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EDITORIAL

Update on the treatment of metastatic renal cell carcinoma

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Abstract

Metastatic renal cell cancer (mRCC) management has undergone a paradigm shift in recent decades. The first revolution came with the emergence of vascular endothelial growth factor inhibitors; there was a second wave with the unprecedented success of checkpoint inhibitors, and then the latest approach, which is becoming the new care standard in mRCC, of combining these two strategies in different ways. Updated results of Checkmate-214 after 42 mo of follow-up were consistent with previously published results showing the superiority of nivolumab/ipilimumab over sunitinib in progression free survival (PFS), overall survival (OS), and objective response rate (ORR) in intermediate and high-risk patients. However, several studies presented at the American Society of Clinical Oncology 2020 suggested that the best place, and so far, the only one for nivolumab/ipilimumab is the frontline setting. The update on Keynote-426 after 23 mo of follow-up showed no superiority of pembrolizumab/axitinib over sunitinib in favorable-risk mRCC, suggesting that it should no longer be the first line of choice in low-risk patients. Finally, the phase III Checkmate 9ER trial results revealed the superiority of nivolumab/cabozantinib *vs* sunitinib in PFS, OS, and ORR, providing a new first-line option among all International Metastatic RCC Database Consortium risk patients. Some phase II clinical trials also presented this year showed promising results with new combination therapies such as nivolumab/sitravatinib, cabozantinib/atezolizumab, and lenvatinib/pembrolizumab, providing promising grounds upon which to start phase III studies. In addition, other works are using novel therapeutic agents with different mechanisms of action, including telaglenastat (a glutaminase inhibitor), entinostat [an inhibitor of histone deacetylases (HDACs)],

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and olaparib and talazoparib, poly(ADP-ribose) polymerase inhibitors widely used in other tumors. However, some questions regarding mRCC management still need to be addressed, such as head-to-head comparisons between the current options, treatment sequencing, non-clear cell mRCC, and the role of biomarkers to ascertain the best treatment choice.

Key Words: Metastatic renal cell carcinoma; Systemic treatment; Immune checkpoint inhibitors; Antiangiogenic; Update; Biomarkers

Core Tip: Kidney cancer therapeutics is a fast-changing field, and the outcome of metastatic renal cell carcinoma (mRCC) has thus improved considerably in recent years with the introduction of different combinations of immune checkpoint and vascular endothelial growth factors inhibitors. State-of-the-art systemic therapy regimens must be addressed to be in a position to offer patients the best options. The aim of this editorial is to provide an update and insight on future directions on mRCC management.

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INTRODUCTION

Historically, the therapeutic strategy for metastatic renal cell carcinoma (mRCC) relied on cytokines. These drugs had a moderate response rate and were associated with substantial side effects[1].

Since then, the treatment of mRCC has improved considerably with the introduction and regulatory approval of agents that block vascular endothelial growth factor (VEGF) or mechanistic target of rapamycin (mTOR) pathways and significantly improve objective response rates (ORR) and/or median progression free survival (PFS) compared to previous treatment approaches. Since 2005, the United States Food and Drug Administration and the European Medicines Agency have approved VEGF receptors; tyrosine kinase inhibitors (TKIs) sorafenib, sunitinib, pazopanib, axitinib, cabozantinib, and lenvatinib; the anti-VEGF antibody bevacizumab (in combination with interferon); and mTOR inhibitors everolimus and temsirolimus to treat mRCC[2].

Despite the notable efficacy of these targeted therapies, which changed the treatment landscape, tumor resistance to TKI made it necessary to investigate different treatment mechanisms. In this context, stimulating the immune system through drugs targeting the so-called checkpoint pathways through the blockage of programmed cell death 1 (PD1), programmed cell death ligand 1 (PDL1), and the cytotoxic T-lymphocyte antigen 4 have been tested in RCC with successful results. As a result, nivolumab was the first immune checkpoint inhibitor (ICI) approved based on data from the phase III Checkmate 025 study of nivolumab *vs* everolimus in patients who had received prior antiangiogenic therapy for mRCC[3].

Combination therapies, based on the rationale that using drugs that work by different mechanisms may decrease the likelihood of cancer resistance, emerged in an effort to improve outcomes. The treatment landscape for first-line therapy has thus changed dramatically in recent years with the publication of a phase III clinical trial (CT) that showed three combinations' advantage over sunitinib: (1) Nivolumab/ipilimumab (Checkmate-214), which proved a higher overall survival (OS), PFS, and ORR in intermediate and high-risk patients[4,5]; (2) Avelumab/axitinib, which showed longer PFS (JAVELIN Renal 101)[6]; and (3) Pembrolizumab/axitinib, which proved higher in OS, PFS, and ORR among all International Metastatic RCC Database Consortium (IMDC) risk patients (KEYNOTE-426)[7]. This work has led to the current standard practice recommendations set in the European Association of Urology[8],

Table 1 Results from clinical trials

Checkmate 214	Nivolumab/ipilimumab (*n* = 425)	Sunitinib (*n* = 422)
Minimum follow-up	42 mo	42 mo
OS IP	52%; 47 (35.6-NE) mo	39% 26.6 (22.1-33.5) mo
ORR IP	42% (37-47)	26% (22-31)
CR IP	10%	1%
Checkmate 025	Nivolumab (*n* = 410)	Everolimus (*n* = 411)
Minimum follow-up	5 yr	5 yr
OS	26% (22.2-29.8)	18% (17.6-22.1)
ORR	23% (19-27)	4% (2-7)
mDOR	18.2 (12.9-25.8) mo	14 (8.3-19.2) mo
Keynote 426	Pembrolizumab/axitinib (*n* = 432)	Sunitinib (*n* = 429)
Minimum follow-up	23 mo	23 mo
OS	74%	66%
	HR: 0.68; 95%CI: 0.55-0.85; $P < 0.001$	
PFS favorable risk	20.8 (15.4-28.8) mo	18 (12.5-20.8) mo
Checkmate 9ER	Nivolumab/cabozantinib (*n* = 323)	Sunitinib (*n* = 328)
Minimum follow-up	10.6 mo	10.6 mo
PFS	16.6 (12.5-24.9)	8.3 (7-9.7)
OS	NR (NE)	NR (22.6-NE)
ORR	55.7% (50.1-61.1)	27% (22.4-32.3)
CR	8%	4.6%
Adverse events grades 3-5	60.6%	50.9%

PFS: Progression free survival; OS: Overall survival; ORR: Objective response rate; CR: Complete response; mDOR: Median duration of objective response; NR: No results; NE: Not ended; HR: Hazard ratio; CI: Confidence interval; IP: Poor risk.

ESMO[9], and National Comprehensive Cancer Network guidelines[10].

UPDATES IN AMERICAN SOCIETY OF CLINICAL ONCOLOGY GENITOURINARY, AMERICAN SOCIETY OF CLINICAL ONCOLOGY, AND ESMO CONGRESSES

American Society of Clinical Oncology genitourinary 2020

Updated results of Checkmate 214 after 42 mo of follow-up have been presented[11]. These results were consistent with the superior performance of nivolumab/ipilimumab *vs* sunitinib in intermediate and poor-risk patients. An OS of 52% with nivolumab/ipilimumab *vs* 39% with sunitinib [hazard ratio (HR): 0.66; 95% confidence interval (CI): 0.55-0.80]; ORR of 42% with nivolumab/ipilimumab *vs* 26% with sunitinib ($P = 0.0001$); and complete response (CR) of 10% with nivolumab/ipilimumab *vs* 1% with sunitinib have been observed (Table 1).

The final analysis of Checkmate 025 after 5 years of follow-up was also presented [12]. An OS of 26% with nivolumab *vs* 18% with everolimus; ORR of 23% with nivolumab *vs* 4% with everolimus; and median duration of objective response (mDOR) of 18.2 mo with nivolumab *vs* 14 mo with everolimus were presented (Table 1).

The first phase II in-human study of the hypoxia-inducible factor (HIF)-2α inhibitor Midkine (MK)-6482 was also presented[13]. This is an oral agent with antiangiogenic activity. Preliminary results on 55 patients treated in the second, third, and fourth line settings revealed a disease control of 80%, ORR of 24%, and tumor reduction of 67%. The median PFS was 11 mo. After 1 year, 30% continued under treatment, which was

well tolerated. These results provided promising grounds upon which to start the phase III trial (MK-6482 005 against everolimus).

Finally, another interesting approach was the combination of nivolumab/sitravatinib, a novel TKI that modulates the tumor microenvironment in order to render it more responsive to immunotherapy[14]. Administration in the first, second, and third line settings (n = 40) demonstrated a tumor reduction of 92%, disease control of 90%, ORR of 39%, and PFS of 10.5 mo. Again, this is promising data for the next phase III trial.

American Society of Clinical Oncology 2020

Updated data for Keynote-426 after a minimum follow-up of 23 mo were presented [15]. OS was 74% with pembrolizumab/axitinib *vs* 66% with sunitinib. Patients with favorable-risk disease no longer presented a significant difference in OS or PFS, with a median PFS of 20.8 mo with pembrolizumab/axitinib and 18 mo with sunitinib. However, patients with IMDC intermediate or poor-risk disease showed significant differences in OS and PFS with an HR of 0.63 for OS and 0.69 for PFS. The CR rate increased from 6% at 12 mo of follow-up[16] to 9% after 23 mo. A new *post hoc* analysis of the relationship between depth of response and OS showed that in patients receiving pembrolizumab/axitinib, deeper responses, as measured by percent shrinkage of target lesions, correlated to better OS (See Table 1).

Two studies, the OMNIVORE study[17] (n = 83) and the HCRN GU16-260 study[18] (n = 123), were presented to investigate whether treating mRCC patients with nivolumab initially and later adding ipilimumab in patients with either stable or progressive disease would be as effective as an upfront combination therapy. The results showed only 4% and 11% additional partial responses, respectively, suggesting that delaying treatment with ipilimumab decreased the overall efficacy of upfront combination treatment.

The results of the phase II FRACTION-RCC CT[19] to assess nivolumab/ipilimumab after progression to an ICI (PD-1) were also presented (n = 46). The ORR was 15.2%, which suggests that this combination should ideally be administered as first-line therapy.

However, one study showed the results of a phase II bevacizumab/erlotinib study in 83 patients, of which 50% had hereditary leiomyomatosis (HLRCC) and 50% had sporadic (PSRCC) advanced papillary RCC[20]. This combination proved to be very active in papillary RCC, especially in HLRCC, with an ORR of 64%, tumor shrinkage of 95%, and PFS of 21.1 mo.

Finally, a phase III study (SAVOIR) with savolitinib *vs* sunitinib for papillary RCC with abnormal *MET* gene was presented (n = 60)[21]. The results showed a PFS of 7.0 and 5.6 mo in the savolitinib and sunitinib groups, respectively, with better tolerability in the savolitinib group. Initial data look promising, despite the small cohort study.

ESMO 2020

The results of Checkmate 9ER[22], a phase III study of nivolumab/cabozantinib *vs* sunitinib in previously untreated mRCC with a clear cell component, were presented. Patients were stratified by IMDC, PD-L1, and region (n = 651). At a median follow-up of 18.1 mo, nivolumab/cabozantinib led to higher rates of PFS, OS, and ORR *vs* sunitinib (Table 1), with consistent improvements observed across all pre-specified subgroups according to IMDC risk and PD-L1 expression. The combination was generally well tolerated, and patients had significantly better quality of life than those treated with sunitinib. These results support nivolumab/cabozantinib as a potential first-line option for patients with advanced renal cell carcinoma in every IMDC risk (Table 1).

The results of COSMIC 021, a phase II study that tested an escalation dose of cabozantinib from 40 mg to 60 mg with atezolizumab in first-line treatment, was also reported[23]. Data of 70 mRCC patients were presented, showing encouraging clinical efficacy with reasonable safety profiles. The findings suggested that PD-L1+ tumors with high CD8+ T cell infiltrates were more likely to respond to therapy. There is a phase III study (CONTACT-03) currently underway to confirm this combination's efficacy.

A phase II trial of lenvatinib plus pembrolizumab in 104 mRCC patients that were not responding to treatment with immunotherapy was also presented[24]. The ORR was 51%, PFS 11.7 mo, and mDOR 12.2 mo. These results are currently being studied in the phase III CLEAR trial [(lenvatinib + pembrolizumab) *vs* (lenvatinib + everolimus) *vs* sunitinib].

FUTURE DIRECTIONS AND BIOMARKERS

Updates and new trials presented in conferences this year may establish new care standards for mRCC. The update of Keynote 426 presented during American Society of Clinical Oncology (ASCO) 2020[15] suggested that pembrolizumab/axitinib should no longer be offered as the first line of choice of treatment in favorable risk mRCC. Moreover, the results of Checkmate 9ER presented at ESMO[22] showed some advantages of nivolumab/cabozantinib over sunitinib in first-line treatment among all IMDC subgroups and proposed it as a potential first-line option for mRCC.

At this point, there are multiple combination options for first-line treatment and the medical community is divided over which choice is better - two immunotherapies or immunotherapy plus an antiangiogenic drug - considering that the different combinations appear to have similar rates of efficacy, and there are no clear recommendations as to which is the most appropriate for each patient. More data and longer follow-up are needed to clarify the issue and learn whether there are certain populations who would benefit more from one of these combinations, as well as head-to-head comparisons between the combination therapies approved for first-line treatment. Additionally, biomarker-based studies are advisable when several approaches are available and clinical criteria are insufficient to guide treatment strategies.

Until then, taking into account the usual caveats pertaining to this practice, some insight may be gleaned from comparing CTs. At ASCO 2020, for example, the current first-line treatments in intermediate and high-risk mRCC patients (Checkmate 214[11] and Keynote-426[15]) were compared and discussed. Regarding OS data, outcomes in KEYNOTE426 appear to be slightly better at 2 years, and the ORR appears to be slightly higher with pembrolizumab/axitinib in KEYNOTE-426 (55%) than with nivolumab/ipilimumab in Checkmate 214 (42%). However, the percentage of patients who experienced primary progression with tumor growth while on treatment is more striking: 27% for nivolumab/ipilimumab and approximately half that, 15%, for pembrolizumab/axitinib. In clinical practice, pembrolizumab/axitinib appears to be the better choice, compared with nivolumab/ipilimumab, for a patient who needs a response to a rapidly progressing disease or to ameliorate symptoms, based on this cross-study comparison. For other patients, the adverse event profile of each combination would likely help to choose the most appropriate treatment.

An additional consideration is that the choice of first-line treatment may impact selection of second-line therapy. Starting with a combination of immune therapy only forces an automatic choice to use an antiangiogenic drug in the second line. However, starting with a combination of immune therapy and an antiangiogenic makes the second-line choice less clear. For this reason, more data are needed on the most suitable order of therapy for the population at large and specific groups, such as high *vs* slow-growing disease. Indeed, some ongoing CTs are trying to find the best alternative in second and third lines: Atezolizumab/cabozantinib *vs* cabozantinib (CONTACT-03)[25]; MK-6482 *vs* everolimus[26].

Also noteworthy is the recent trend toward three-part strategies, with various ongoing CTs, which have so far provided only preliminary results, including nivolumab + ipilimumab +/- cabozantinib (COSMIC 313)[27]; and the PDIGREE study [28], which proposes the use of nivolumab and ipilimumab followed by nivolumab or nivolumab with cabozantinib.

Conversely, other trials, such as the Checkmate 209-8Y8[29] and the KEYNOTE-427, are looking at maintaining monotherapies. The former proposes the use of nivolumab alone after nivolumab/ipilimumab in intermediate to poor-risk mRCC, while the latter studies the use of pembrolizumab in the frontline setting, showing promising activity (ORR of 36.4%, and disease control of 57.3%)[30].

Another field of study pertains to neoadjuvants and adjuvants, where either nivolumab or pembrolizumab is being evaluated in treatment before surgery (NCT02595918 and NCT02212730, respectively). The PROSPER trial (NCT03055013) assesses nivolumab in neoadjuvant and adjuvant use in node-positive or stage T2-T4 patients compared to observation[31].

