressing residual disease is crucial for several reasons:

1. **Prognostic Implications**: The presence of residual disease often correlates with poorer overall survival and progression-free survival outcomes. Patients with residual disease after initial treatment typically have a higher risk of recurrence and metastasis, necessitating closer monitoring and more aggressive subsequent treatments.
2. **Therapeutic Optimization**: Understanding the biology and behaviour of residual disease can inform the development of more targeted and effective therapies. This may include the use of novel agents or combination therapies specifically designed to eradicate residual tumour cells that are resistant to initial treatment.
3. **Quality of Life**: Reducing or eliminating residual disease can significantly improve the quality of life for patients. Residual disease can lead to symptoms such as pain, organ dysfunction, and other complications, which can be mitigated through effective treatment strategies.
4. **Research and Development**: Studying residual disease provides valuable insights into the mechanisms of resistance to current therapies. This knowledge can drive the development of next-generation treatments and contribute to the overall advancement of cancer therapy.

In summary, the treatment of residual disease in mRCC is a critical component of patient management that has significant implications for survival, quality of life, and the development of future therapeutic approaches. Addressing this challenge requires ongoing research, innovative treatment strategies, and a comprehensive understanding of the underlying tumour biology[12–14].

According to the study by Fabien Moinard-Butot et al. presented at ASCO GU 2023, treating residual disease in metastatic renal cell carcinoma (mRCC) significantly improves patient outcomes. Out of 80 patients initially treated with systemic therapy, 12 (15%) had progressive disease, 23 (29%) had stable disease, 36 (45%) had a partial response, and 9 (11%) achieved complete response. Following additional treatment for residual disease, the complete response rate increased to 24%, with 19 patients achieving complete response. This approach not only enhanced overall survival by converting partial and stable responses to complete responses but also improved quality of life by better management of symptoms. Local treatments included nephrectomy (n=4), nephrectomy with retroperitoneal lymph node dissection (n=2), lung resection with mediastinal lymph node dissection (n=1), lung resection (n=1), mediastinal lymph node dissection (n=1), liver microwave ablation (n=1), and retroperitoneal lymph node dissection (n=1). Viable renal cell carcinoma was confirmed in 7 out of 10 patients who underwent resection. Patients with systemic and local treatments had a median follow-up of 54.3 months, with significant improvements in progression-free survival and quality of life. The median time from the start of systemic treatment to the treatment of residual disease was 19.1 months (7.7-37.1 months). These findings highlight the critical role of addressing residual disease to optimize therapeutic outcomes in mRCC patients[12].

Therapeutic strategies for residual RCC

Therapeutic strategies for residual renal cell carcinoma (RCC) include a combination of surgical interventions, local ablative therapies, systemic treatments, and emerging approaches. Surgical options such as nephrectomy, lung resection, and lymph node dissection are employed to remove the primary tumour and metastatic sites, reducing the tumour burden. Local ablative therapies like radiofrequency ablation, cryoablation, and stereotactic body radiation therapy (SBRT) target specific areas of residual disease to destroy cancer cells. A multidisciplinary approach, involving regular tumor board discussions and continuous monitoring, ensures individualised and adaptive treatment plans, ultimately improving patient outcomes and quality of life.

In an earlier study conducted by Alt et al., metastasectomy significantly improved survival outcomes for patients with mRCC15. The study showed that complete surgical resection of metastases increased the median cancer-specific survival (CSS) to 4.8 years, compared to 1.3 years for those without complete resection. The 5-year CSS rate was notably higher at 49.4% for patients who had complete metastasectomy, versus 13.9% for those who did not. Despite these encouraging results, it is important to note that very few patients in the study received the treatment options available today[15].

In the study by Lyon et al., the efficacy of complete metastasectomy for mRCC was examined in the context of more recently approved systemic therapies. This research included 586 patients who underwent nephrectomy between 2006 and 2017, with 158 (27%) of these patients receiving complete metastasectomy. Notably, 93% of the patients who underwent complete metastasectomy did not receive systemic therapy for the index metastasis. The results demonstrated a significant survival benefit: the two-year cancer-specific survival (CSS) rate was 84% (132 out of 158 patients) in those who underwent complete metastasectomy, compared to 54% (231 out of 428 patients) in those who did not ($p < 0.001$). In addition, complete metastasectomy was associated with a significantly reduced risk of death from RCC (HR 0.47, 95% CI 0.34-0.65, $p < 0.001$), even after adjusting for age, gender, timing, number, and location of metastases. Of the 158 patients treated with complete metastasectomy, 72% developed subsequent metastasis, with a median metastasis-free survival of 1.4 years.

These findings suggest that complete surgical resection of metastases continues to offer substantial benefits in the post-cytokine era and should be considered for suitable patients through a process of shared decision-making[16].

According to the study by Yip et al., nephrectomy following immune checkpoint inhibitor (ICI) therapy is both safe and effective for patients with metastatic renal cell carcinoma (RCC). The study found that nephrectomy post-ICI therapy did not significantly increase perioperative complications or readmission rates compared to similar surgeries without prior ICI treatment. The 90-day complication rate was 24%, with a median hospital stay of 3 days. Furthermore, the study reported a complete pathologic response in 5% of patients and highlighted an estimated 3-year overall survival rate of 82%, demonstrating the feasibility and potential benefit of nephrectomy as a consolidative therapy in select patients[17].

Compared with the study by Yip et al., which assessed nephrectomy following ICI therapy and reported manageable perioperative risks and a lower complication rate, the research by Pignot et al. reveals a higher postoperative complication rate of 55%, including major complications and one surgery-related death. This difference is attributed to the significant surgical complexities caused by inflammatory infiltration due to prolonged ICI exposure, which made finding dissection planes challenging in 82% of cases. Despite these challenges, Pignot et al. demonstrated promising efficacy, with 73% of patients free from progression and 54% free from systemic treatment one year after surgery. These findings suggest that, while nephrectomy following ICIs presents substantial surgical challenges, it can still be an effective strategy to achieve long-term remission in selected mRCC patients[18].