Generally speaking, ongoing trials are moving away from sunitinib as the control arm and focus their research on triple therapies or novel therapeutic agents. PIVOT-9, a phase III randomized study, compares NKTR-214 plus nivolumab *vs* sunitinib or cabozantinib in previously untreated mRCC (NCT03729245). A phase II CT (NCT03634540) is studying the combination of HIF-2α inhibitor (PT2977) and cabozantinib.

Telaglenastat, a glutaminase inhibitor, is being studied in previously treated mRCC in combination with cabozantinib and everolimus in two phase II trials (CANTATA and ENTRATA, respectively), and entinostat, an orally available inhibitor of HDACs,

is being considered in several combination therapies[32].

Poly(ADP-ribose) polymerase inhibitors, widely used in other tumors, have been proposed for RCC: Olaparib for patients with DNA repair gene mutations and talazoparib with avelumab.

Finally, the great challenge in mRCC treatment remains to find predictive and prognosis biomarkers. Interesting data are emerging from mRCC patients enrolled in CTs. PD-L1 expression, for example, was associated with poor outcomes in a meta-analysis[33]; but as a predictive marker, the results have been varied[4,34]. Genes have also been studied, including BRCA1-associated protein, which correlates with a poor survival[35], and PBRM1 mutation, which was associated with a longer PFS in the sunitinib and atezolizumab/bevacizumab group in IMotion150[36]. Another attempt to find a gene expression signature tool was made in IMmotion 151[34], where tumors characterized by angiogenesis-high signatures had better PFS with sunitinib and tumors with T effector/interferon-γ-high or angiogenesis-low signatures exhibited better outcomes with atezolizumab/bevacizumab. However, to date, the only predictive biomarker likely to be validated in a phase III randomized controlled trial is the IMDC risk model.

CONCLUSION

In conclusion, we are hopeful that in the coming years, patients and oncologists will continue to move away from a "one-size-fits-all" approach to treatment sequencing and instead move toward a more personalized treatment paradigm in mRCC.

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REVIEW

New approaches for patients with advanced radioiodine-refractory thyroid cancer

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Abstract

The cumulative evidence over the past decades has shown that the incidence of differentiated thyroid carcinoma (DTC) has exponentially increased. Approximately 10% of patients with DTC exhibit recurrent or metastatic disease, and about two-thirds of the latter will be defined as refractory to radioactive iodine (RAIR) treatment. Since this condition implies 10-year survival rates less than 10% after detection, using available treatments, such as systemic and targeted therapies, have become increasingly relevant. The initiation of these treatments aims to reach stabilization, tumor volume reduction, and/or symptom improvement and it should be decided by highly specialized endocrinologists/oncologists on the basis of patient's features. Considering that despite enlarged progression-free survival was proven, multikinase inhibitors remain non-curative, their benefits last for a limited time and the side effects potentially cause harm and quality of life reduction. In this context, molecular testing of cancer cells provides a promising spectrum of targeted therapies that offer increased compatibility with individual patient needs by improving efficacy, progression free survival, overall survival and adverse events profile. This review article aims to provide a summary of the current therapeutic strategies in advanced RAIR-DTC, including approved target therapies as well as those for *off-label* use, RAI resensitization agents, and immunotherapy.

Key Words: Advanced differentiated thyroid cancer; Radioactive iodine refractory thyroid cancer; Multikinase inhibitors; Systemic therapy; Target therapy

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Core Tip: The incidence of differentiated thyroid carcinoma has increased due to the rising detection of low-risk small carcinomas. Nevertheless, approximately 10% of patients exhibit advanced disease and two-thirds of the latter will be defined as radioactive iodine (RAI) refractory. After detection, 10-year survival rates are less than 10%, therefore the role of systemic and targeted therapy in these patients has become increasingly relevant in recent years. This review article aims to provide a summary of the current therapeutic strategies in iodine-refractory thyroid cancer, including approved target therapies as well as those for off-label use, RAI resensitization agents, and immunotherapy.

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INTRODUCTION

The cumulative evidence over the past decades has shown that the incidence of differentiated thyroid carcinoma (DTC) has increased exponentially, probably due to the rising detection of low-risk small carcinomas[1]. Nevertheless, approximately 10% of patients with DTC exhibit a more aggressive behavior in which persistent or recurrent distant metastatic disease is developed, and about two-thirds of them will be defined as refractory to radioactive iodine (RAI) treatment[2]. This condition cannot be defined by a single criterion, but it rather comprises a spectrum of scenarios included into any of the following: (1) Lack of initial RAI uptake in all or some of the metastatic foci in a whole-body scan (diagnostic or following a therapeutic dose) or lose of the ability to take up RAI after previous evidence of uptake; (2) Disease progression in a patient who has received RAI; (3) Disease progression in a patient who has received 600 mCi of ^{131}I of cumulative activity; and/or (4) Locally advanced disease for whom surgical resection is not feasible and RAI uptake status cannot be assessed[2]. After the detection of radioiodine refractory (RAIR) disease, 10-year survival rates may decrease to less than 10%[2]. Therefore, using second-choice treatments, such as systemic and targeted therapy, in these patients has become increasingly relevant in recent years. This review article aims to provide a summary of the current therapeutic strategies for patients with RAIR thyroid cancer, including approved target therapies as well as those prescribed for *off-label* use, RAI resensitization agents, and immunotherapy.

MOLECULAR PATHWAYS OF THYROID CANCER

The underlying carcinogenic molecular pathways of differentiated thyroid cancer have been well defined. The MAPK signaling pathway is one of the most extensively studied[3]. Driver mutations such as in *BRAF* and *RAS* oncogenes, as well as fusions involving tyrosine kinase receptors, lead towards a constitutive activation of the downstream events resulting in cell proliferation, dedifferentiation, and cancer cell survival. These mutations could be targeted with specific therapies which result in cell growth inhibition[3,4]. Meanwhile, multikinase inhibitors (MKIs) confer their anti-tumor effect in radioiodine-refractory metastatic thyroid cancer by other effects, mainly through their anti-angiogenic activity[4]. The main molecular signaling pathways involved in thyroid carcinogenesis and the most significant inhibitors are summarized in Figure 1.

INITIATION OF SYSTEMIC THERAPY

The initiation of health agencies approved systemic therapy or the enrollment of a patient in a clinical trial should be managed by highly specialized endocrinologists/oncologists. The aim of this treatment will be to reach stabilization, tumor volume reduction, and/or symptom improvement[2,4]. Nevertheless, it should be

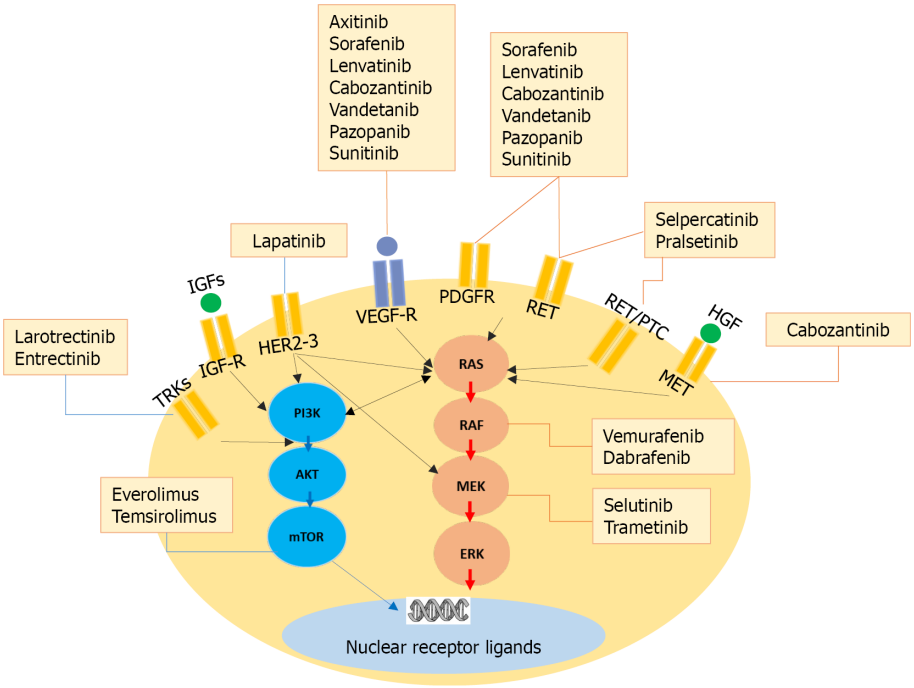

Figure 1 Major molecular signaling pathways involved in thyroid carcinogenesis and its most significant inhibitors.

decided on an individualized basis and under a coordinated decision taken together with patients, considering that target and multikinase inhibitor-based therapies remain non-curative and their benefits in terms of extending progression-free survival last for a limited time. Furthermore, the side effects of these therapies may have the potential to cause harm and significantly reduce the patient's quality of life[4]. Thus, the assessment of tumor burden, disease progression, symptoms, or a high risk of local complications is essential[2]. If available, genetic interrogation should be granted in order to initiate a selective TKI (either an approved drug or from clinical trials) in a patient with a progressive advanced RAIR-DTC that carries a specific target mutation [5]. If not genetic alterations are found, RAIR-DTC patients and those having tumor lesions in which the sum of diameter is larger than 2 cm and showing < 12-mo progression should be considered for multikinase inhibitors[2]. Additionally, all patients with DTC-related imminent symptoms and potentially symptomatic disease should be guaranteed treatment initiation[2]. This is a simplistic view but may help to decide the correct moment of treatment initiation when no other therapies are no longer amenable. A proposed decision-making algorithm for systemic therapy initiation in RAIR-DTC is shown in Figure 2. The main available agents studied in the treatment of RAIR-DTC are summarized in Table 1.

MULTIKINASE INHIBITORS (SORAFENIB AND LENVATINIB)

Multikinase inhibitors block several signaling pathways responsible for tumor proliferation and survival, with varying degrees of potency[2]. However, the main target for MKIs is the vascular endothelial growth factor receptor (VEGFR) and therefore the inhibition of tumor angiogenesis[3]. That is why they are also called antiangiogenic MKIs. These MKIs have demonstrated in phase III trials, an increase in the median progression free-survival (mPFS) from 11 to 18 mo, and objective responses of 12% to 64%[6,7]. We should consider that these drugs are usually tumoristatic and will eventually lose their effect due to *on-target* or *off-target* resistance, after which, another therapy will be needed. To date, only one *post-hoc* analysis of the SELECT study has demonstrated improved overall survival in a subgroup of patients receiving an Lenvatinib *vs* placebo[8].

Sorafenib

Sorafenib inhibits the VEGFR 1, 2, and 3, platelet-derived growth factor, RET, c-kit, and less potently, BRAF kinases[9]. In the phase III DECISION trial, patients treated with sorafenib (n = 207) had a significantly longer PFS over patients receiving placebo

Table 1 Available agents studied in the treatment of radioiodine refractory-differentiated thyroid carcinoma

Agent and national clinical trial number[1]	Molecular target	Phase	Dosage	Enrolled patients (*n*)	PR (%)	mPFS (mo)	Common AEs	Serious AEs (grade ≥ 3)	Withdrawal due to AEs
Sorafenib[6]; NCT00984282	VEGFR1–3, PDGFR, RET, c-kit, BRAF	III	400 mg orally twice daily	207	10.8	12.2	Hand– foot skin reaction (76%), diarrhea (69%), alopecia (67%), rash (50%)	Hand-foot skin reaction (20%), hypertension (10%), weight loss (6%)	19%
Lenvatinib[7]; NCT01321554	VEGFR1–3, FGFR1–4, PDGFR, RET, c-kit	III	24 mg per d in 28-d cycles	261	63.2; 65 (4 complete response + 165 partial response)	18.3	Hypertension (68%), diarrhea (59%), fatigue (59%), decreased appetite (50%), decreased weight (46%), nausea (41%)	Hypertension (42%), proteinuria (10%), decreased weight (10%), fatigue (9%), diarrhea (8%)	14%
Cabozantinib [28]; NCT01811212	VEGFR2, MET, FLT3, RET, c-kit	II	60 mg/d orally	25	40	12.7	Fatigue (44%), weight loss (36%), diarrhea (36%), hand– foot skin reaction (32%), hypertension (24%)	Hypophosphatemia (16%), lipase/amylase increase, neutropenia, fatigue, weight loss (12%)	
Axitinib[71]; NCT00094055	VEGFR, PDGFR, c-kit	II	5 mg twice daily	60	30	18.1	Fatigue (50%), diarrhea (48%), nausea (33%), anorexia (30%), hypertension (28%), stomatitis (25%), weight loss (25%), and headache (22%)	Hypertension (12%), proteinuria (5%), fatigue (5%)	
Vandetanib [72]; NCT00537095	VEGFR2/3, EGFR, RET	II	300 mg/d	72	8.3	11.1	Diarrhea (74%), hypertension (34%), acne (27%), asthenia, anorexia (26%), nausea, rash (25%), fatigue, QTc prolongation (23%)	QTc prolongation (14%), diarrhea (10%), asthenia (7%), fatigue (5%)	33%
Sunitinib[73]; NCT00381641	PDGFR, FLT3, c-kit, VEGFR, RET	II	37.5 mg/d orally	35	31	12.8	Neutropenia (34%), leukopenia (31%), fatigue (26%), HFS (26%), diarrhea (26%)	Neutropenia (34%), leukopenia (31%), diarrhea, hand/foot syndrome (17%), fatigue (11%)	11%
Pazopanib [74]; NCT00625846	VEGFR, PDGFR, c-kit	II	800 mg/d orally in 4-wk cycle	37	49	11.7	Fatigue (78%), skin and hair hypopigmentation (75%), diarrhea (73%), nausea (73%)	Raised alanine aminotransferase level (11%)	5%
Dovitinib[75]; NCT02964144	FGFR, VEGFR	II	500 mg/d orally for five days, followed by a 2-d rest every week	40	20.5	5.4	Diarrhea (54%), anorexia (36%), vomiting (26%), fatigue (23%), and nausea (21%)	Neutropenia (13%)	20%
Apatinib[31]; NCT03167385	VEGFR2, c-Kit, c-SRC	II	750 mg/d orally (*n* = 10, group I) - 500 mg/d orally (*n* = 10, group II)	20	90 (I); 70 (II)	18.4	Hand– foot skin reaction (95%), proteinuria (90%) and hypertension (80%)		
Lapatinib[76]; NCT01947023	HER2/3	I	750 mg initial dose, escalated to 500 mg daily; + Dabrafenib 150 mg twice daily	13	60	15		Lymphocytic toxicity (7%)	
Vemurafenib [58]; NCT01286753	BRAF V600E	II	960 mg orally twice daily	51	VEGFR naive: 39%; Previous VEGFR:	VEGFR naive: 18.8; Previous VEGFR:	Rash (73%), fatigue (69%), alopecia, dysgeusia (54%), creatinine increase, weight decrease	Skin squamous cell carcinoma (23.5%), lymphopenia, and increased γ-glutamyl-transferase (8%)	27%

					27%	8.9	(50%), arthralgia, anorexia, nausea, skin papilloma (46%)		
Dabrafenib [57]; NCT00880321	BRAF V600E	I	150 mg twice daily	13	29	11.3	Skin papillomas (57%), hyperkeratosis (36%), alopecia (29%)	Elevated lipase, elevated amylase, fatigue, febrile neutropenia and squamous cell carcinoma (7%)	0%
Selumetinib [66]; NCT00559949	MEK-1/2, RAS, BRAF V600E	II	100 mg twice daily for 28-d cycles	39	3	8	Rash (77%), fatigue (49%), diarrhea (49%), peripheral edema (36%)	Rash (18%), fatigue (8%)	15%
Larotrectinib [33]; NCT02122913	NTRK fusions	II	100 mg twice daily	153	129 (95%); 24 (16%) complete response	28.3	Fatigue (30%), cough, constipation (27%), dizziness, alanine aminotransferase increase (25%)	Anemia (10%), decreased neutrophil count (5%)	2%
Entrectinib [36]; NCT02097810 (STARTRK-1) NCT02568267 (STARTRK-2)	NTRK fusions	II	600 mg/d orally	54	50	10	Dysgeusia (47%), fatigue, constipation (28%), diarrhea (27%), edema peripheral, dizziness (24%)	Anemia (12%), weight gain (10%)	4%
Everolimus [62]; NCT01118065	mTOR	II	10 mg/d orally	33	3	12.9	Mucositis, acneiform rash, fatigue, cough	Fatigue (8%), weight loss, infection (6%)	
Temsirolimus [63]; NCT01025453	mTOR	II	Temsirolimus (25 mg IV weekly) + sorafenib (200 mg twice daily)	36	22	12		Hyperglycemia (19%), fatigue (13%), anemia (11%), oral mucositis, alanine aminotransferase increased (8%)	14%

[1]from ClinicalTrials.gov.

PR: Partial response; AE: Adverse event; VEGFR: Vascular endothelial growth factor receptor; NTRK: Neurotrophic tropomyosin receptor kinase.

(*n* = 209) (10.8 *vs* 5.8 mo, respectively; HR, 0.587; 95%CI: 0.45–0.76; *P* < 0.0001)[6]. The clinical benefit rate (CR + PR + SD > 6 mo) was 54%, with a PR rate of 12.2% and an SD > 6 mo of 41.8%[6]. The median duration of PR was 10.2 mo. An improvement in OS could not be demonstrated, probably because a large proportion of patients in the placebo arm (71%) crossed over to treatment[6]. In the last metanalysis that included 636 patients from 15 studies receiving sorafenib, 26% of patients (95%CI: 0.19-0.34) achieved a PR, and 44% (98%CI: 0.39-0.48) an SD[10]. PFS time ranged from 9 to 21.3 mo and OS ranged from 10 to 56 mo[10]. In an exploratory analysis of the phase III trial, patients who received open-label sorafenib after progression under the placebo arm achieved a comparable PFS to those receiving sorafenib from the beginning of the trial (9.6 *vs* 10.8 mo)[11]. This could suggest that delaying the initiation of sorafenib could not have a significant impact on the effectiveness. Also, in the same analysis, patients who continued receiving sorafenib after progression had a still longer PFS in comparison to patients who initially received placebo (6.7 *vs* 5.8)[11], meaning that sorafenib could still be an option in patients when an alternative drug is not available or not possible. In our real-life experience with sorafenib (*n* = 18), 72% had SD ≥ 6 mo and 11% demonstrated PR with a PFS of 16.5 mo[12].

The most frequent adverse events during sorafenib treatment were hand-foot skin reaction, diarrhea, fatigue, alopecia, weight loss, and rash[6,10,12]. HFS reaction and hypertension were the most frequent grade 3-4 AEs, reported from to and from to, respectively[6,10,12]. As reported with other MKIs, dose reductions and interruptions were frequent, however, drug withdrawal was uncommon[6,10,12]. The recommended initial dose of sorafenib is 400 mg twice a day[13]. In an exposure-response model, initial lower doses of sorafenib (600 or 400 mg/d) were associated with improved tolerability but reduced PFS. However, a strategy of 800 mg/d for an initial two cycles followed by dose reductions seemed likely to maintain efficacy while possibly mitigating some AEs[14]. The summary of the efficacy and safety of sorafenib in patients with thyroid cancer reported by clinical trials is shown in Table 2.

Table 2 Summary of the efficacy and safety of sorafenib in patients with thyroid cancer reported by clinical trials

Ref.	*n*	Type	PR, %	SD, %	Median PFS (mo)	Median OS (mo)	Most frequent AE	Most frequent grade 3-4 AE
Gupta-Abramson *et al* [77], 2008	27	DTC	26	59	19	-	HFS, 93%	Hypertension, 13%
Kloos *et al*[78], 2009	33	PTC	15	57	16	23	Fatigue, 85%	Fatigue, 16%
Hoftijzer *et al*[79], 2009	31	DTC	25	34	14.5	-	HFS, 66%	HFS, 18%
Cabanilas *et al*[59], 2010	13	DTC	20	60	19		HFS, 60%	-
Keefe *et al*[80], 2011	47	DTC/PD	38	47	22	32.4	-	-
Ahmed *et al*[81], 2011	19	DTC	16	-	-	-	Dermatology (other than HFS), 88%	HFS, 44%
Chen *et al*[82], 2011	9	DTC	33	44	10.5	-	Alopecia, 100%	-
Marotta *et al*[83], 2012	17	DTC	30	41	9	10	HFS, 88%	
Schneider *et al*[84], 2012	31	DTC	31	42	18	34.5	HFS, 71%	HFS, 22%
Capdevilla *et al*[85], 2012	16	DTC	19	50	13.3	23.6	HFS and diarrhea, 62%	HFS, 23%
Brose *et al*[6], 2014	207	DTC	12	42	10.8	.	HFS, 73.6%	HFS, 20.3%
Benekli *et al*[86], 2014	14	DTC	-	43	21.3	-	-	HFS, 22%
Dadu *et al*[87], 2008	51	DTC	-	-	-	56	-	-
Luo *et al*[88], 2014	8	DTC	50	37	9.4	12.8	Alopecia, 75%	Hypocalcemia and serum amylase increased, 12.5%
Gallo *et al*[89], 2015	20	DTC	25	40	8.2	28.4	Fatigue, 95%	Gastrointestinal symptoms, 15%
Kim *et al*[90], 2018	98	DTC	25	37	9.7	-	HFS, 76%	HFS, 41%
Jerkovich *et al*[12], 2019	18	DTC	11	72	16.5	-	HFS, 67%	HFS, 14%

DTC: Differentiated thyroid carcinoma. PR: Partial response; PFS: Progression free survival; SD: Stable disease; OS: Overall survival; AE: Adverse event.

Lenvatinib

Lenvatinib inhibits FGFR1, -2, -3, -4, PDGFR, VEGFR1, -2, -3, RET, and KIT kinases [15]. In phase III clinical trial SELECT, median PFS was significantly longer in patients treated with lenvatinib in comparison to those receiving placebo (18.3 *vs* 3.6 mo, respectively; HR, 0.21; 99%CI: 0.14-0.31; $P < 0.001$)[7]. The response rate was 64.8% (CR 1.5% and PR 63.2%), with a median time to response of only 2 mo[7]. Real-life studies published afterward had reported PR from 31% to 69%, SD from 20% to 60%, and PFS from 10 to 13.8 mo[16-23]. This apparent lower efficiency of lenvatinib in observational data could be explained by the fact that these studies included patients with more than one prior MKI treatment, ECOG PS ≥ 3, more comorbidities, and patients who did not start with a full dose (24 mg per day). In fact, in our experience with lenvatinib (n = 22), when we excluded patients that would have not met the SELECT inclusion criteria, PR increased from 31.8% to 50% and PFS from 13.7 to 22 mo[23]. Hypertension was the most common adverse event (63%-83%) in almost all studies[7,16-19,21,23] and the most frequent grade 3-4 adverse event, occurring in 31%-42% of cases[7,23]. Other adverse effects include diarrhea, fatigue, decreased appetite, and decreased weight[7,16-23]. The recommended initial dose is 24 mg per day[13]. A lower initial dose and longer dose interruptions led to lower response rates and shorter progression-free survival[24,25]. A summary of the efficacy and safety of lenvatinib in patients with thyroid cancer reported by phase III clinical trial and real-life studies is shown in Table 3.

Cabozantinib

Cabozantinib is a RET, vascular endothelial growth factor receptor-2 (VEGFR2), and MET kinases inhibitor agent currently approved for the treatment of advanced medullary thyroid cancer[26]. However, it has also been studied in 15 patients with RAI-refractory DTC in a phase I clinical trial, with promising efficacy[27]. Ten of the

Table 3 Summary of the efficacy and safety of lenvatinib in patients with thyroid cancer reported by phase III clinical trial and real-life studies

Ref.	*n*	Patients with prior TKIs %	CR %	PR %	SD %	Median PFS (mo)	Median OS (mo)	Most frequent AE	Most frequent grade 3-4 AE
Schlumberger *et al*[7] 2015	261	25	1	63	23	18.3	-	Hypertension, 68%	Hypertension, 42%
Berdelou *et al*[16], 2017	75	68	0	31	51	10	-	Fatigue, 75%	Hypertension 35%
Jasim *et al*[17], 2017	25	31	0	50	28	-	-	Hypertension 64%	Hypertension 40%
Sugino *et al*[18], 2018	29	13	0	69	21	-	-	Hypertension 76%	-
Locati *et al*[19], 2019	94	64	0	36	41	10.8	23.8	Fatigue, 13%	Fatigue, 8%
Lee *et al*[20], 2019	57	89	0	38	60	5.1	19.3	General weakness 43%	
Masaki *et al*[21], 2019	42	10	0	62	24	13.8	-	Hypertension, 83%	Proteinuria, 36%
Aydemirli *et al*[22], 2020	39	77	2	33	37	9.7	18.3	Hypertension and fatigue, 64%	Hypertension, 28%
Jerkovich *et al*[23], 2020	22	59	4	32	32	13.7	-	Hypertension, 64%	Hypertension, 23%

TKIs: Tyrosine kinase inhibitors; CR: Complete response; PR: Partial response; SD: Stable disease; PFS: Progression free survival; OS: Overall survival; AE: Adverse event.

included patients were previously treated with VEGF inhibitors, mostly sorafenib. Cabozantinib was administered at a starting dose of 140 mg daily. A partial response was observed in 8 (53%) patients, 5 with prior VEGF inhibitors treatment. On the other hand, a phase II trial is currently ongoing, which involves a cabozantinib therapy in RAIR-DTC patients who experienced disease progression after second- or third-line VEGFR-targeted therapy[28]. Partial response was reached in 10 (40%) of the 25 enrolled patients, with a starting dose of 60-80 mg daily. The median PFS and OS were 12.7 and 34.7 mo, respectively[28].

Exelixis announced by the end of 2020 that, at a planned interim analysis, the phase III COSMIC-311 pivotal trial met the co-primary endpoint, demonstrating a significant reduction in the risk of disease progression or death of 78% of patients receiving cabozantinib compared to placebo (HR, 0.22, 96%CI: 0.13-0.36; $P < 0.0001$) in patients with RAIR differentiated thyroid cancer who have progressed after up to two prior VEGFR-targeted therapies. The safety profile was consistent with that previously observed for cabozantinib. In 2021, Exelixis® announced that the United States Food and Drug Administration (FDA) approved cabozantinib as a second/third line additional treatment for patients with RAIR thyroid cancer[29]. With this third MKI approved, there will surely be a change in defining first and second line of treatment according to the drug potency.

Apatinib

Apatinib, also known as rivoceranib, is a tyrosine kinase inhibitor that selectively inhibits the *VEGFR2*. Apatinib inhibits VEGF-mediated endothelial cell migration and proliferation thus blocking new blood vessel formation in tumor tissue. This agent also mildly inhibits c-Kit and c-SRC tyrosine kinases[30]. A recent phase II study performed in 20 patients with advanced thyroid cancer showed promising results with an objective response rate (ORR) of 80%, a median PFS of 18.4 mo (95%CI: 9.2-36.8 mo) and a median OS of 51.6 mo (95%CI: 29.2-not reached). The most common adverse events included palmar-plantar erythrodysaesthesia syndrome (19/20), proteinuria (18/20) and hypertension (16/20)[31].

SELECTIVE KINASE INHIBITORS

NTRK inhibitors (larotrectinib and entrectinib)

Neurotrophic tropomyosin receptor kinase (*NTRK*) fusions have been reported in

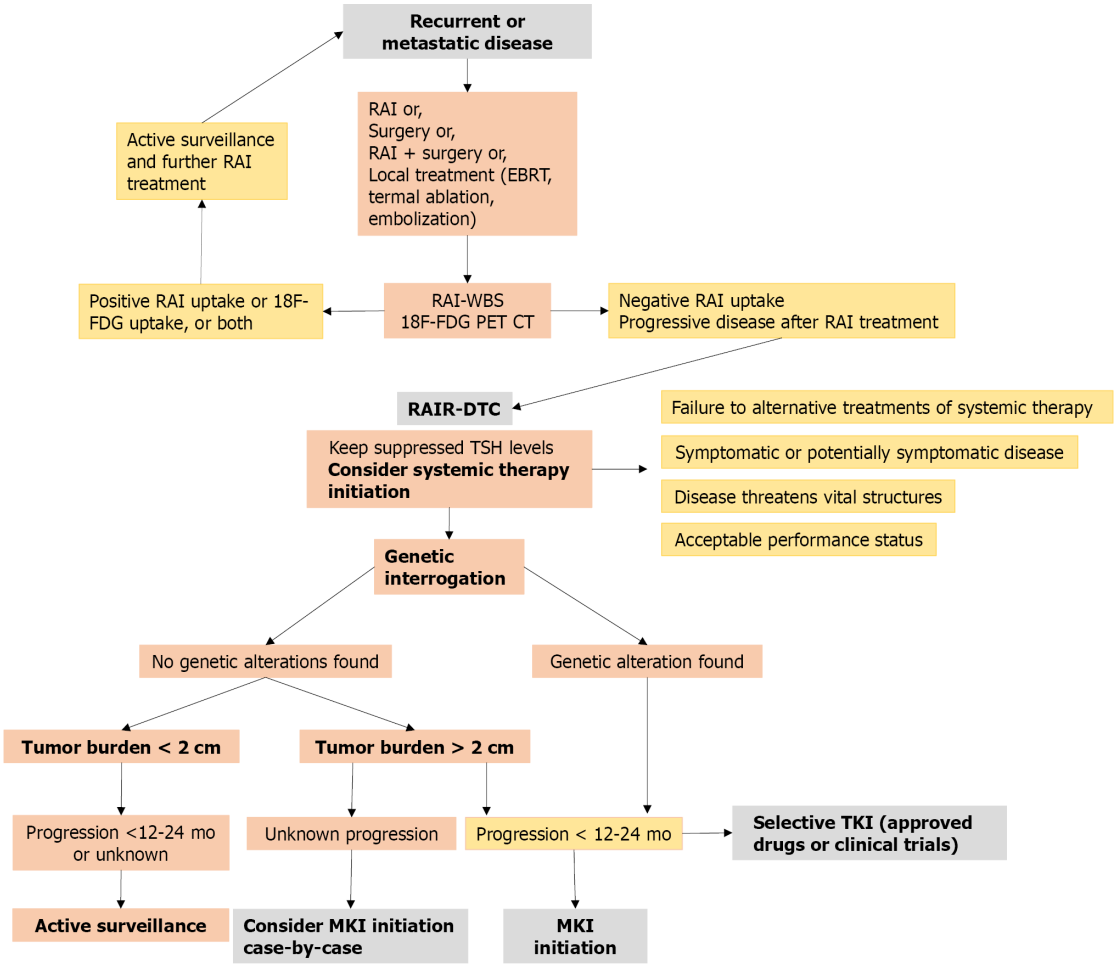

Figure 2 Proposed decision-making algorithm for systemic therapy initiation in radioiodine refractory-differentiated thyroid carcinoma.

variable percentages of patients with DTC (2%-25%)[32]. Larotrectinib and Entrectinib are highly selective inhibitors of *TRK* receptors and have been approved by the FDA for the treatment of any solid tumor-bearing an *NTRK1-3* fusion mutation (tumor-agnostic indication). Entrectinib also inhibit altered oncogenic expression of *ALK* and *ROS1*, which are much less frequent in DTC[32].

In a pooled analysis of three-phase 1/2 clinical trials, out of 24 patients with DTC bearing an *NTRK* fusion who received larotrectinib, 79% experienced an objective response[33]. This drug showed durable responses with a median time of 35 mo in the overall group of patients with solid tumors[33]. Also, larotrectinib seems to be active within the central nervous system (CNS)[33], which makes it an indispensable option when brain metastases are present in patients harboring this fusion, knowing that they have a worse outcome in patients with differentiated thyroid cancer[34]. Most frequent adverse events were primarily grade 1 and 2 and included fatigue (30%), cough, constipation (27%), dizziness (25%), and alanine aminotransferase increase (25%). The most common grade 3 or worse treatment-emergent adverse events (regardless of attribution) were anemia (10%) and decreased neutrophil count (5%)[33]. We recently showed our experience with Larotrectinib in a patient with RAIR DTC who had a rapid progression on MKI therapy (sorafenib and lenvatinib), and who had a complete response to treatment including the disappearance of multiple CNS metastasis[35].