In a retrospective cohort study of 522 patients undergoing 740 metastasectomies for mRCC at two high-volume centres between 2005 and 2020, it was found that fewer than 10% experienced major complications (Clavien-Dindo III-V) within 30 days of surgery. Significant factors associated with postoperative complications included age, body mass index, ASA score, concurrent nephrectomy, multiple metastatic sites, pancreatic resection, and metastasis size. Despite these risks, the study concluded that favourable perioperative outcomes are achievable in well-selected patients at specialised centres[19].

In a study by Ferriero et al., a 10-year single-centre experience was analyzed to assess the impact of metastasectomy on survival outcomes in patients with RCC. This prospective study included patients treated with either partial or radical nephrectomy who developed oligometastatic disease during follow-up. Results showed that patients who underwent metastasectomy had significantly improved OS compared to those who received systemic treatment only. The 2-year, 5-year, and 10-year OS probabilities were notably higher in the metastasectomy group, with rates of 93.8%, 82.8%, and 79.5%, respectively[20].

The benefit of surgical metastasectomy (SM) for patients with mRCC remains uncertain due to a lack of high-level evidence on its survival benefits in the context of systemic therapy. A meta-analysis of 56 retrospective studies suggests that SM may benefit selected mRCC patients, particularly those with oligometastatic disease and favourable risk profiles, with median OS ranging from 36 to 142 months compared to 8 to 27 months for non-SM patients. Currently, there is limited data on the role of SM after TKI therapy and no data on its role following immune checkpoint inhibitor ICI exposure. Despite the lack of randomised clinical data, existing studies support SM as a viable option for prolonging survival and avoiding systemic therapy in selected patients with limited metastases and good health status[14].

Schoenhals et al. demonstrate the efficacy of SBRT in managing oligoprogressive mRCC. By targeting limited sites of progression without altering systemic therapy, SBRT extended the median modified mPFS to 9.2 months. Patients receiving SBRT while on immunotherapy showed a significantly longer median mPFS (>28.4 months). The treatment was well-tolerated, with most toxicities being grade 1 or 2[21].

Two recent studies have highlighted the evolving role of radiotherapy in treating mRCC. The study by Tang et al. demonstrates the feasibility and efficacy of SBRT in lieu of systemic therapy for oligometastatic RCC. This approach achieved a high local control rate of 97% and a 1-year progression-free survival rate of 64%, with minimal severe adverse effects. The study challenges the traditional view of RCC as radioresistant, showing that modern SBRT techniques can effectively manage oligometastatic RCC, offering a less toxic alternative to systemic therapies[22] Likewise, Ali et al.'s review on the role of SBRT in RCC provides comprehensive evidence that contemporary radiotherapy techniques yield high local control rates exceeding 90% and maintain low rates of grade 3-4 toxicities. This indicates that RCC is no longer considered radioresistant with advanced radiotherapy modalities[23]. Both studies underscore the potential of SBRT to extend survival and improve quality of life in mRCC patients by providing effective local control with minimal toxicity, thereby deferring or reducing the need for systemic therapy[22,23].

In a recent study by Chalkidou et al., a prospective, registry-based, single-arm, observational evaluation was conducted across 17 NHS radiotherapy centres in England to assess the efficacy of SBRT in patients with extracranial oligometastatic solid cancers. The study included 1422 patients and demonstrated high overall survival rates of 92.3% at 1 year and 79.2% at 2 years[24].

In a recent meta-analysis by Zaorsky et al., SBRT demonstrated significant efficacy and safety in treating oligometastatic RCC. The study, which included 28 studies with 1602 patients and 3892 lesions, found a 1-year local control rate of approximately 90% for both extracranial and intracranial metastases. The 1-year survival rates were 86.8% for extracranial and 49.7% for intracranial disease. Importantly, the incidence of grade 3-4 toxicity was very low, at 0.7% for extracranial and 1.1% for intracranial disease. These findings suggest that SABR is a safe and effective treatment option for RCC metastases[25].

Local treatment of metastases, such as metastasectomy or radiotherapy, remains controversial in mRCC. A systematic review of comparative studies found that patients undergoing complete metastasectomy had better survival and symptom control, including pain relief in bone metastases, compared to those receiving incomplete or no metastasectomy. However, the evidence was limited by high risks of bias and confounding[26].

In conclusion, multidisciplinary management of residual RCC following first-line systemic therapy is crucial for optimizing patient outcomes. A combination of cytoreductive nephrectomy, metastasectomy, and SBRT has shown promising results in managing mRCC. These strategies aim to reduce tumour burden, delay systemic therapy, and improve quality of life. A personalised approach is essential, where treatment decisions are tailored based on the patient's disease progression, risk factors, and overall health status. By integrating surgical and local ablative techniques with systemic therapies, clinicians can effectively manage residual disease, potentially achieving long-term disease control and enhancing patient survival.

Future directions

1. **Research on Mechanisms of Resistance**: Further studies are needed to understand the biological mechanisms underlying resistance in residual RCC to develop targeted therapies.
2. **Innovative Therapeutic Approaches**: Investigate new drug combinations and novel agents that can effectively target resistant tumour cell populations in residual disease.
3. **Personalised Medicine**: Enhance personalised treatment plans by utilizing advanced genomic profiling to tailor therapies based on individual tumour characteristics and heterogeneity.
4. Integration of Multidisciplinary Care: Promote a multidisciplinary approach, combining surgical, local ablative, and systemic treatments to optimize patient outcomes.
5. **Clinical Trials**: Conduct more clinical trials focused on the efficacy of combining systemic therapies with local treatments like SBRT and metastasectomy for managing residual RCC.

Conflict of interest

Advisory boards: Yüksel Ürün has served on advisory boards for Abdi-İbrahim, Astellas, AstraZeneca, Bristol Myers-Squibb, Deva, Eczacıbaşı, Gen ilaç, Gilead, GSK, Janssen, Merck, MSD, Novartis, Pfizer, Roche. **Travel, honoraria or consultation fees**: Yüksel Ürün received honoraria or has served as a consultant for Abdi-İbrahim, Astellas, Bristol Myers-Squibb, Deva, Eczacıbaşı, Gen İlaç, Gilead, GSK, Janssen, Merck, Novartis, Pfizer, Roche.

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The current state of digital pathology, molecular diagnostics and biobanking in renal cancer: Kidney Cancer Association Consensus Statement

Author

J.P. Blackmur[*1,2], J.O. Jones[*1,2], A. Laird[3,4], A.Y. Warren[1], B.C. Leibovich[5], D.J. George[6], S. La Rosa[7], L. Pickering[8], G.D. Stewart[1,2] on behalf of the KCA Think Tank participants 2023 and 2024

[*] *Authors contributed equally.*

Affiliation

1. Cambridge University Hospitals NHS Foundation Trust, UK; 2. University of Cambridge, UK; 3. NHS Lothian, UK; 4. University of Edinburgh, UK; 5. Mayo Clinic, USA; 6. Duke Cancer Center, USA; 7. Kidney Cancer Association; 8. Royal Marsden Hospital, UK

Corresponding author

James P. Blackmur, james.blackmur1@nhs.net

Abstract

Introduction: Digital pathology and molecular diagnostics are known to augment research and routine clinical care, however are yet to be widely implemented in RCC. Biobanking underpins much of the research on RCC, however wider co-ordination may streamline progress. We aimed to assess the current state of practice with digital pathology, molecular diagnostics and biobanking for renal cancer, and to produce consensus statements to direct future efforts.

Methods: Participants invited to the Kidney Cancer Association (KCA) Think Tanks during the European International Kidney Cancer Symposium (IKCS) meeting in 2023 and 2024 discussed how these strategies might be utilised, with a view to setting international priorities and facilitating future research collaborations. Between meetings, an online survey was advertised to clinicians via the KCA email list and social media, with the aim of capturing wider opinions on these issues.

Results: The survey highlighted that while there is clear interest in digital pathology and molecular diagnostics, few centres are using these technologies routinely. Barriers included funding, training and time along with ethical, legal and intellectual issues. Think Tank discussions led to the development of six statements: the adoption of digital pathology should be prioritised in RCC; prospective validation and standardisation are needed for predictive molecular testing in clear cell RCC; molecular diagnostics may fulfil unmet needs in non-clear cell RCC; Artificial Intelligence has the potential to improve multiple aspects of RCC diagnosis & management; international co-operation would facilitate the introduction of digital pathology and molecular diagnostics; standardised approaches to biobanking will facilitate high-quality RCC research.

Conclusions: While the implementation of digital pathology, molecular diagnostics and international biobanking present several challenges, these can be addressed through strategic planning, investment in infrastructure, and a focus on training and change management. Overcoming these hurdles would allow the full potential of these technologies to be realised.

Introduction

Despite the progress made in the treatment of renal cell carcinoma (RCC), particularly with the advent of VEGF-directed tyrosine kinase inhibitors (TKIs) and Immune Checkpoint Inhibitors (ICPIs)[1], and more recent developments in adjuvant immunotherapy[2], there remain several key questions and areas of unmet need in the treatment of people suffering from RCC. These questions cross the spectrum of stages of the disease, including how to improve early detection, who to treat with a small renal mass and which treatment to use, selection of patients for adjuvant therapy, optimal treatment sequencing for patients with incurable disease, and the management of non-clear cell RCC subtypes. The development of molecular diagnostics and digital pathology are two active areas of research that might be directly translated into clinical practice to improve treatment in these areas.

Digital pathology can be defined as "the acquisition, management, sharing and interpretation of pathology information in a digital environment"[3]. The development of digital pathology may offer several benefits. In routine care, the digital format may allow faster sharing between hospitals to achieve primary diagnosis or second opinion. It may allow access to new methods for quantitative image analysis, or the development of AI-assisted diagnostic systems. The wider sampling area captured by these AI methods may counter the issue of intratumoral heterogeneity that can limit some biopsy-based approaches[4], though the adoption of digital pathology approaches has to be underpinned by standardised tumour sampling methods. Sharing in digital format also overcomes the physical limits of tissue availability, especially for rare conditions or cases where biopsies are not recommended. There may also be wider benefits, such as improved education of doctors in training in the key specialties involved[5], and less need for on-site storage of glass slides.

Molecular diagnostics is the use of molecular biology techniques (analysis of DNA, RNA and proteins) to aid diagnosis, predict disease course, select treatment and monitor the effectiveness of therapies. While some molecular markers have been shown to have prognostic importance in research settings, none have made it to routine care in RCC[6]. Other markers have shown promise for treatment selection, particularly RNA signatures[7,8] which are being assessed in prospective studies such as BIONIKK9 & OPTIC-RCC[10], and circulating KIM-1 in the IMmotion010 study[11]. However, at present there is no consensus on the signatures used, and these remain a research tool. Adjuvant immunotherapy is a relatively new development in RCC, however, based on the clinical likelihood of benefit a significant number of patients will be overtreated with the associated risk of ICPI toxicity, so research is needed to improve patient selection[2]. In non-clear cell RCC, the use of molecular tests is essential to diagnose some rarer subtypes, such as those in the WHO category of molecularly defined tumours[12,13]. These are available at some centres, but clarity is needed on when these tests should be done to balance the risk of missing rare cases against the cost of widespread testing.

Biobanking efforts underpin laboratory research into kidney cancer. However, these studies are often locally organised and differ in the samples they collect, subsets targeted, and associated clinical data. Sharing and collation of samples into larger sets to increase the power to answer a particular research question can be challenging, both within the same country, and internationally. Digital pathology and molecular diagnostics are known to augment research and routine clinical care[14–17], however, they seem aspirational in RCC and are yet to be widely implemented. Coordination of biobanking efforts may streamline progress in kidney cancer research. Participants invited to the Kidney Cancer Association (KCA) Think Tanks during the European International Kidney Cancer Symposium (IKCS) meeting in 2023 (Edinburgh, UK) and 2024 (Sitges, Spain) discussed how these strategies might be utilised for renal cancer, to set international priorities and facilitate future research collaborations.