Entrectinib also blocks *ROS1* and *ALK* and was specifically designed to have systemic activity and cross the blood–brain barrier. In an analysis of three-phase I or II trials, two out of four patients had a PR with entrectinib[36]. Most AE were grade 1-2 and included dysgeusia (47%), fatigue (28%), and constipation (28%). The most common grade 3 or 4 treatment-related AE were anemia (12%) and weight gain (10%)[36].

Resistance to larotrectinib and entrectinib

TRK fusion-positive cancers can develop resistance to *TRK* inhibition[37]. This resistance can be classified into *off-target* (new additional mutations that may occur in

the tumor) or *on-target* (within the same altered receptor, due point mutations that lead to amino acid substitutions in the solvent front, the gatekeeper residue or the *xDFG* motif)[38]. Mutations in the *NTRK* kinase domain cause resistance to *TRK* inhibitors by interfering with binding of the inhibitor, altering the kinase domain conformation or altering ATP-binding affinity[38].

New drugs are currently in development for those patients who develop *on-target* resistance, among them, selitrectinib and repotrectinib. Due to their small size, these low molecular weight molecules are able to engage the ATP-binding pocket while avoiding the steric penalties of kinase domain substitutions[39,40]. Selitrectinib is currently the drug with which the most experience has been gained. Thirty-one patients with solid tumors with *NTRK* fusions, previously treated with a *TRK* inhibitor (larotrectinib, entrectinib or PLX7486) with a median duration of prior therapy of 11 mo (range 2-30 mo) received treatment with selitrectinib. In patients with *TRK* kinase domain mutations (the majority of which involved the solvent front), the ORR was 45%[41].

Selective RET inhibitors (selpercatinib and pralsetinib)

RET/PTC rearrangements are present in 5%-25% of papillary thyroid carcinomas[42], although the occurrence of these mutations may be less frequent in advanced DTC [43]. Selpercatinib and pralsetinib, are kinase inhibitors that selectively target *RET* kinase, and were approved by the FDA for the treatment of advanced or metastatic *RET* fusion-positive thyroid cancer. In the phase 1/2 trial LIBRETTO-001, among 19 *RET* fusion-positive, non-medullary thyroid cancer patients, objective response was reported in 79%[44]. At 1 year, 71% of responses were ongoing, and 64% of the patients were free of progression[44]. The most common grade 3 or 4 adverse events included hypertension (21%), increased alanine aminotransferase (11%), increased aspartate aminotransferase (9%), hyponatremia (8%), and diarrhea (6%)[44].

In the phase 1/2 ARROW trial, praseltinib demonstrated objective responses in 75% (9/12), with a median duration of response of 14.5 mo, and 67% of responding patients continuing treatment[45]. Most treatment-related adverse events were grade 1-2, and included increased aspartate aminotransferase (31%), anemia (22%), increased alanine aminotransferase (21%), constipation (21%) and hypertension (20%)[45].

Mutation-specific kinase inhibitors -*RET* and *NTRK* inhibitors, as well as *BRAF* inhibitors-produced higher and durable objective responses[32,33,42,43]. Although prolongation of progression-free survival has not yet been demonstrated in phase III clinical trials, they seem to be promising options for RAIR thyroid cancer patients. In line with this, the implementation of molecular screening strategies seems to be necessary to improve the clinical course of these patients.

Resistance to selpercatinib and pralsetinib

Evidence on acquired resistance mechanisms to *RET*, both *on target* and *off-target*, is recently arising. Selpercatinib and pralsetinib were oriented to target gatekeeper mutations, such as *RET V804* and *S904F* which was associated with resistance to *RET*-targeted kinase inhibitors, as vandetanib[46]. Nevertheless, five *RET* kinase domain mutations at three non-gatekeeper residues were identified from selpercatinib and pralsetinib-resistant medullary thyroid cancer cell lines in a recent experimental study [47]. Information on acquired resistance to these drugs obtained from studies on non-small cell lung cancer (NSCLC) is slightly more extensive. For example, it was found acquired *RET G810R/C/S/V* mutations in *RET* fusion-positive tumors from patients who developed resistance to selpercatinib[48] and pralsetinib treatments[49]. Other reports of acquired selpercatinib resistance with *MET* amplification were demonstrated, in which probably this could be overcome by combing selpercatinib with crizotinib[50]. On the other hand, it was postulated that the combination of pralsetinib or selpercatinib with a selective *MET* inhibitor -such as capmatinib, savolitinib, or tepotinib- could offer acceptable tolerability and efficacy in NSCLC patients[51].

These experimental findings have shown the imperative need to develop next-generation targeted *RET* agents focused on both gatekeeper and non-gate keeper mutations for on- and off-target resistance in order to develop and validate combination therapies.

OFF-LABEL DRUGS FOR DIFFERENTIATED THYROID CARCINOMA

Considering the time-limited benefits of *FDA*-approved kinase inhibitors treatment in RAI-refractory thyroid cancer, it became necessary to develop additional new

therapeutic lines that would enhance compatibility with individual patient needs by improving efficacy and adverse events profile. Several targeting agents are being studied in advanced differentiated thyroid cancers, but none of them have been approved yet (Table 1). A summary of some relevant ongoing clinical trials for the treatment of advanced RAIR-DTC are shown in Table 4.

SELECTIVE BRAF INHIBITORS

Combination of dabrafenib-trametinib

BRAF oncogene mutations are present in approximately 50% of PTCs, while it has been observed that it rises to over 90% when an anaplastic transformation emerges from a prior history of PTC[52]. Under this premise, a clinical study using the combination dabrafenib 150 mg twice daily + trametinib 2 mg daily (selective inhibitors of *BRAF V600E* kinase and *MEK1-2* kinase, respectively) in 23 patients with locally advanced, unresectable, or metastatic ATC[53], prompted the rapidly FDA approval for these patients. This study showed an overall response rate of 61%, with complete and partial response rates of 4% and 57%, respectively. Progression free survival for at least 6 mo was seen in 64% of these patients and overall survival was 80% at 1 year. The most common adverse events were fatigue (44%), fevers (31%), and nausea (31%), and the most common grade 3 and 4 adverse event was anemia (13%) [53].

In our setting, where access to molecular tests and target therapies is not widely available yet, we have reported the cases of two patients with metastatic and locally unresectable ATC, in whom the use of dabrafenib-trametinib (D-T) provided a dramatic reduction of the cervical mass with a minimal residual loco-regional disease, and even allowed surgical resection on one of them. Besides, a partial and complete response to the pulmonary metastatic disease was also observed[54,55].

The combination of D-T was studied in a phase II clinical trial that included 53 patients with *BRAF* mutated RAIR-PTC with disease progression within the last year [56]. The participants were randomized to Arm A (dabrafenib 300 mg daily, n = 26) or Arm B (dabrafenib 150 mg daily + trametinib 2 mg daily, n = 27). Cross-over to Arm B was allowed at the time of progression. Out of 25% of patients had prior therapy with multi-kinase inhibitors. Preliminary results exhibited partial responses in 10 (38%) and 9 (33%) patients from Arm A and B, respectively. Progression-Free Survival for patients who received D-T was 11.4 mo, with a median follow-up of 13 mo. The treatment-related adverse events were similar to previously reported trials[56].

Dabrafenib and vemurafenib in RAIR-DTC

Dabrafenib and vemurafenib have been approved as single agents for the treatment of advanced melanoma, but they also have been evaluated in phase 2 trials in patients with *BRAF V600E*–mutated PTC[57,58]. Both *BRAF* inhibitors are effective also in papillary carcinoma, although the outcomes have not been as robust as for ATC, so neither are currently approved for this use. In general terms, objective responses were seen for up to half of patients treated with either vemurafenib or dabrafenib in different trials and clinical experiences[57-59]. Among them, a randomized, multi-institutional, open-label phase 2 trial was conducted over two arms of patients with *BRAF V600E*–mutated PTC[57]. Arm A employed dabrafenib as a single agent and arm B, the combination of dabrafenib with trametinib. Partial responses were reached in 10 of 26 patients (38%) from arm A, and 9 of 17 (33%) from arm B, with median PFS of 11.4 and 15.1 mo, respectively. Common adverse events included fever, diarrhea, anemia, fatigue, nausea, alopecia and skin reactions[57]. Meanwhile, a non-randomized, open-label, multicenter phase 2 vemurafenib trial was conducted in two cohorts of patients with *BRAF V600E*–mutated PTC. Cohort 1 was comprised of 26 patients who had never received multikinase VEGFR inhibitors, in which the best overall response (partial response) was reached in 12 patients (38%), with a median duration of PFS of 18.8 mo (14.2–26), and the median OS had yet to be reached. In cohort 2 were included 25 patients who previously received MKIs treatment. Partial response rates were seen in 27.3%, with a median PFS of 8.9 mo. The most common adverse events reported were rash, fatigue, weight loss, dysgeusia, and alopecia. Serious adverse events were seen in 62% and 68% of the patients in cohort 1 and 2, respectively, including benign and malignant skin lesions and cerebrovascular accidents, among others[58].

Table 4 Some relevant ongoing clinical trials for the treatment of advanced radioiodine refractory-differentiated thyroid carcinoma (thru March 11, 2021, from clinicaltrials.gov)

NCT number	Title	Status	Interventions	Characteristics	Population	Dates	Locations
NCT04554680	Clinical Trial in RAI-Refractory Thyroid Carcinoma Evaluating BRAF & MEK Blockade for Redifferentiation Therapy	Recruiting	Drug: Dabrafenib and trametinib	Study type: Interventional Phase: Phase 2 Study design: Allocation: N/A; Intervention model: Single group assignment; Masking: None (open label); Primary purpose: Treatment outcome; Measures: The proportion of participants attaining at least one tumor lesion with lesional dosimetry of ≥ 2000 cGy with I-131 dose of =	Enrollment: *n* = 5 Age: 21-99 yr Sex: All	Study start: December 30, 2020 Study completion: April 2022	National University Hospital, Singapore, Singapore
NCT01709292	Vemurafenib Neoadjuvant Trial in Locally Advanced Thyroid Cancer	Active, not recruiting	Drug: Vemurafenib (all groups) Drug: Vemurafenib (Post Surgery) - Group A + C Other: Post Surgery - Group B	Study type: Interventional Phase: Phase 2 Study design: Allocation: NonRandomized intervention; Model: Parallel assignment; Masking: None (open label); Primary purpose: Treatment outcome; Measures: Percent change in ERK (extracellular-signal regulated kinase) phosphorylation and tumor size, objective response rate	Enrollment: *n* = 24 Age: 18 yr and older Sex: All	Study start: November 7, 2012 Study completion: November 30, 2020	University of Texas MD Anderson Cancer Center, Houston, Texas, United States
NCT03167385	Phase 2 Trial of Apatinib Mesylate in Locally Advanced/ Metastatic Differentiated Thyroid Carcinoma	Unknown	Drug: Apatinib mesylate	Study type: Interventional Phase: Phase 2 Study design: Allocation: N/A; Intervention model: Single group; assignment; Masking: None (open label); Primary purpose: Treatment outcome; Measures: Disease control rate, progression free survival, overall survival, objective response rate	Enrollment: *n* = 20 Age: 18 to 75 yr Sex: All	Study start: March 22, 2017 Study completion: December 31, 2020	Tianjin Medical University Cancer Institute and Hospital, Tianjin, Tianjin, China
NCT03753919	Durvalumab Plus Tremelimumab for the Treatment of Patients With Progressive, Refractory Advanced Thyroid Carcinoma - The DUTHY Trial	Recruiting	Drug: Durvalumab Drug: Tremelimumab	Study type: Interventional Phase: Phase 2 study Design: Allocation: N/A; Intervention model: Single group assignment; Masking: None (open label); Primary purpose: Treatment outcome; Measures: Progression-free survival rate at 6 mo, overall survival rate at 6 mo, overall response rate,	Enrollment: 46 Age: 18 yr and older Sex: All	Study start: April 2 Study completion: July 2021	Instituto Catalán de Oncología de Hospitalet, L'Hospitalet de Llobregat, Barcelona, Spain; Hospital Provincial de Castellón, Castelló, Valencia, Spain; Hospital Clínic Barcelona, Barcelona, Spain; Hospital Universitari Vall d'Hebron, Barcelona, Spain; MD Anderson Cancer Center, Madrid, Spain; Hospital Clínico San Carlos, Madrid, Spain; Hospital Universitario 12 de

				duration of response, median progression-free survival, incidence of treatment, emergent adverse events (safety and tolerability), median overall survival, response status after start of study treatment			Octubre, Madrid, Spain; Hospital Universitario HM Sanchinarro, Madrid, Spain; Hospital Universitario La Paz, Madrid, Spain; Hospital Universitario Ramón y Cajal, Madrid, Spain; and 5 more
NCT00537095	Efficacy and Safety of Vandetanib (ZD6474) in Patients With Metastatic Papillary or Follicular Thyroid Cancer	Active, not recruiting	Drug: Vandetanib Other: Placebo	Study type: Interventional Phase: Phase 2 Study design: Allocation: Randomized; Intervention model: Parallel assignment; Masking: Double (participant, investigator); Primary purpose: Treatment outcome; Measures: Time to tumor progression, disease control rate at 6 mo, objective response rate, time to death	Enrollment: *n* = 165 Age: 18 yr and older Sex: All	Study start: September 29, 2007 Study completion: December 2021	Research Site, Brussels, Belgium; Research Site, Odense, Denmark; Research Site, Angers Cedex 9, France Research Site, Angers Cedex, France; Research Site, Bordeaux Cedex, France; Research Site, Caen Cedex 5, France; Research Site, Caen Cedex, France; Research Site, Lyon Cedex, France; Research Site, Lyon, France; Research Site, Marseille Cedex 9, France; and 12 more
NCT03602495	Donafenib in 131I-Refractory Differentiated Thyroid Cancer	Recruiting	Drug: Donafenib Drug: Placebo	Study type: Interventional Phase: Phase 3 Study design: Allocation: Randomized; Intervention model: Parallel assignment; Masking: Double (participant, investigator); Primary purpose: Treatment outcome; Measures: Progression-free survival, overall survival, objective response rate, disease control rate, time to disease progression	Enrollment: *n* = 204 Age: 18 yr and older Sex: All	Study start: August 29, 2018 Study completion: December 2021	Peking Union Medical College Hospital, Beijing, Beijing, China

Selective mTOR inhibitors (everolimus, temsirolimus)

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that exerts as an essential regulator of cell growth-related processes[60]. Everolimus and temsirolimus are two *mTOR* inhibitors that demonstrated clinical benefits in other cancers like advanced renal carcinoma, metastatic breast cancer, and pancreatic neuroendocrine tumors, in which they were approved by the FDA[61]. Since the mTOR pathway is over-activated in thyroid cancer, some studies have tested these agents' effects on advanced thyroid cancer, with promising outcomes[62,63].

Everolimus was evaluated in a single-arm, multicentric phase II study that included 31 patients with aggressive RAIR-DTC, among other thyroid tumor histologies. There was one PR (3%) but 27 patients (82%) had SD, for a clinical benefit rate of 84.8% and a median PFS for 12.9 mo. Median OS was not reached and 2-year OS was 73.5%[62]. For its part, a phase 2 study that enrolled 36 patients with metastatic RAIR-DTC evaluated the efficacy of the combination of oral sorafenib (200 mg twice daily) and intravenous temsirolimus (25 mg weekly)[63]. A partial response was reached in 8 patients (22%), while stable and progression disease was seen in 21 (58%) and 1 (2%) patients, respectively. The mPFS at one year was 30.5% and the most common toxicities included hyperglycemia, fatigue, anemia, and oral mucositis. The authors concluded that this combination appears to have better response rates in patients with RAI-refractory thyroid cancer who received no prior treatment, regardless of whether *RAS* or *RAF* mutation was present[63].

Redifferentiation agents

It has been well described that activating *BRAF* mutations induce loss of differentiated

features required for response to radioiodine treatment, while its blockade would restore radioiodine uptake in experimental models[64]. In patients with radioiodine-refractory differentiated carcinoma with somatic *BRAF* or *RAS* mutations, treatment with the specific targeted inhibitors may restore radioiodine responsiveness in up to two-thirds of patients, permitting iodine therapeutic administration leading to tumor shrinkage in up to one-third[57-59]. On the other hand, constitutive activation of MAPK pathway causes inhibition of a variety of thyroid genes, including NIS, leading to the investigation of selective MAPK blocking agents as Selumetinib, as redifferentiation agent[64,65].