Materials and methods

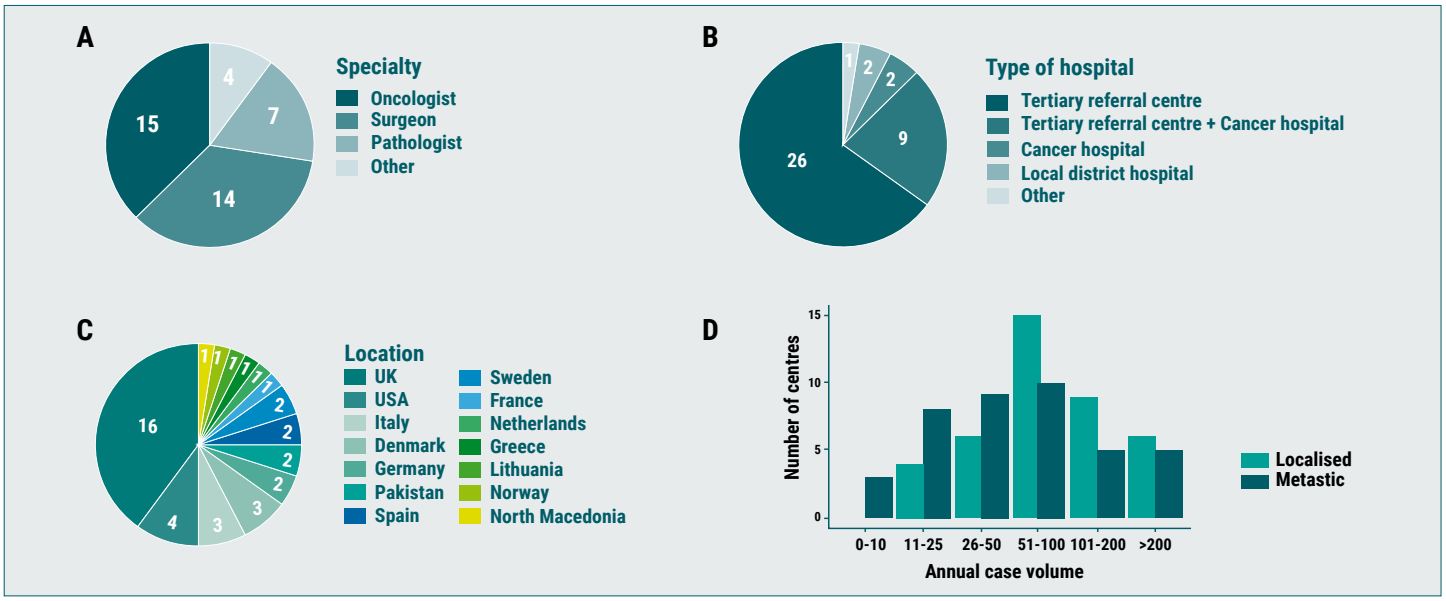
The KCA Think Tank coalition brings together a select group of prominent thought leaders in kidney cancer. The aim is to share expertise in the RCC field and identify gaps in resources and knowledge that limit advances in RCC care. Participants of the KCA Think Tank ahead of the 2023 IKCS: Europe Edinburgh, Scotland considered the status of digital pathology, molecular diagnostics and biobanking in kidney cancer. Following the meeting, an online survey was advertised to clinicians working on kidney cancer via the KCA email list and social media August-October 2023, to capture wider opinions on these issues. As part of the KCA Think Tank ahead of the 2024 IKCS: Europe Sitges, Spain, the panel considered which molecular diagnostic and pathology techniques should be prioritised, how availability of molecular diagnostic and digital pathology techniques should be advanced and how coordinated biobanking might be achieved. A diverse group of stakeholders was involved including oncologists, surgeons, pathologists, scientists, representatives from patient advocacy groups and pharmaceutical companies.

Results

Survey of Digital Pathology and Molecular Diagnostics

There were 40 individual responses to the survey, from surgeons (14), oncologists (15), pathologists (7) and other specialties (4) (Fig 1A). Over 90% of responses were from tertiary centres or dedicated cancer hospitals (Fig 1B). 16 responders were from the UK, 18 were from 11 different European nations, 4 from the USA and 2 from Pakistan (Fig 1C). There was wide variation in case volume in both localised and metastatic disease, with 8 centres treating fewer than 25 cases of RCC each year, and 5 centres treating over 200 cases (Fig 1D).

Figure 1: Survey response demographics



Over 60% of centres reported having access to digital pathology facilities (Fig 2A), though only 10% used it routinely (in over half of cases) in standard care (Fig 2B). 49% of centres were using digital pathology to some extent in research studies (Fig 2C), and over 80% of responders were interested in contributing to wider digital pathology research (Fig 2D). Cost and staffing were the leading barriers to introducing digital pathology in either research or routine clinical practice (Fig 2E).

Molecular diagnostics were only used to aid diagnosis routinely in three centres, and in just one to aid treatment selection (Fig 2F&G). Specialist IHC stains, translocation studies and tumour DNA sequencing are the most widely available (Fig 2H). The majority of responders felt that better access to molecular diagnostics would help the management of RCC (Fig 2I). Cost and staffing were again identified as key barriers (Fig 2J).

Figure 2: Survey responses on digital pathology and molecular diagnostics

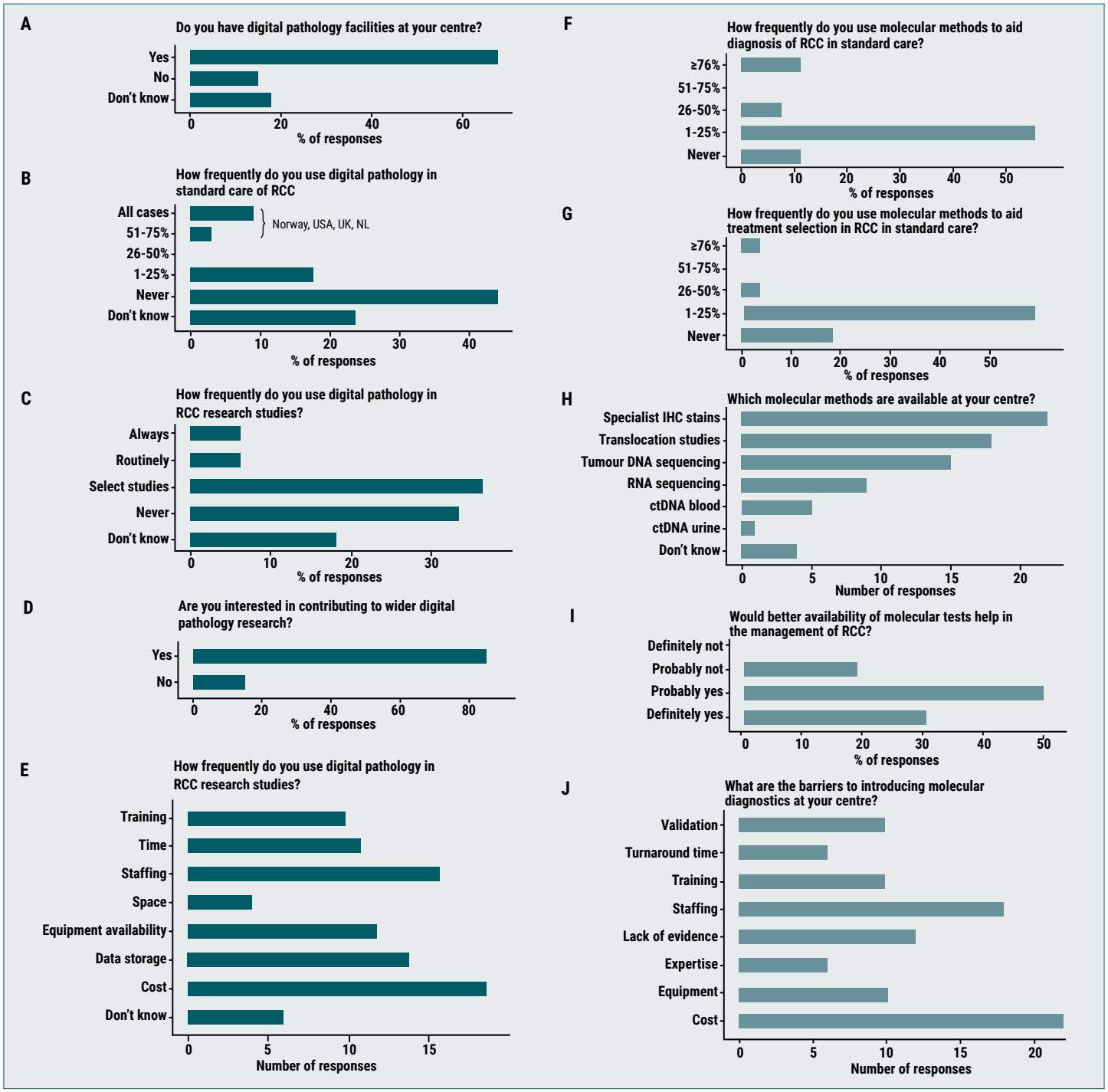
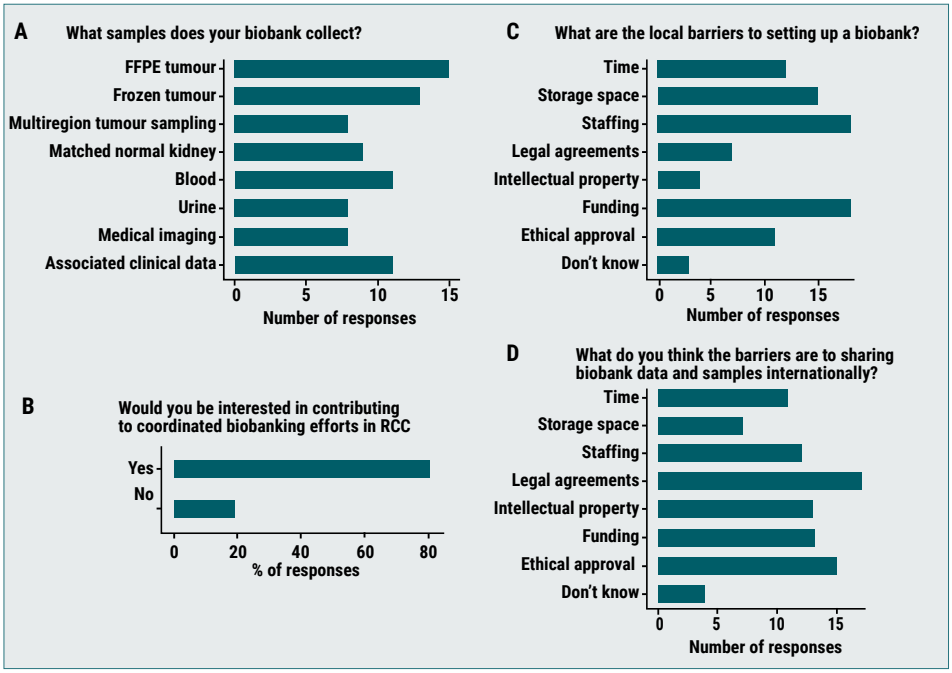


Figure 3: Survey responses on biobanking



Most centres contributed to an existing RCC biobank collecting a wide range of samples (Fig 3A). Encouragingly, 80% of responders were interested in contributing to coordinated biobanking efforts (Fig 3B). Staffing and funding were the leading barriers to setting up local biobanking, while legal and intellectual property considerations were more important when international data and sample sharing were considered (Fig 3C&D).