Selumetinib

Selumetinib is a *MEK1–2*, *RAS* and *BRAF V600E* inhibitor which efficacy was evaluated in 32 RAIR-DTC patients enrolled in a multicenter, open-label, phase II trial [66]. There were 1 partial response (3%), 21 stable disease (54%), and 11 progressive diseases (28%). Median PFS was 32 wk, and it was seen that *BRAF V600E* mutants had a longer median PFS compared with patients with BRAF wild-type cancer (33 *vs* 11 wk, respectively). This suggest a potential beneficence of Selumetinib based on underlying genetic disorders. The most common adverse events included rash, fatigue, diarrhea, and peripheral edema[66]. A phase III trial is currently in progress which continues to explore selumetinib's redifferentiation benefits in a larger number of participants[66] (Table 2).

Immunotherapy

In recent years, there has been significant progress in the field of oncological immunotherapy. Several immunotherapeutic agents have now been approved by the FDA for the treatment of a variety of malignancies, including melanoma, non-small cell lung cancer, renal and breast carcinomas, among others[67]. In this line, several phase I studies research the use of immunotherapy in the treatment of advanced differentiated thyroid cancer focuses on restoring immune surveillance[68]. The recent identification of blocking antibodies of CTLA-4 and PD-1 to their corresponding ligands (CD80/86 and PD-L1/PD-L2 respectively) enhances the effector T cells and inhibits the regulatory suppressor cells. Thus, the evidence of PD-1 (+) T cell in thyroid tumors involved lymph nodes in PTC patients suggests the potential utility of immune checkpoint inhibitors like pembrolizumab (as a single agent or in combination with MKIs) for advanced thyroid cancers[68]. Only a few immunotherapy trials in patients with thyroid cancer have been published to date, but several trials are ongoing.

Pembrolizumab

Pembrolizumab is an anti–PD-1 monoclonal antibody that exhibits antitumor activity by blocking interaction between PD-1 and its ligands[68]. Patients with advanced thyroid cancer were enrolled in the nonrandomized, phase Ib KEYNOTE-028 trial conducted to evaluate its safety and antitumor activity in 22 patients with advanced papillary or follicular thyroid cancer. Pembrolizumab 10 mg/kg was administered every 2 wk up to 24 mo or until confirmed progression or intolerable toxicity. SD was achieved by 57% (4/7) of patients with follicular histology and 60% (9/15) of patients with papillary histology and two patients reached partial response for 8 and 20 mo. Median PFS was 7 mo and median overall survival was not reached. Diarrhea and fatigue were the most common adverse events[69]. This study suggests that pembrolizumab may be effective and have a favorable safety profile in PD-L1–positive thyroid cancer, providing a baseline for future research[69].

Other ongoing single-arm multicenter phase II study combine lenvatinib and pembrolizumab in patients with RAIR-DTC[70]. Patients were excluded if they had received previous VEGFR-directed multikinase therapy. The lenvatinib starting dose was 20 mg/d orally and pembrolizumab was 200 mg IV every 3 wk. The preliminary results showed that out of 29 evaluable patients, 18 (62%) had a partial response, 10 (35%) had stable disease and the clinical benefit rate was 97%. The PFS at 12 mo was 74%, and median PFS was not yet reached. The most common adverse events were hypertension (47%), weight loss (13%), maculopapular rash (13%), leukopenia (7%), diarrhea (7%), and oral mucositis (7%)[70]. While the results are promising, the continuation of this study will help determine the magnitude of the responses.

CONCLUSION

In conclusion, therapeutic options for patients with advanced radioiodine-refractory differentiated thyroid carcinoma have been increasingly evolving and fine-tuned. While the introduction of new therapies for multiple molecular targets has made it possible to extend progression-free survival, their impact on overall survival is still unclear. Based on the improving knowledge of the underlying molecular mechanisms in these patients, novel agents under study bring us a new scope for the near future. Thus, increasingly tailored therapy focused on critical molecular pathways will be offered, allowing to overcome drug evasion mechanisms, enhance efficacy, minimize adverse events, and finally achieve an overall survival improvement in these patients.

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MINIREVIEWS

Immunotherapy: A new standard in the treatment of metastatic clear cell renal cell carcinoma

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Abstract

Renal cell cancer (RCC) represents 2%-3% of all adulthood cancers and is the most common malignant neoplasm of the kidney (90%). In the mid-nineties of the last century, the standard of treatment for patients with metastatic RCC was cytokines. Sunititib and pazopanib were registered in 2007 and 2009, respectively, and have since been the standard first-line treatment for metastatic clear cell RCC (mccRCC). Renal cell cancer is a highly immunogenic tumor with tumor infiltrating cells, including CD8+ T lymphocytes, dendritic cells, natural killer cells (NK) and macrophages. This observation led to the design of new clinical trials in which patients were treated with immunotherapy. With the growing evidence that proangiogenic factors can have immunomodulatory effects on the host's immune system, the idea of combining angiogenic drugs with immunotherapy has emerged, and new clinical trials have been designed. In the last few years, several therapeutic options have been approved [immunotherapy and immunotherapy/tyrosine kinase inhibitors (TKI)] for the first-line treatment of mccRCC. Nivolumab/ipilimumab is approved for the treatment of patients with intermediate and poor prognoses. Several checkpoint inhibitors (pembrolizumab, nivolumab, avelumab) in combination with TKI (axitinib, lenvatinib, cabozantinib) are approved for the treatment of patients regardless of their International mRCC Database Consortium prognostic group and PD-L1 expression. There is no specific and ideal biomarker that could help in selecting the ideal patient for the appropriate first-line treatment.

Key Words: Renal cell carcinoma; Immunotherapy; Checkpoint inhibitors; Biomarkers; Tumor microenvironment; Programmed cell death 1 receptor

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Core Tip: Renal cell cancer is a highly immunogenic tumor infiltrated by cells, including CD8+ T lymphocytes, dendritic cells, natural killer cells and macrophages. This observation led to the design of new clinical trials in which patients were treated with immunotherapy. With the growing evidence that proangiogenic factors can have immunomodulatory effects on the host's immune system, the idea of combining angiogenic drugs with immunotherapy has emerged, and new clinical trials have been designed. In the last few years, several therapeutic options have been approved (immunotherapy and immunotherapy/tyrosine kinase inhibitors) as first-line treatment for metastatic clear cell renal cell cancer.

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INTRODUCTION

Renal cell cancer (RCC) represents 2%-3% of all adulthood cancers and is the most common malignant neoplasm of the kidney (90%)[1]. Clear cell cancer (75%) is the most prevalent histological subtype of RCC, followed by papillary (10%), chromofobe (5%), collecting ducts (0.4%-1.8%) and unclassified (4%-6%)[2]. RCC typically occurs in the fifth and sixth decade of life and is twice as frequent in men than in women[3]. At the time of diagnosis, one-third of all patients have metastatic disease, while a quarter of all patients, with initially localized disease, relapse after nephrectomy[4]. According to two prognostic models, Memorial Sloan Kettering Cancer Center (MSKCC) and International mRCC Database Consortium (IMDC), metastatic RCC (mRCC) patients can be divided into 3 prognostic categories: favorable, intermediate and poor risk[5,6] (Table 1).

In the mid-nineties of the last century, the standard of treatment for patients with metastatic RCC was cytokines, typically interferon-alpha and interleukin 2. Beside the high toxicity profile of cytokines, patients who were treated achieved an objective response rate (ORR) of 10-20%, while the median overall survival (OS) was 11-14 mo [7-9].

Renal clear cell carcinoma is commonly associated with Von Hippel-Lindau (VHL) gene mutations (70% of patients) located on chromosome 3p and mediates cell apoptosis in response to hypoxia[10,11]. If this mutation is present, apoptosis does not occur, hypoxia-induced factor (HIF) accumulates and activates vascular endothelial growth factor (VEGF), and platelet growth factor (PDGF) and others engage in the angiogenesis process, which is one of the key promoters of cell growth in RCC[12]. This knowledge leads to the development of new antiangiogenetic drugs. Other mutations, such as PBRM1 (40%), SETD28 (15%) and BAP1 (15%), have recently been discovered. Sunititib and pazopanib were registered in 2007 and 2009, respectively and have been the standard first-line treatment for mRCC ever since. The median survival of patients treated with these drugs is 24-29 mo, while the objective response rate (ORR) is 30%-33%[13,14].

RCC is a highly immunogenic tumor with infiltrating cells, including CD8+ T lymphocytes, dendritic cells, natural killer cells (NK) and macrophages. This observation led to the design of new clinical trials in which patients were treated with immunotherapy[15]. Checkpoint inhibitors are monoclonal antibodies targeting the link between programmed cell death protein 1 (PD-1) and its ligands PD-L1 and PD-L2[16]. The PD-1 receptor is located on T cells, while PD-L1 and PD-L2 are present on other immune cells. The ligand can be found on both tumor cells and immune infiltrate cells, allowing them to bind to the PD-1 receptor of T-cells and escape the host immune response[17,18]. Checkpoint inhibitors block this interaction and permit the host's immune response to the tumor[16].

Nivolumab is humanized PD-1 monoclonal antibody. The first data on nivolumab in mRCC were the results of the phase I Checkmate 033 trial, where nivolumab was

Table 1 Poor prognostic factor

Poor prognostic factor	MSKCC	IMDC
Time from diagnosis to treatment	< 12 mo	< 12 mo
Hemoglobin	< lower limit of normal	< lower limit of normal
Corrected serum calcium	> 10 mg/dl (2.5 mmol/L)	> upper limit of normal
Karnofsky performance score	< 80%	< 80%
Neutrophil count	/	> upper limit of normal
Platelet count	/	> upper limit of normal
Lactate dehydrogenase	> 1.5 x upper limit of normal	/
Good risk	0 risk factor	0 risk factor
Intermediate risk	1 or 2 risk factors	1 or 2 risk factors
Poor risk	3, 4 or 5 risk factors	3, 4, 5 or 6 risk factors

MSKCC: Memorial Sloan Kettering Cancer Center; IMDC: International mRCC Database Consortium.

investigated in pretreated patients. The objective response rate was 24%; after a median follow-up of 63.9 mo, the ORR was 29%, the median duration of response (DOR) was 12.9 mo, and the median OS was 22.4 mo[19]. In the phase 2 trial, nivolumab was again investigated in pretreated mRCC patients. Patients received 0.3 mg/kg, 2 mg/kg or 10 mg/kg nivolumab. There was no difference in PFS in these subgroups. At 3 years, ORR was 21% while OS was 41%[20]. The phase 3 trial, CheckMate 025, investigated nivolumab in comparison to everolimus in pretreated patients. The primary endpoint was OS, while the secondary endpoints were response rates and safety profile. The median OS in patients treated with nivolumab was 25 mo, compared to 1.6 mo with everolimus (HR 0.73). Differences in OS were recorded across all subgroups of patients regardless of PD-L1 expression. The objective response rate was 25% in the nivolumab cohort and 5% in the everolimus cohort. There was no significant difference in PFS of 4.6 *vs* 4.4 mo for nivolumab and everolimus, respectively. Grade 3 and 4 adverse events were reported in 19% of patients in the nivolumab group and 37% of patients in the everolimus group[21]. The results of this trial led to FDA approval of nivolumab as a second-line treatment of mccRCC.

In April 2018, nivolumab and ipilimumab combination therapy was approved by the FDA for the first-line treatment of intermediate- and poor-risk mRCC patients. This approval was a result of the phase 3 trial, CheckMate 214, which compared nivolumab and ipilimumab *vs* sunitinib in treatment-naïve patients. The trial included 1096 patients, 847 of whom were intermediate- and poor-risk IMDC risk groups. Patients were randomized 1:1. The primary endpoints were OS, PFS and ORR in intermediate- and poor-risk patients, while the secondary endpoints were OS, PFS and ORR in the intended-to-treat (ITT) population. Intermediate- and poor-risk patients in the nivolumab/ipilimumab group had significantly longer PFS than those in the sunitinib group. The favorable-risk prognostic group had longer PFS when treated with sunitinib. Patients with PD-L1 expression > 1% had significantly longer PFS when treated with nivolumab/ipilimumab *vs* sunitinib, while the treatment groups did not differ in patients with PD-L1 < 1%. Nivolumab/ipilimumab significantly prolonged patient OS compared to sunitinib. There were 46% grade 3-4 adverse events in the nivolumab/ipilimumab group *vs* 63% in the sunitinib group[22]. After 48 mo of follow-up, patients in the intermediate- and poor-risk groups treated with nivolumab/ipilimumab achieved significantly longer overall survival[23].

Nivolumab also proved efficacious in patients with brain metastasis: the ORR was 12%, and the PFS was 2.7 mo[24]. When nivolumab was combined with ipilimumab, the ORR and PFS were 29% and 9 mo, respectively[25].

Angiogenesis is one of the key initiators of disease in RCC, which itself is an immunogenic tumor. In patients with VHL gene mutations, instead of apoptosis, HIF accumulates and activates VEGF and PDGF, which mediate the activation of the angiogenesis process[10-12]. It has been shown that accumulation of VEGF leads to suppression of the host's immune response. It also interferes with monocyte differentiation into mature dendritic cells that are essential for the activation of the host's immune system. VEGF increases the number of myeloid suppressing cells present in

the tumor infiltrates that disable the activity of tumor infiltrating lymphocytes, the expression of PD-L1 in dendritic cells, as well as PD-1 and CTLA-4 on immune cells. It inhibits the differentiation of progenitor cells into CD4+ and CD8+ cells. Proangiogenic factors also modify the expression of proteins on endothelial cells, blocking the infiltration of the tumor by immune cells[26,27]. With the growing evidence that proangiogenic factors can have immunomodulatory effects on the host's immune system, the idea of combining angiogenic drugs with immunotherapy emerged, and new clinical trials have been designed[28].

Atezolizumab is a humanized monoclonal PD-L1 antibody investigated in combination with bevacizumab *vs* sunitinib. After the phase I study reported a 40% ORR , a phase II study was conducted (atezolizumab or atezolizumab/bevacizumab or sunitinib), and ORRs of 32%, 25% and 29%, respectively, were observed. In the ITT population, the PFS difference was not significant, while in the PD-L1-positive patients, a significant difference was noticed in the cohort treated with atezolizumab/bevacizumab *vs* sunitinib. PFS was not significant when atezolizumab alone was compared with sunitinib in PD-L1-positive patients[29]. The phase 3 trial, IMmotion 151, followed these results and compared atezolizumab/bevacizumab *vs* sunitinib in treatment-naïve patients. Patients were randomized 1:1 according to the MSKCC score, PD-L1 expression (< 1% *vs* > 1%), and presence of liver metastases. Patients with sarcomatoid tumor features were also included. The co-primary endpoints were PFS in the PD-L1-positive population and OS in the ITT population. Secondary endpoints were PFS, ORR and duration of response in the ITT population. In the PD-L1-positive patients, PFS was 11.2 mo (atezolizumab/bevacizumab) in comparison to 7.7 mo (sunitinib), HR 0.74. In the ITT population, PFS was 11.2 mo (atezolizumab/bevacizumab) *vs* 8.4 mo (sunitinib), HR 0.83. The ORR in the PD-L1+ population was 43% (atezolizumab/bevacizumab) *vs* 35% (sunitinib), while the ORR in the ITT population was 37% *vs* 33% (atezolizumab/bevacizumab *vs* sunitinib)[30]. After 24 mo of follow-up, there were no differences in survival (HR 0.93) in the ITT population[31]. Considering the results of IMmotion 150 and 151, data subanalysis was performed according to the molecular profile of tumor tissue. IMmotion 150 patients were classified into angio-high, T effector-high and myeloid-high. The subanalysis showed that angio-high patients had a higher benefit from TKIs and were in the favorable prognostic group, while T effector-high patients had a greater benefit from immunotherapy and were in the intermediate and poor prognostic groups. It was also observed that patients with BAP1 mutations had a worse prognosis and shorter PFS when treated with sunitinib, while patients with PBRM1 mutations had a worse prognosis and shorter PFS when treated with immunotherapy. IMmotion 151 included patients with sarcomatoid features, who generally had a worse prognosis. The results of this subanalysis showed that half of these patients were T effector-high, had higher PD-L1 expression and achieved the highest benefit from immunotherapy[29,32].