At the 2024 Think Tank Meeting, the discussion aimed to establish a consensus regarding which diagnostic techniques should be prioritised based on their potential to be widely implemented and offer significant clinical value. The aim was to ensure investment in these technologies would yield practical benefits for diagnosis and treatment at a broader scale. Participants were asked to rank diagnostic methods considering their clinical utility and practicality, the outcome is summarised in Figure 4. This approach highlighted the balance between the complexity of the technologies and their potential to improve patient outcomes significantly. Blood-based biomarkers were felt to have excellent utility and practicality if they can be developed. The following statements were also developed from discussions at the 2024 Think Tank.

Consensus Statements

- Statement 1: The adoption of digital pathology should be prioritised in RCC
- Statement 2: Prospective validation and standardisation are needed for predictive molecular testing in clear cell RCC
- Statement 3: Molecular diagnostics may fulfil unmet needs in non-clear cell RCC
- Statement 4: Artificial Intelligence has the potential to improve multiple aspects of RCC diagnosis & management
- Statement 5: International cooperation would facilitate the introduction of digital pathology and molecular diagnostics
- Statement 6: Standardised approaches to biobanking will facilitate high-quality RCC research

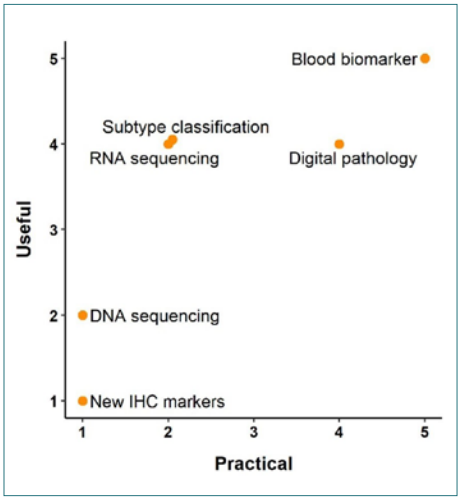
Statement 1: The adoption of digital pathology should be prioritised in RCC

There was strong agreement that digital pathology is a critical area of development, seen as a necessary evolution to meet the current and future needs of pathology services. While not the most advanced technology, digitization of Haematoxylin and Eosin (H&E) stains was recognised as foundational for further pathological analysis. It was deemed one of the more practical steps towards digital pathology due to its scalability and the potential to enhance the accessibility and quality of diagnostic reviews. Furthermore, the integration of artificial intelligence (AI) and machine learning was discussed as a transformative element that could leverage digitised images to not only enhance diagnostic precision but potentially predict patient outcomes18. This prediction capability could reduce the need for more invasive and costly tests, thus democratizing advanced diagnostic capabilities, especially in underserved regions or smaller healthcare facilities lacking specialised pathology expertise.

Statement 2: Prospective validation and standardisation are needed for predictive molecular testing in clear cell RCC

In clear cell RCC, current diagnostic methods (particularly H&E supported by IHC for protein markers) are usually sufficient to achieve the diagnosis. The primary research focus is on predictive markers that can be used to assign patients to current or emerging treatment combinations. Tumour DNA testing may identify mutations in genes including *VHL*, *BAP1* or *PBRM1*, though these findings are not

Figure 4: Priorities for development

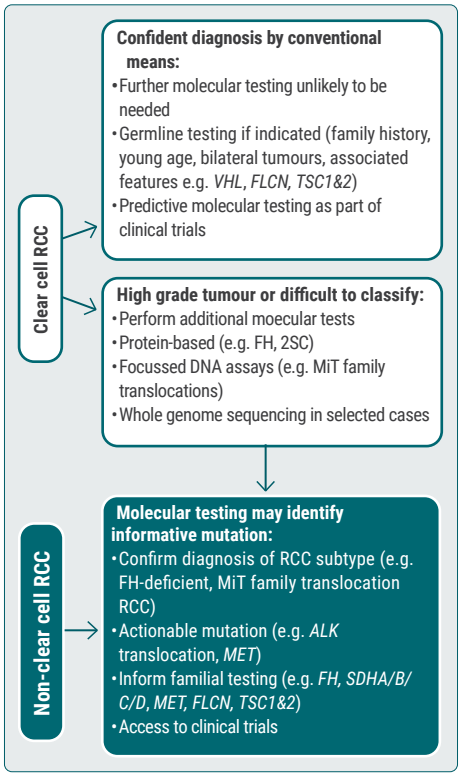


necessarily actionable, and so of limited value6. The development of RNA signatures is exciting, but consensus on the signatures used and validation in prospective trials is needed before wider use. General use may then be limited by heterogeneity4,[7–10]. Blood-based biomarkers, including protein and cfDNA-ased[19,20], were identified as key priorities for further research; if they could be implemented, they would be practical and have widespread utility in clear cell RCC, avoiding the need for tissue re-sampling or the risk of tumour heterogeneity confounding the results. Given the complex intratumoral, immune and metabolic heterogeneity of RCC, new developments in single-cell and spatial transcriptomics may help to better understand aetiology, stratify patients, guide management strategies, and identify therapeutic targets[21–23]. This area is the subject of much research interest, however, cost, time, access to tissue (particularly if assessing via renal biopsy) and identification of clinically actionable results will remain a challenge to widespread integration into healthcare pathways.

Statement 3: Molecular diagnostics are of particular value in non-clear cell RCC

In non-clear cell RCC, molecular testing has potential given the current unmet need. It may confirm the subtype of non-clear cell RCC, especially in borderline cases and in the 'molecularly defined' subtypes from the WHO 2022 classification[24,25]. The correct identification of the subtype may provide prognostic information for the patient and clinician, particularly if aggressive variants are found, such as some adult MiT family translocation RCC[26]. There may be hereditary variants, such as in FH or SDH genes, which may guide further screening of the patient or family members[27]. There may be actionable mutations, for example in ALK-rearranged RCC, or MET in papillary RCC[25,28]. Correct identification of non-clear cell RCC variants, underpinned by molecular methods, is also critical for access to prospective clinical trials, which may provide novel treatment for these underrepresented subtypes of RCC. A proposed approach is summarised in Figure 5.