Cosmic-021 was a phase 1b trial that investigated the efficacy of atezolizumab in combination with cabozantinib in different solid tumors. One of the cohorts consisted of mccRCC patients. Seventy patients were included in the study: 34 patients were treated with cabozantinib 40 mg, and 36 patients were treated with cabozantinib 60 mg and 1200 mg atezolizumab. Most of the patients were in the intermediate prognostic group. After a median follow-up of 11.5 mo (cabozantinib 60 mg) *vs* 22 mo for cabozantinib 40 mg, the ORR in the cabozantinib 60 mg group was 58% *vs* 47% in the cabozantinib 40 mg group. The median PFS was 19.5 mo (cabozantinib 40 mg) and 20.4 mo (cabozantinib 60 mg). Two years PFS was 67% (cabozantinib 40 mg) and 71% (cabozantinib 60 mg). Treatment-related grade 3-4 adverse events were reported in 71% (cabozantinib 40 mg) and 67% (cabozantinib 60 mg) of the patients. The most common adverse events were hypertension, hypophosphatemia, diarrhea and elevation of liver enzymes[33].

The Contact-03 trial investigating atezolizumab in combination with cabozantinib in patients with mRCC who have progressed on previous immunotherapy is underway [34].

Pembrolizumab is a humanized monoclonal PD-L1 antibody studied in combination with axitinib in a phase 1b trial. The response rate was 73%[35]. In the randomized phase 3 clinical trial (Keynote-426), pembrolizumab/axitinib was compared to sunitinib. Patients were randomized 1:1. The primary endpoints were OS and PFS in the ITT population, while the secondary endpoint was ORR. After 12.8 mo of follow-up, the one-year OS was 89.9% (pembrolizumab/axitinib) *vs* 78.3% (sunitinib), HR 0.53, $P < 0.0001$. PFS was 15.1 mo (pembrolizumab/axitinib) *vs* 11.1 mo (sunitinib), HR 0.69, $P < 0.0001$. The ORR was 59.3% and 37.5% in the pembrolizumab/axitinib *vs* sunitinib group, respectively. Treatment-related grade 3 adverse events accounted for 75.85% of the patients in the combination cohort. Benefit was observed across all

subgroups analyzed regardless of the IMDC risk score or PD-L1 expression[36]. At 27 mo, PFS and OS were significantly longer in all subgroups of patients[37]. Pembrolizumab was investigated in combination with levantinib in a phase 2 trial (Keynote 146) in patients with mccRCC who were previously treated with immunotherapy. The primary endpoint of the trial was an ORR of 51%, a median PFS of 11.7 mo, and a median DOR of 9.9 mo[38]. The phase 3 trial, CLEAR/Keynote 581, investigated pembrolizumab/Lenvatinib *vs* everolimus/Lenvatinib *vs* sunitinib in patients with mccRCC. The primary endpoint was PFS, while the secondary endpoints were ORR and OS in the ITT population. All three prognostic MSKCC and IMDC risk score groups were included in the trial. After 26.6 mo of follow-up, PFS in the group of patients treated with pembrolizumab/Lenvatinib *vs* those treated with sunitinib was 23.9 *vs* 9.2 mo (HR 0.39, $P < 0.0001$). In patients treated with everolimus/Lenvatinib *vs* sunitinib, PFS was 14.7 and 9.2 mo, respectively, HR 0.65, $P < 0.0001$. Median overall survival was not reached; however, OS was longer with pembrolizumab/Lenvatinib than with sunitinib, HR 0.66, $P = 0.005$. There was no significant OS difference in patients treated with everolimus/Lenvatinib and patients treated with sunitinib, HR 1.15, $P = 0.30$. The objective response rate in the pembrolizumab/Lenvatinib cohort *vs* the everolimus/Lenvatinib *vs* sunitinib cohort was 71%, 53.5%, and 36.1%, respectively. Median DOR in the pembrolizumab/Lenvatinib cohort *vs* everolimus/Lenvatinib *vs* sunitinib was 25.8, 16.6 and 14.6 mo, respectively. All subgroups of patients had a benefit in PFS when treated with pembrolizumab/Lenvatinib. Grade 3 or higher toxicity was observed in 82.4% *vs* 83.1% and 71.8% of the patients treated with pembrolizumab/Lenvatinib, everolimus/Lenvatinib and sunitinib, respectively. The most common grade 3 toxicities were diarrhea, hypertension, and elevated lipase and triglyceride levels[39].

Avelumab is a humanized PD-L1 monoclonal antibody. It was investigated in a phase 1b trial in combination with axitinib in treatment-naïve patients with mccRCC. The objective response rate was 58%[40]. The phase 3 trial, JAVELIN Renal 101, compared avelumab/axitinib with sunitinib in patients who were not previously treated. The co-primary endpoints were PFS and OS in PD-L1-positive patients, while the secondary endpoint was PFS in the ITT population. In PD-L1-positive patients, PFS was 13.8 mo for avelumab/axitinib in comparison to 7.2 mo for patients treated with sunitinib, HR 0.61, $P < 0.0001$. In the ITT population, PFS was 13.8 mo for avelumab/axitinib in comparison to 8.4 mo for patients treated with sunitinib, HR 0.69, $P < 0.0001$. In the PD-L1-positive population, the ORR was 55.2% in the avelimab/axitinib group and 25.5% in the sunitinib group. Adverse grade 3 or higher events were reported in 71.2% of patients treated with avelumab/axitinib and 71.5% of patients treated with sunitinib[41]. At 13 mo PFS was significantly longer for the patients treated with avelumab/axitinib *vs* sunitinib in both PD-L1 positive (HR 0.62, $P < 0.0001$, 13.8 *vs* 7 mo) and ITT populations (HR 0.69, $P < 0.0001$, 13.3 *vs* 8 mo). Data for OS are still pending[42]. In May 2019, this combination was approved for the first-line treatment of mccRCC patients, regardless of the IMDC score prognostic subgroup.

In January 2021, nivolumab in combination with cabozantinib was approved by the FDA for the first-line treatment of patients with mRCC based on the results of the CheckMate 9ER trial. The trial included treatment-naïve patients, regardless of the PD-L1 expression or IMDC prognostic score. Patients were randomized into two cohorts: nivolumab/cabozantinib and sunitinib. The primary endpoint was PFS, and the secondary endpoints were OS and ORR. At 18.1 mo, PFS and OS were both significantly longer in the nivolumab/cabozantinib *vs* the sunitinib cohort in all patient subgroups analyzed[43] in Table 2.

Most of the trials that examined the efficacy of immunotherapy or immunotherapy/TKI combinations did not include mnccRCC. Some of the retrospective trials with immunotherapy reported ORRs of 9-20%. The greatest benefit occurred in patients with the papillary histology subtype[44,45]. In the phase 2 trial, Keynote 427, pembrolizumab was investigated in previously untreated mnccRCC patients. Most of the patients had papillary subtype (72%). In the ITT population, the ORR was 24.8%, while the ORRs of papillary, chromofobe and nonclassified subtypes patients were 25.4%, 9.5% and 34.6%, respectively. The twelve-month PFS and OS were 22.8% and 72%. After 11 mo of follow-up, the median DOR was not reached in either subgroup of patients[46].

Nivolumab was investigated in the phase 3b/4 trial, Checkmate 374, which included treatment-naïve patients as well as patients previously treated with a maximum of 3 Lines of therapy. Most of the patients (66%) were treatment naïve. After 11 mo of follow-up, the median OS was 16.3 mo, with no difference in OS between patients regardless of PD-L1 expression. The median PFS was 2.2 mo. At one year, PFS was 14%. The median DOR was 10.2 mo, and ORR was 13.6%[47]. The Cosmic-021

Table 2 Results of phase 3 studies in first line treatment of patients with metastatic clear cell renal cell cancer

Drug/Study	No. of patients	Follow-up (mo)	PFS (mo)	OS (mo)	ORR, %	Ref.
Nivolumab/Ipilimumab *vs* Sunitinib (Checkmate 214)	1096	48	ITT 12.2 *vs* 12.3; HR 0.89; I/P risk 11.2 *vs* 8.3; HR 0.74	ITT NR *vs* 38.4; HR 0.69; I/P risk 48.1 *vs* 26.6; HR 0.65; F risk; HR 0.93	ITT 39.1 *vs* 32.4; I/P risk 41.9 *vs* 26.8; F risk 29.6 *vs* 51.6	[24]
Pembrolizumab/Axitinib *vs* Sunitinib (Keynote 426)	861	27	ITT 15.4 *vs* 11.1; HR 0.71; $P < 0.0001$	ITT NR *vs* 35.7; HR 0.68; $P = 0.0003$	ITT 60 *vs* 40	[39]
Avelumab/Axitinib *vs* Sunitinib (Javelin 101)	560	13	ITT 13.3 *vs* 8; HR 0.69; $P < 0.0001$; PD-L1 + 13.8 *vs* 7; HR 0.62; $P < 0.0001$	ITT NR; HR 0.80; $P = 0.0392$; PD-L1 + NR; HR 0.83; $P = 0.1301$	ITT 52.5 *vs* 27.3; PD-L1 + 55.9 *vs* 27.3	[44]
Nivolumab/Cabozantinib *vs* Sunitinib (Checkmate 9ER)	651	18.1	ITT 16.6 *vs* 8.3; HR 0.51; $P < 0.0001$	ITT NR *vs* NR; HR 0.60; $P = 0.0010$	ITT 55.7 *vs* 27.1	[45]
Pembrolizumab/Lenvatinib *vs* Everolimus/Lenvatinib *vs* Sunitinib (Clear/Keynote 581)	1069	26.6	ITT Pembro/lenva *vs* sunitinib 23.9 *vs* 9.2; HR 0.39; $P < 0.000$; Everolimus/lenva *vs* sunitinib; 14.7 *vs* 9.2; HR 0.65; $P < 0.0001$	ITT Pembro/lenva *vs* sunitinib NR *vs* NR; HR 0.66; $P = 0.005$; Evero/lenva *vs* sunitinib NR *vs* NR; HR 1.15; $P = 0.30$	ITT Pembro/lenva *vs* Evero/lenva *vs* sunitinib; 71% *vs* 53.5% *vs* 36.1%	[41]

phase 1b trial analyzed the efficacy of atezolizumab in various solid tumors. One of the cohorts was patients with mnccRCC. These patients were treated with cabozantinib 40 mg and 1200 mg of atezolizumab.

According to the IMCD, all three prognostic subgroups were included in the trial, and most of them were in the intermediate prognostic group. After a median follow-up of 9.2 mo, the ORR was 33%, with no difference between subgroups. The median DOR was 7.9 mo. Grade 3-44 adverse events were reported in 30% of the patients, and a low phosphorus level was the most common adverse event[48]. The Calypso trial, phase 1b/2, examined the combination of durvalumab and savolitinib in patients with papillary mnccRCC previously treated, as well as treatment naïve. The primary endpoint was ORR, while the secondary endpoints were PFS, OS and safety. The trial included all IMDC score prognostic groups. Most of the patients (63%) were in the intermediate prognostic group. Median follow up was 8.9 mo. In the ITT population, the ORR was 27%, while the median PFS was 3.3 mo. In the subgroup of patients who were treatment naïve, the ORR was 27%, and the median PFS was 12.2 mo. Fifteen out of 42 patients included had grade 3-4 toxicities[49] (Table 3).

Predictive biomarkers

Is there a biomarker that can predict the response to either immunotherapy or tyrosine kinase inhibitors (TKIs)? One of the essential promoters of cell growth in RCC is angiogenesis. Patients in the favorable prognostic group had abundant tumor infiltrates with blood vessels. However, RCC is also an immunogenic tumor with inflammatory tumor infiltrates and is a characteristic in patients with intermediate and poor prognoses. The Bionikk trial assessed the response to immunotherapy and TKI therapy relative to the molecular tumor profile (35 genes). Patients were classified into four subgroups: group 1 (immune-low), group 2 (angio-high), group 3 (normal-like), and group 4 (immune-high). They were randomized so that groups 1 and 4 were treated with either nivolumab or nivolumab/ipilimumab, while patients in groups 2 and 3 received either sunitinib or nivolumab/ipilimumab. Primary endpoint was ORR. In group 1, the ORR was 33.3% and 20.7% for patients treated with nivolumab/ipilimumab or nivolumab, respectively. There was no difference in ORR between patients in group 4 who were treated with nivolumab *vs* nivolumab/ipilimumab 42.9% *vs* 41.2%. In group 2, the ORR was 58.3% *vs* 34.5% in patients treated with sunitinib *vs* nivolumab/ipilimumab. A very small number of patients were included in group 3, and responses were only achieved in patients treated with the nivolumab/ipilimumab combination[50]. PD-L1 is the most commonly analyzed biomarker that predicts the response to immunotherapy. Several trials pointed out that high expression of PD-L1 in patients with RCC is a predictor of poor prognosis[21,23]. Checkmate 025 reported that nivolumab is superior to everolimus in previously treated patients. Higher expression of PD-L1 was related to worse prognosis regardless of whether patients were treated with nivolumab or everolimus. The median OS was longer in PD-L1-negative patients regardless of the treatment[21].

Table 3 Results of checkpoint inhibitors in treatment of patients with metastatic clear cell renal cell cancer

Drug/Study	Phase	Indication	Follow-up	Results	Ref.
Pembrolizumab (Keynote 427)	II	mnccRR	11	ITT ORR 24.8%; ORR Papillary *vs* phromophobe *vs* unclasified 25.4% *vs* 9.5% *vs* 34.6%; 12 mo PFS 22.8%; 12 mo OS 72%	[50]
Nivolumab (Checkmate 374)	IIIb/IV	mnccRR	11	ITT; OS 16,3 mo; PFS 2,2 mo; ORR 13,6%	[51]
Atezolizumab/Cabozantinib (Cosmic 021)	Ib	mnccRR	9,2	ITT ORR 33%	[52]
Durvalumab/Savolitinib (Calypso)	Ib/II	mnccRCC-papillaryuntreated or previously treated	8,9	ITT; ORR 27%; PFS 3,3 mo; Untreated ORR 29%; PFS 12,2	[53]

In the Checkmate 214 trial, intermediate- and poor-risk patients who were also PD-L1 positive had longer PFS when treated with nivolumab/ipilimumab *vs* sunitinib. There was no PFS difference in the PD-L1-negative population[22]. According to the JAVELIN Renal 101 and Keynote 426 trials, all subgroups of patients had significantly longer PFS regardless of the prognostic group or PD-L1 expression[37,42]. Different histology subtypes of RCC have different TMB values. The lowest TMB is found in chromofobic subtype, and the highest was found in the papillary and clear cell histology subtypes[51]. In other malignancies, such as lung cancer and melanoma, TMB is a predictor of a favorable response to treatment. Although they have relatively low TBM, patients with RCC have higher rates of response to immunotherapy[52,53]. The results of trials that analyzed the prognostic value of TBM in RCC are inconclusive [54,55]. A retrospective analysis showed that TMB values do not correlate with either survival or PD-L1 expression[56]. Subanalysis of the IMmotion 150 trial showed that TMB did not influence the response to nivolumab[31]. Tumor infiltrates in RCC consist of CD8+ T lymphocytes, dendritic cells, NK cells and macrophages[15]. Some trials have shown that if tumor infiltrates are abundant with CD8+ cells and M1 macrophages, patients have a better prognosis, while infiltrates rich in regulatory T cells and M2 macrophages predict poor prognosis[57-60]. Other trials indicated that if tumor infiltrate is abundant with CD8+, patients will have a better response to immunotherapy[61]. IMmotion 150 and IMmotion 151 confirmed these results[29,31].

To date, there are no biomarkers that can predict the response to immunotherapy. Some drugs approved for first-line treatment may benefit many patients regardless of prognostic group or PD-L1 expression[36,39,42]. Further investigations are warranted to improve the selection of patients for the best possible choice of first-line therapy.