Figure 5: Framework for the use of molecular testing in RCC



Statement 4: Artificial Intelligence has the potential to improve multiple aspects of RCC diagnosis & management

The integration of AI and machine learning in digital pathology was unanimously seen as a transformative shift. This consensus reflects a broad recognition of the potential for AI to not only speed up the diagnostic process but also to provide deeper insights into complex pathological images, potentially supporting personalised treatment plans and improving outcomes. The combination of digital pathology and machine learning has, for example, shown potential in inferring mutation status and quantitating vascularity, which correlates with angiogenesis gene expression clusters and has the potential to personalise treatment selection[29,30]. The use of AI in digital pathology could also facilitate remote diagnostics, making expert pathological analysis available even in geographically isolated regions. There are substantial challenges with integrating AI into existing medical infrastructures; the need for substantial data sets to train algorithms and the importance of ensuring tools are reliable and transparent. There is also a need for robust data infrastructure, the integration of AI tools into existing medical workflows, and ensuring the security and privacy of sensitive medical data.

Statement 5: International cooperation would facilitate the introduction of digital pathology and molecular diagnostics

Great emphasis should be placed on the importance of collaborative research efforts to pool resources, share data, and standardise procedures across institutions and borders. Such collaboration could accelerate the development of new diagnostic tools and therapeutic strategies, increasing the pace at which scientific discoveries are translated into clinical applications.

Statement 6: Standardised approaches to biobanking will facilitate high-quality RCC research

Biobanking can benefit significantly from national and international collaboration. By pooling resources and expertise, researchers can access a diverse array of biological samples and associated data, crucial for studies on diseases that vary significantly across different populations and ethnic groups. International collaboration can particularly help in standardising methodologies for collection, storage and analysis; essential for ensuring the compatibility and comparability of research outcomes. Examples like the UK Biobank[31] and the All of Us Research Program[32] in the USA illustrate successful large-scale biobanking initiatives that support a wide range of research aimed at improving the prevention, diagnosis, and treatment of various diseases. However, challenges to data sharing and privacy regulations complicate international collaboration. Standardisation is particularly required to reduce variability in protocols for sample collection, storage, and data recording which can lead to issues in data quality and reproducibility of research findings. Sharing standard-operating procedures and expansion of existing successful kidney-specific biobanking initiatives (for example TRACERx Renal[33] or the Scottish Collaboration On Translational Research

into Renal Cell Cancer (SCOTRRCC)[34]) may facilitate even greater translational research into the unanswered questions eluded to above. In addition, specialised biobanks of live-preserved tumour tissues and tumour grafts in mice may enable functional studies and accelerate drug development[35].

Barriers to the implementation of digital pathology and molecular diagnostics

Several barriers were identified across broad themes by the survey and Think Tanks. Many centres have however shown how digital pathology can be integrated into clinical workflows effectively, allowing pathologists to review cases efficiently, in a similar way to the review of radiology images[36–39].

Cost: High implementation costs are a significant barrier to the widespread implementation of molecular diagnostics. Strategic financial support is required, both for acquiring the necessary technology and for sustaining and updating systems, and training personnel to use them effectively. While the adoption of whole-genome sequencing might offer comprehensive data, high cost and complex data management might limit its immediate practicality compared to more straightforward technologies like digital H&E staining, which could be more rapidly integrated into clinical practice at a lower cost.

Education and Training: Ongoing education is required to keep pace with the rapid advancements in technology. This education should not only cover technical skills but also focus on analytical aspects, enhancing the ability of medical professionals to interpret complex data effectively.

Integration within existing healthcare infrastructure: Ensuring compatibility between new digital systems and older medical record systems can be complex and requires careful planning and execution. Interdisciplinary teams are crucial in addressing the technical challenges of integrating new diagnostic technologies into existing healthcare frameworks. For instance, pathologists and IT specialists need to work together to ensure that digital pathology systems are compatible with electronic health records and other clinical information systems, facilitating seamless workflows that support rather than disrupt clinical operations.

Data management and security: robust systems need to be in place to store, manage, and protect patient information. This includes adhering to data protection regulations, which vary by region and can complicate the sharing of digital images across platforms and borders. Ensuring compliance with international data protection laws and maintaining the highest standards of data security is imperative to protect patient information from unauthorised access.

Ethical considerations: Adoption of widespread genetic testing or technologies that might significantly alter patient interactions with healthcare systems requires careful consideration. One of the primary ethical concerns raised was the potential for genetic and molecular diagnostics to generate results that might not have clear clinical implications, for example identifying genetic markers without established therapeutic strategies or prognostic significance could cause unnecessary anxiety or confusion. A patient-centred approach is required, ensuring that technological advancements lead to genuine improvements in patient care, such as more precise diagnostics, personalised treatment plans, or better disease management. By focusing on these aspects, the adoption of new technologies can enhance rather than complicate the patient care process.

Challenges to Biobanking

Similarly, key challenges to Biobanking were identified, and exemplar projects are summarised in box 1.

Box 1: National and international approaches to biobanking

Germany	A decentralised approach, with regions or institutions developing their own biobank with distinct processes and standards. This diversity can lead to rich, localised collections but also poses challenges for standardization and data sharing on a national scale[40]. Accompanying patient registries are particularly useful for survival data.
Denmark	A well-integrated model within the healthcare system, the country has a centralised biobank[41]. This integration allows for high-quality sample collection and storage, as well as meticulous data management, standardised across the country. Danish biobanks are particularly noted for their comprehensive ethical oversight and systematic patient consent processes, which are streamlined to facilitate research while protecting donor rights.
USA	Several large-scale biobanking initiatives exist, such as the All of Us Research Program, which aims to collect and analyze biological samples from one million participants to advance personalised medicine[32]. The U.S. also hosts disease-specific biobanks, such as those supported by the National Cancer Institute Cooperative Group Program and National Clinical Trials Network (https://nctnbanks.cancer.gov/) and the Cancer Genome Atlas Program[42]. These biobanks often focus on collecting a range of data types, from genomic data to detailed clinical information, supported by substantial technological and financial resources.
European Union	Cross-border research collaborations are supported through initiatives like BBMRI-ERIC (Biobanking and BioMolecular resources Research Infrastructure - European Research Infrastructure Consortium, https://www.bbmri-eric.eu/), which facilitates access to biobanks across Europe, enhancing their utility for multinational research studies.
Scotland	The Scottish Collaboration On Translational Research into Renal Cell Cancer (SCOTRRCC) is an example of a urological surgery lead bioresource which utilised standard operating procedures across seven centres in Scotland to collect renal tissue, blood and urine, along with high-quality clinical information[34].
UK	TRACERx Renal is a prospective translational research study, combining the multicentre collection of kidney tissue, blood and urine with cutting-edge basic science research to understand the evolution of renal cancer and develop future biomarkers[33].

Sample collection, preservation and data management: High-quality sample collection and preservation are prerequisites for a successful biobank, often requiring sophisticated equipment and facilities. Each sample must be associated with accurate and comprehensive metadata to provide context for researchers, such as the health status of the donor, the conditions under which the sample was collected, and any treatments the donor was undergoing at the time. Robust data systems are required to handle the vast amounts of information generated. Furthermore, as the field of biomedicine advances, techniques for analysing biobank samples are also evolving; decisions on when and how to analyse finite tissue resources are important considerations.

Local, National and International Regulation- Biobanks must adhere to strict regulations like the EU's General Data Protection Regulation (GDPR) and the US's Health Insurance Portability and Accountability Act (HIPAA), which safeguard privacy and personal data. While ethical concerns, particularly regarding informed consent and the rights of donors, are central to biobanking operations, these laws can create barriers, particularly to international collaboration. Donors must be fully informed about the use of their samples and data, with the ability to withdraw consent at any time. Ethical oversight, typically managed by institutional review boards or ethics committees, ensures compliance with ethical standards and helps maintain public trust.

Centralised vs Decentralised structures: These two approaches carry benefits and compromises. Decentralisation allows for tailored approaches that meet specific regional or institutional needs, promoting innovation and specialisation, with unique methodologies tailored to specific research goals. Centralisation can lead to significant efficiencies in terms of resource use, funding, and data management, and can facilitate larger-scale research studies by providing a consistent and comprehensive collection of samples and data.

Funding and infrastructure: These are critical for both facility set-up and maintenance (particularly given the specialised equipment required), along with sample processing, storage, and data management. Government funding is particularly crucial as it typically provides the foundational support for many national and international biobanking initiatives. However, securing consistent funding can be challenging due to budgetary constraints and shifting research priorities.

Conclusion

While the implementation of digital pathology and molecular diagnostics presents several challenges, these can be addressed through strategic planning, investment in infrastructure, and a focus on training and change management. Overcoming these hurdles is essential for leveraging the full potential of these technologies to enhance diagnostic accuracy, improve patient outcomes, and facilitate more collaborative approaches in medical diagnostics.

Biobanking is also seen to have huge potential. Utilisation is challenging due to the lack of transparent and well-publicised processes of proposal application and review, and many biobanks not having well-annotated clinical data, including therapy and outcome information. Despite the hurdles to international collaboration in biobanking, the potential benefits of such efforts are immense. By working together, countries and institutions can leverage the strengths of diverse populations to gain insights that would be challenging to obtain in isolation, crucial for the advancement of global health and precision medicine. Integration of biobanks with electronic health record systems is potentially game-changing, enabling enrichment of the value of samples with detailed clinical annotations and ensuring that research can provide insights into disease progression and treatment efficacy.

Conflict of interest

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Think tank participants and contributors

Blackmur, James P; Jones, James O; Laird, Alexander; Warren, Anne; Monroe, Kendall; Vaughan, Gretchen; Chitale, Radha; Leibovich, Bradley; George, Daniel; La Rosa, Salvatore; Pickering, Lisa; Stewart, Grant D; Albiges, Laurence; Barata, Pedro; Battle, Dena; Beisland, Christian; Bex, Axel; Brugarolas, James; Bukavina, Laura; Charnley, Natalie; Escudier, Bernard; Fendler, Annika; Grünwald, Viktor; Henske, Elizabeth P; Julian, Juan Carlos; Lund, Lars; Kapur, Payal; Malouf, Gabriel; McDermott, David; McNee, Karen; Msaouel, Pavlos; Nilssen, Frode; Porta, Camillo; Procopio, Giuseppe; Staehler, Michael; Suarez, Cristina; Thorlund, Mie; Toma, Marieta; Turajlic, Samra; Vaishampayan, Ulka; Verkarre, Virginia; Voss, Martin; Young, Kate.

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Conceptualisation- JPB, JOJ, GDS, LP, SLR

Methodology- JPB, JOJ, AL, GDS, LP, SLR, DG

Think Tank Participants: JPB, JOJ, AL, KM, GV, RC, BL, DG, SLR, GDS, LA, PB, DB, CB, AB, JB, LB, NC, BE, AF, VG, EPH, JJC, LL, GM, DM, KM, PM, FN, CP, GP, MS, CS, MTh, MTo, ST, UV, VV, MV, KY.

Writing- Original draft: JPB, JOJ.

Writing- draft editing: JPB, JOJ, AL, AYW, BL, DG, SLR, LP, GDS.

Writing- final review and editing: JPB, JOJ, AL, AYW, KM, GV, RC, BL, DG, SLR, GDS, LA, PB, DB, CB, AB, JB, LB, NC, BE, AF, VG, EPH, JJC, LL, PK, GM, DM, KM, PM, FN, CP, GP, MS, CS, MTh, MTo, ST, UV, VV, MV, KY.

Supervision: GDS, LP, SLR, DG

JPB and JOJ act as guarantors for the contents of the article.

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