CONCLUSION

We are witnessing the evolution of mccRCC treatment. Starting with interferon-alpha and interleukin 2 in the late twentieth century, the first TKI was administered in 2007. In the last few years, several therapeutic options have been approved (immunotherapy and immunotherapy/TKI) as first-line treatment options. Nivolumab/ipilimumab is approved for the treatment of patients with intermediate and poor prognoses. Several checkpoint inhibitors (pembrolizumab, nivolumab, avelumab) in combination with TKIs (axitinib, lenvatinib, cabozantinib) are approved for the treatment of patients regardless of their IMDC prognostic group and PD-L1 expression. There is no specific and ideal biomarker that could help select the ideal patient for the appropriate first-line treatment. If patients are symptomatic, have visceral metastasis and require prompt response, then checkpoint inhibitors/TKIs are deemed most beneficial. If the patient is asymptomatic, then other factors, such as toxicity profile, may influence the first-line treatment option.

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MINIREVIEWS

Role of radiotherapy in oligometastatic breast cancer: Review of the literature

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Abstract

Metastatic breast cancer has been historically considered as an incurable disease. Radiotherapy (RT) has been traditionally used for only palliation of the symptoms caused by metastatic lesions. However, in recent years the concept of oligometastatic disease has been introduced in Cancer Medicine as a clinical scenario with a limited number of metastases (≤ 5) and involved organs (≤ 2) with controlled primary tumor. The main hypothesis in oligometastatic disease is that locoregional treatment of primary tumor site and metastasis-directed therapies with surgery and/or RT may improve outcomes. Recent studies have shown that not all metastatic breast cancer patients have the same prognosis, and selected patients with good prognostic features as those younger than 55 years, hormone receptor-positive, limited bone or liver metastases, a low-grade tumor, good performance status, long disease-free interval (> 12 mo), and good response to systemic therapy may provide maximum benefit from definitive treatment procedures to all disease sites. While retrospective and prospective studies on locoregional treatment in oligometastatic breast cancer demonstrated conflicting results, there is an increasing trend in favor of locoregional treatment. Currently, available data also demonstrated the improvements in survival with metastasis-directed therapy in oligometastatic breast cancer. The current review will discuss the concept of oligometastases and provide up-to-date information about the role of RT in oligometastatic breast cancer.

Key Words: Breast cancer; Oligometastatic; Radiotherapy; Locoregional treatment; Ablative therapy; Metastasis-directed therapy

Core Tip: Radiotherapy (RT) has been traditionally used for only palliation of the

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INTRODUCTION

Breast cancer is the most common cancer in females worldwide, with an estimated 276480 new cases, and the second most common cause of cancer death with an estimated 42170 deaths in 2020[1]. Metastasis at the time of diagnosis has been observed in 3%-10% of breast cancer patients and has been considered in the past unlikely to be cured[2]. However, the metastatic disease has a broad spectrum ranging from a single metastasis to widespread dissemination, and it has been observed that not all metastatic patients have the same prognosis.

The concept of oligometastases was first described by Hellman and Weichselbaum [3] in 1995, and they hypothesized that patients with oligometastases should be considered as candidates for curative therapeutic strategies. Oligometastases was described as a clinical scenario with a limited number of metastases (1 to 5) and involved organs (≤ 2) with controlled primary tumors[3]. The exact number of metastasis for the concept of oligometastases has not been clearly defined yet; however, most studies evaluating oligometastatic disease included patients with five or less metastasis[4,5].

While the standard treatment for metastatic disease includes systemic therapy with or without palliative radiotherapy (RT), recent studies are evaluating the role of ablative therapies to metastases and locoregional treatment to the primary tumor site in oligometastatic breast cancer[6-9]. In recent years, the prognosis of breast cancer has improved with the introduction of novel systemic therapies, even in patients with metastatic disease[10,11]. Some patients with good prognostic features may achieve complete response for more than 5 years after systemic therapy[12]. Several factors affect the prognosis in breast cancer patients with oligometastatic disease as the disease-free interval between primary cancer and metastasis formation, number of metastatic lesions, metastatic sites, hormone receptor status, human epidermal growth factor 2 (Her2) status, and pN stage[13-15]. Systemic therapy and local treatment to both primary and metastatic lesions may improve outcomes in such selected patients with metastatic breast cancer. Herein, we will review the impact of RT in oligometastatic breast cancer for both metastatic and primary tumor sites.

SHOULD WE PERFORM LOCOREGIONAL TREATMENT IN OLIGOMETASTATIC BREAST CANCER PATIENTS?

In the past, the locoregional treatment in metastatic breast cancer was believed to have a role only for palliation of the symptoms caused by the local progression of the tumor. However, beginning from the early 2000s, with the advent of novel systemic therapies as new chemotherapeutic agents, anti-HER2 agents, hormonal therapies, immunotherapies, and cyclin-dependent kinase inhibitors, the destiny of patients with metastatic breast cancer have changed. A significant number of patients showed at least good partial response both in the primary and metastatic sites, which led to questioning the idea of treating these patients with some form of locoregional treatment based on the idea that the primary tumor could be a source of reseeding of cancer outside the breast. The National Cancer Database study revealed that surgery

to the primary site when added to systemic therapy in patients with stage IV breast cancer significantly improved survival[16]. A similar retrospective study using the Surveillance, Epidemiology, and End Results database also showed that median survival was longer in metastatic breast cancer patients who had surgery to the primary site than patients who did not (36 mo *vs* 21 mo, $P < 0.001$)[17]. However, the prospective phase III ABCSG-28 POSYTIVE trial that randomized metastatic breast cancer patients to surgery followed by systemic therapy or systemic therapy alone could not demonstrate an overall survival (OS) benefit for the surgery arm[18]. Another study from India randomized 350 patients with *de novo* metastatic breast cancer who had an objective tumor response after 6-8 courses of chemotherapy to locoregional treatment to primary or no locoregional treatment arms[19]. At a median follow-up of 23 mo, no statistically significant difference in OS was observed between treatment arms (19.2 mo *vs* 20.5 mo, $P = 0.79$). However, locoregional treatment was associated with improved locoregional progression-free survival (PFS) but shorter distant PFS[19]. In another study by Soran *et al*[20], 274 treatment naïve metastatic breast cancer patients were randomized to receive locoregional treatment followed by systemic therapy *vs* systemic therapy alone. With a median follow-up of 55 mo, median survival was significantly longer in the locoregional treatment arm compared to patients with systemic therapy alone arm (46 mo *vs* 37 mo, $P = 0.005$). Unplanned subgroup analysis of this study showed that improvement in survival was observed in patients with estrogen receptor/progesterone receptor positive, Her2 negative disease, younger than 55 years, and with solitary bone-only metastasis[20].

Several ongoing trials are evaluating the impact of locoregional treatment on survival in metastatic breast cancer. Early results of the ECOG E2108 trial that randomized 256 patients whose disease responded to initial systemic therapy, or stayed stable, to systemic therapy plus locoregional treatment or systemic therapy alone, showed that there was no significant difference in 3-year OS (68.4% *vs* 67.9%, $P = 0.63$); however, the locoregional recurrence or progression was significantly higher in the systemic therapy alone arm (3-year rate 25.6% *vs* 10.2%, Gray test $P = 0.003$)[21]. Preliminary results of another multicentric prospective ongoing trial (TBCRC 013) evaluating the impact of surgery on OS in metastatic breast cancer patients who responded to first-line systemic therapy showed that the addition of surgery to systemic therapy had no impact on OS even in responders to first-line systemic therapy[22]. JCOG1017 PRIM-BC trial comparing surgery to primary plus systemic therapy with systemic therapy alone has completed accrual, and results of this trial are being expected[23]. Ongoing SUBMIT (NCT01392586) trial is also investigating whether upfront surgery in patients with metastatic breast cancer will result in an improvement of the 2-year survival compared to the survival achieved by systemic therapy and delayed local treatment or systemic therapy alone[24]. The details of prospective randomized trials investigating the role of locoregional treatment in metastatic breast cancer are given in Table 1. The final results of these prospective randomized studies will hopefully clarify the exact role of locoregional treatment in metastatic breast cancer patients.

There is no prospective randomized study comparing surgery with surgery plus RT or RT alone as a locoregional treatment in metastatic breast cancer. A retrospective study by Gultekin *et al*[7] evaluating the impact of locoregional treatment in 227 oligometastatic breast cancer patients showed that locoregional treatment per se did not affect OS and PFS, however, surgery and RT when used together improved OS and PFS. The authors also observed that patients with solitary metastasis had longer PFS than patients with multiple metastases. In another retrospective study, Le Scodan *et al*[8] compared 320 metastatic breast cancer patients who received exclusive locoregional RT with or without surgery with 261 metastatic breast cancer patients who did not receive locoregional treatment. In this study, 78% of patients had exclusive locoregional RT, and patients with locoregional treatment had longer 3-year OS rates (43.4% *vs* 26.7%, $P < 0.001$). Although there was no statistically significant difference in locoregional treatment modalities regarding survival outcomes, multifactorial analysis in the Le Scodan *et al*[8] study showed that age at diagnosis, visceral metastases, involvement of multiple sites, endocrine treatment, and locoregional treatment were independent prognostic factors for OS[8]. Retrospective studies published within the last decade investigating the impact of locoregional treatment on primary tumor sites are detailed in Table 2.

There is still no consensus about the efficacy of locoregional treatment in metastatic breast cancer. There is again no consensus about the optimal treatment strategy as surgery alone or surgery plus RT or RT alone when locoregional treatment is indicated. Based on the available data, locoregional treatment may be offered to patients who have a long-life expectancy, such as those younger than 55 years, have

Table 1 Prospective randomized phase III trials investigating the role of locoregional treatment in *de novo* metastatic breast cancer

Ref.	*n*	Treatment	Patients	Median follow-up (mo)	Outcomes
Khan *et al*[21] (ECOG-ACRIN E2108)	256	Primary systemic therapy: LRT (n = 125); No LRT (n = 131)	NR	59	3-yr OS: 68.4% *vs* 67.9%, P = 0.63 3-yr locoregional recurrence/progression: 10.2% *vs* 25.6%, P = 0.003
Fitzal *et al*[18] (ABCSG-28 POSYTIVE)	90	Arm A: Primary surgery + systemic therapy (n = 45) Arm B: Primary systemic therapy (n = 45)	Arm A: More cT3 and cN2 tumors	37.5	Stopped early Median OS (mo): 34.6 *vs* 54.8, P = 0.267 Time to distant progression (mo): 13.9 *vs* 29.0, P = 0.0668
Soran *et al*[20] (MF07-01)	274	LRT + systemic therapy (n = 138) Systemic therapy (n = 136)	LRT arm: More ER/PR (+), less triple negative tumors	54.5 *vs* 55	Median OS (mo): 46 *vs* 37, P = 0.005 Unplanned subgroup analysis: Improvement in survival: ER/PR (+), HER2 (-), < 55 yr, solitary bone-only metastasis
Badwe *et al*[19] (NCT00193778)	350	Primary systemic therapy: LRT (n = 173); No LRT (n = 177)	Similar patient and tumor characteristics	23	Median OS (mo): 19.2 *vs* 20.5, P = 0.79 Median LR-PFS (mo): not attained *vs* 18.2, P < 0.0001 Median distant-PFS (mo): 11.3 *vs* 19.8, P = 0.012

NR: Not reported; LRT: Locoregional treatment; c: Clinic; T: Tumor; N: Node; ER: Estrogen receptor; PR: Progesterone receptor; OS: Overall survival; HER2: Human epidermal growth factor receptor 2; LR: Locoregional; PFS: Progression-free survival.

hormone receptor-positive, HER2 positive, bone or limited liver metastases, presence of a low-grade tumor, good performance status, good response to systemic therapy, and a limited number of metastases[8,25].

SHOULD WE TREAT METASTASES IN OLIGOMETASTATIC BREAST CANCER PATIENTS?

Traditionally, the standard treatment is systemic therapy for metastatic breast cancer patients; however, long-term complete response with systemic therapy alone is rare [12]. Given that progression in metastatic breast cancer patients frequently occurs at sites of known metastases rather than new metastatic lesions, local ablative therapies to metastatic sites may provide therapeutic benefit[9,26]. In addition to surgery and radiofrequency ablation, stereotactic body RT (SBRT) or stereotactic ablative RT (SABR), which allows highly conformal dose distribution using high dose per fraction with a low number of fractions, may be used as local ablative therapies to metastases to prevent progression[26,27].

Response to systemic therapy is a significant prognostic factor in metastatic breast cancer[4]. In a retrospective study by Weykamp *et al*[28], the 2-year local control and OS rates were reported as 89% and 62%, respectively, in patients with oligometastatic disease. The authors also observed that solitary metastasis and young age were independent factors for PFS and OS, respectively[28]. In another study by Kobayashi *et al*[29], 75 oligometastatic breast cancer patients who had a complete or partial response after systemic therapy and treated with local therapy were retrospectively evaluated, and it was demonstrated that complete response or no evidence of disease rates were significantly better in patients with a single organ metastasis than with two organ metastases (P = 0.002)[29]. In this retrospective study, the multidisciplinary treatment improved OS compared to systemic therapy alone[29].

Few studies have investigated the role of SBRT as a local treatment of metastases in oligometastatic disease including metastatic breast cancer patients (Table 3)[4-6,9,26,28,30,31]. Studies in the literature showed that the maximum benefit from SBRT to all metastatic sites was provided in young patients whose primary breast cancer was controlled, with a limited number of metastases, low tumor volume, only bone metastases, good response to systemic therapy, long disease-free interval (> 12 mo), and hormone receptor-positivity[4,29,30].

Table 2 Retrospective studies published within the last decade investigating the impact of locoregional treatment to the primary tumor site in de novo metastatic breast cancer

Ref.	*n*	Treatment	Patient	Median follow-up (mo)	Outcomes
Ma *et al*[35]	987	Surgery (*n* = 463) No surgery (*n* = 524)	Surgery arm: More T1-2, HR-positive, solitary metastasis, bone only metastasis	NR	Median survival (mo): 45 *vs* 28, *P* < 0.001 Better survival in surgery after systemic therapy than primary surgery Triple negative, brain metastases: No benefit of surgery
Lane *et al*[16] (NCDB)	24015	Systemic therapy alone (*n* = 13505) Surgery before systemic therapy (*n* = 4552) Systemic therapy before surgery (*n* = 5958)	Surgery after systemic therapy arm: Younger, more T3-4 and HR-negative	NR	Median OS (mo): 37.5 *vs* 49.4 *vs* 52.8, *P* < 0.001 RT: No impact on OS
Li *et al*[36] (SEER database)	20870	Surgery (*n* = 5779) No surgery (*n* = 15091)	Surgery arm: Younger, more T1-3, N+, Gr III, and less HR+ More chemo and RT received	NR	Surgery arm (± RT): Improved BCSS and OS (*P* < 0.001)
Pons-Tostivint *et al*[37]	4276	LRT (*n* = 1706): Surgery, RT or both No LRT (*n* = 2570)	LRT arm: Younger, more solitary or bone-only metastases	45.3	Median OS (mo): HR-positive, HER2- negative: 61.6 *vs* 45.9, *P* < 0.001 HR-positive, HER2-positive: 77.2 *vs* 52.6, *P* = 0.008 Triple negative: 19 *vs* 18.6, *P* = 0.54 Bone only metastases: 70.4 *vs* 62, *P* < 0.001 Visceral metastases: 83 *vs* 52.7, *P* < 0.001
Choi *et al*[38]	245	LRT (*n* = 82): Surgery, RT or both No LRT (*n* = 163)	LRT arm: < T4, no liver or brain metastasis, and < 5 metastatic sites	40	5-yr LRFS: 62% *vs* 20%, *P* < 0.001 5-yr OS:73% *vs* 45%, *P* = 0.02
Gultekin *et al*[7]	227	LRT (*n* = 188): Surgery, RT or both No LRT (*n* = 39)	LRT arm: Less T3-4 and more solitary metastases	35	5-yr OS: 56% *vs* 24%, *P* < 0.001 5-yr PFS: 27% *vs* 7%, *P* < 0.0001
Nguyen *et al*[39]	733	LRT (*n* = 378): Surgery, RT or both No LRT (*n* = 355)	LRT arm: Younger, more T1-2, N0-1, limited M1 disease	21	5-yr OS: 21% *vs* 14%, *P* < 0.001 5-yr PFS 72% *vs* 46%, *P* < 0.001
Neuman *et al*[25]	186	Surgery (*n* = 69): 13% RT No surgery (*n* = 117)	Surgery arm: More HER2-negative, smaller tumors, more solitary metastasis	52	No difference in OS (*P* = 0.10)

NCDB: National Cancer Database; SEER: Surveillance, Epidemiology, and End Results, RT: Radiotherapy; LRT: Locoregional treatment; T: Tumor; HR: Hormone receptor; HER2: Human epidermal growth factor receptor 2; N: Node, Gr: Grade; M: Metastasis; NR: Not reported; OS: Overall survival; PFS: Progression-free survival; BCSS: Breast cancer-specific survival; LRFS: Local recurrence-free survival.

The prospective studies exploring the role of SBRT to metastatic sites in oligometastatic breast cancer are limited (Table 4)[5,6,9,26,30,31]. Milano *et al*[9] performed hypofractionated stereotactic radiation (50 Gy in 10 fractions) to all sites of disease in 48 breast cancer patients with 1-5 extracranial metastases. The authors observed that some patients who have only bone metastases rather than visceral metastases and with low tumor burden (volume and number of lesions) survived longer than 10 years[9]. Five- and ten-year OS rates after hypofractionated stereotactic radiation was 83% and 75%, for patients with only bone metastases *vs* 31% and 17%, respectively, for patients with not only bone metastases[9]. Trovo *et al*[6] in a prospective phase II trial

Table 3 Retrospective studies investigating the role of radiotherapy as a local treatment of metastases in oligometastatic disease

Ref.	*n*	Treatment	Patients	Median follow-up (mo)	Outcomes
Weykamp *et al* [28]	46	SBRT: Bone, lung, liver, adrenal gland Median 3 frx (1-10)/28 Gy (24-60 Gy)	Inclusion criteria: breast cancer, oligometastatic (≤ 3) or oligoprogressive (1) disease 58 lesions	21	2-yr LC, DC, PFS and OS: 89%, 44%, 17%, and 62%, respectively Solitary metastasis: Poor prognostic factor for DC and PFS Higher age: Poor prognostic factor for OS
Kobayashi *et al* [29]	75	Primary systemic chemotherapy: CR/PR Surgery or RT	Inclusion criteria: breast cancer, ≤ 2 metastatic organs, < 5 metastases, < 5 cm lesions	103	10-yr and 20-yr OS: 59.2% and 34.1%, respectively 10-yr and 20-yr RFS: 27.4% Single organ metastasis, local treatment and shorter DFI: Better RFS
Hong *et al*[4]	361	SBRT 10 frx/50-60 Gy or 3 frx/24-48 Gy	Extracranial oligometastases (≤ 5) Breast cancer (16%)	26.2	3-yr OS, PFS and TMC were 56%, 24%, and 72%, respectively Primary tumor type, interval to metastasis, number of treated metastasis, and mediastinal/hilar LN, liver, or adrenal metastases: Associated with OS All breast cancer patients: RPA class 1 (3-yr OS 75%)
Cha *et al*[40]	49	Endocrine therapy plus LRT (n = 33) 82% RT: Bone, LN Endocrine therapy alone (n = 16)	Inclusion criteria: HR-positive, HER2-negative Similar patient and tumor characteristics	101.6 *vs* 105.6	Median OS (mo): 72.3 *vs* 91, P = 0.272 Median PFS (mo): 30 *vs* 18, P = 0.049

SBRT: Stereotactic body radiation therapy; frx: Fraction, Gy: Gray, CR: Complete response; PR: Partial response; RT: Radiotherapy; LN: Lymph node; LRT: Locoregional treatment; HR: Hormone receptor; HER2: Human epidermal growth factor receptor 2; LC: Local control; DC: Distant control; OS: Overall survival; PFS: Progression-free survival; DFI: Disease-free interval; TMC: Treated metastasis control; RPA: Recursive partitioning analysis.

administered SBRT (30-45 Gy in 3 fractions) or intensity-modulated RT (60 Gy in 25 fractions) to all metastatic sites in 54 oligometastatic breast cancer patients whose primary tumor was controlled. The authors reported that 2-year local control, OS, and PFS rates with a median follow-up of 30 mo were 97%, 95%, and 53%, respectively, and no ≥ grade 3 toxicity was documented[6]. The first randomized phase II study in metastatic cancer is the SABR-COMET study in which 99 patients with the oligometastatic disease were randomized to receive systemic therapy plus palliative RT (8 Gy in 1 fraction or 30 Gy in 10 fractions) or systemic therapy plus SABR to all metastatic sites. Only 18% of the patients were with breast cancer in this study. There was a significant improvement in terms of 5-year OS (17.7% *vs* 42.3%, P = 0.006), 4-year PFS (3.2% *vs* 21.6%, P = 0.001), and local control rates (46% *vs* 63%, P = 0.039) in patients treated with SABR without any significant adverse events[5]. Results of three ongoing prospective randomized studies (SABR-COMET 10, STEREO-SEIN, and NRG-BR002) are being expected to clarify the role of SBRT to all metastatic sites in oligometastatic breast cancer[32-34].

CONCLUSION

Metastatic breast cancer includes a wide spectrum of disease ranging from oligometastatic to disseminated disease. There has been growing interest during the last 20 years in the curative treatment of oligometastatic breast cancer with the advances in systemic therapy. Aggressive local treatment of primary tumor and metastases-directed therapies may improve survival in selected patients, and should especially be suggested to young patients with limited number of metastases. The results of ongoing trials specific to breast cancer will be more helpful in the future.

Table 4 Prospective studies exploring the role of radiotherapy to metastatic sites in oligometastatic disease including primary breast cancer

Ref.	*n*	Treatment	Patients	Median follow-up (mo)	Outcomes
Palma *et al*[5] (SABR-COMET)	99	Palliative RT ± systemic therapy (*n* = 33) 1 frx/8 Gy or 10 frx/30 Gy SABR ± systemic therapy (*n* = 66) Different regimens according to tumor size and location	Inclusion criteria: 1-5 metastases, life expectancy ≥ 6 mo, controlled primary tumor Primary breast cancer (*n*): 5 *vs* 13	51	5-yr OS: 17.7% *vs* 42.3%, *P* = 0.006 4-yr PFS 3.2% *vs* 21.6%, *P* = 0.001 LC 46% *vs* 63%, *P* = 0.039 ≥ Gr 2 toxicity: 9% *vs* 29%, *P* = 0.026 SABR: Gr 5 toxicity (*n* = 3)
Milano *et al*[9]	48	HSRT: ≥ 50 Gy in 10 frx	Inclusion criteria: breast cancer, 1-5 extracranial metastases, primary controlled	52	5- and 10-yr OS: Bone-only oligometastases: 83% and 75% Non-bone-only oligometastases: 31% and 17% (*P* = 0.002) GTV > 25 cc: Poor prognostic factor for LC
Trovo *et al*[6]	54	SBRT: 3 frx/30-45 Gy (*n* = 44) IMRT: 25 frx/60 Gy (*n* = 10)	Inclusion criteria: breast cancer, ≤ 5 extracranial metastases, primary controlled 92 lesions	30	2-y LC: 97% 2-y OS: 95% 1- and 2-yr PFS: 75% and 53%, respectively No ≥ Gr 3 toxicity
Salama *et al* [26]	61	SBRT: Lung, LN, liver, bone, adrenal, soft tissue, pancreas 3 frx/24-48 Gy	Inclusion criteria: 1-5 metastatic sites, life expectancy > 3 mo Breast cancer (11.3%)	20.9	1-yr and 2-yr OS: 81.5% and 56.7%, respectively 1-yr and 2-yr PFS: 33.3% and 22.0%, respectively
Scorsetti *et al* [31]	33	SBRT: 3-4 frx/48-75 Gy	Inclusion criteria: breast cancer, < 5 lung or liver metastases, other metastatic sites stable or responding after chemotherapy 43 lesions	24	1- and 2-yr LC: 98% and 90%, respectively 1- and 2-yr OS: 93% and 66%, respectively 1- and 2-yr PFS: 48% and 27%, respectively No grade 3-4 toxicities
Milano *et al* [30]	40	SBRT doses and fractionation was not mentioned	Inclusion criteria: breast cancer, ≤ 5 metastases	NR	4-yr OS: 59% 4-yr PFS: 38% 4-yr LC: 89% Favorable prognosis: Solitary metastasis, smaller tumor volume, bone-only disease, and stable or regressing lesions

RT: Radiotherapy; frx: Fraction; Gy: Gray; SBRT: Stereotactic body radiation therapy; HSRT: Hypofractionated stereotactic radiotherapy; IMRT: Intensity-modulated radiation therapy; NR: Not reported; OS: Overall survival; PFS: Progression-free survival; LC: Local control; LN: Lymph node; Gr: Grade; GTV: Gross tumor volume.

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ORIGINAL ARTICLE

Retrospective Study

Association of cancer with comorbid inflammatory conditions and treatment in patients with Lynch syndrome

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Abstract

BACKGROUND

Individuals with Lynch syndrome (LS) and hereditary non-polyposis colorectal cancer (HNPCC) are at increased risk of both colorectal cancer and other cancers. The interplay between immunosuppression, a comorbid inflammatory condition (CID), and HNPCC on cancer risk is unclear.

AIM

To evaluate the impact of CIDs, and exposure to monoclonal antibodies and immunomodulators, on cancer risk in individuals with HNPCC.

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METHODS

Individuals prospectively followed in a hereditary cancer registry with LS/HNPCC with the diagnosis of inflammatory bowel disease or rheumatic disease were identified. We compared the proportion of patients with cancer in LS/HNPCC group with and without a CID. We also compared the proportion of patients who developed cancer following a CID diagnosis based upon exposure to immunosuppressive medications.

RESULTS

A total of 21 patients with LS/HNPCC and a CID were compared to 43 patients with LS/HNPCC but no CID. Cancer occurred in 84.2% with a CID compared to 76.7% without a CID (P = 0.74) with no difference in age at first cancer diagnosis 45.5 ± 14.6 *vs* 43.8 ± 7.1 years (P = 0.67). LS specific cancers were diagnosed in 52.4% with a CID *vs* 44.2% without a CID (P = 0.54). Nine of 21 (42.9%) patients were exposed to biologics or immunomodulators for the treatment of their CID. Cancer after diagnosis of CID was seen in 7 (77.8%) of exposed individuals *vs* 5 (41.7%) individuals unexposed to biologics/immunomodulators (P = 0.18). All 7 exposed compared to 3/5 unexposed developed a LS specific cancer. The exposed and unexposed groups were followed for a median 10 years and 8.5 years, respectively. The hazard ratio for cancer with medication exposure was 1.59 (P = 0.43, 95%CI: 0.5-5.1).

CONCLUSION

In patients with LS/HNPCC, the presence of a concurrent inflammatory condition, or use of immunosuppressive medication to treat the inflammatory condition, might not increase the rate of cancer occurrence in this limited study.

Key Words: Lynch syndrome; Hereditary non-polyposis colorectal cancer; Inflammatory bowel disease; Immunosuppression; Biologics

Core Tip: Individuals with hereditary non-polyposis colorectal cancer (HNPCC) are at increased risk of both colorectal cancer and other cancers. When they have a comorbid inflammatory condition (CID) that requires immunosuppression, clinicians may be hesitant to prescribe these medications due to concern of an elevated cancer risk. We show that individuals with HNPCC and CID have a similar cancer risk to those with HNPCC alone, and that the addition of immunosuppression does not increase overall cancer risk, but may increase the risk of LS-specific cancers.

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INTRODUCTION

Lynch syndrome (LS) is the most common hereditary cancer syndrome. Patients with LS have an increased cumulative lifetime risk of developing colorectal, endometrial, ovarian, stomach, small bowel, hepatobiliary, urothelial, and brain cancers[1]. This is explained by a germline pathogenic variant (PV) in one of the DNA mismatch repair (MMR) genes resulting in the translation of a defective enzyme unable to correct errors in base pairing during DNA replication[2]. The defective system leads to the accumulation of mutations, regulatory escape from the cell division cycle, and ultimately cancer[3]. LS accounts for 3% of all newly diagnosed colorectal and endometrial cancers[4]. Individuals who meet Amsterdam II criteria, have MSI-H colorectal cancers, but do not have a MMRPV are also have an elevated risk of colorectal cancer

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[5]. Hereditary non-polyposis colorectal cancer (HNPCC) is an umbrella term that, regardless of MMRPV status, includes individuals with MSI-H cancers and a suggestive family history.

Individuals with HNPCC may have co-existent systemic inflammatory conditions (CID) such as inflammatory bowel disease (IBD) and rheumatic diseases. A deregulated immune system contributes to the pathogenesis of these diseases and various inflammatory mediators and pathways have been implicated[6]. Treatment of moderate to severe inflammatory disease generally involves modulating the immune system with systemic immunosuppressive medications, in particular monoclonal antibodies and immunomodulators alone or in combination[7]. Because the immune system is known to protect against cancer by detecting neoantigens presented by cancer cells[8], of particular importance in HNPCC individuals with immunogenic MSI-H cancers[9,10], clinicians may be hesitant to prescribe these medications in patients with HNPCC due to concern of an elevated cancer risk. Limited data exists regarding the impact of CID and immunosuppressive medication exposure on the cancer risk in HNPCC.

Our primary aim was to evaluate the impact of CID on the cancer risk in HNPCC by comparing HNPCC individuals with and without a CID. Our secondary aim was to assess the effect of monoclonal antibody and/or immunomodulator exposure on cancer risk in HNPCC patients with concurrent CID.

MATERIALS AND METHODS

This study was approved by Cleveland Clinic Institutional Review Board (IRB 2884). HNPCC individuals enrolled in the David G. Jagelman Hereditary Colorectal Cancer Registries at the Sanford R. M.D. Center for Hereditary Colorectal Neoplasia at the Cleveland Clinic from 1979 to 2019 who met inclusion criteria were included in the study. HNPCC was defined as individuals with an MSI-H tumor and belonging to a family fulfilling Amsterdam II criteria. Individuals with comorbid IBD including ulcerative colitis (UC) and Crohn's disease (CD), and rheumatic diseases including rheumatoid arthritis and other inflammatory arthritides, psoriasis, ankylosing spondylitis, spondyloarthritis, systemic sclerosis, scleroderma, dermatomyositis, polymyositis, lupus, sarcoidosis, mixed connective tissue disease and undifferentiated connective tissue disease were included.

Variables extracted from the medical record included demographics, age at first cancer diagnosis and last follow up, MMRPV, sex, race, smoking history, personal and family history of LS-specific (colorectal, endometrial, urothelial, and small bowel) and other cancers, cancer stage and comorbid disease history (age at diagnosis, presenting signs and symptoms, treatments, exposure to biologics and/or immunomodulators with type, dose and duration of treatment noted for each medication).

The primary aim was to compare the proportion of individuals with HNPCC who develop cancer based on CID status. Cases (HNPCC with CID) were matched to controls (HNPCC without CID) in a 1:2 ratio. Controls were randomly chosen from the registry after matching for presence and type of MMRPV, age at last follow up, and gender. We compared the proportion of patients who had developed any cancer up to last follow up or death between the two groups. In a subgroup analysis, we then compared proportion of patients who developed colorectal cancer in HNPCC patients with and without IBD.

Our secondary aim was to compare the proportion of CID patients (n = 21) who developed cancer with and without exposure to a monoclonal antibody and/or immunomodulator therapy. Patients were divided into two groups based on any exposure to these medications. Duration of exposure was determined through the electronic medical record or paper chart review by duration of prescription length and provider notes. Immunosuppressive medications included anti-tumor necrosis factors (TNF) (infliximab, adalimumab, certolizumab pegol, etanercept and golimumab), anti-integrins (natalizumab and vedolizumab), anti-interleukins [anakinra, tocilizumab, sarilumab, ixekizumab, guselkumab, ustekimumab), janus kinase inhibitor (tofacitinib), and immunomodulators (methotrexate, azathioprine and 6-mercaptopurine (6MP)]. The proportion of individuals who developed a cancer was calculated from the year of diagnosis of comorbid disease until last follow up or death.

Continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR). Categorical variables are presented as number and percentage. Student *t*-test or Mann-Whitney-*U* test was used to compare continuous variables. Categorical variables were compared using *chi*-square test or Fisher exact

test. For the primary aim, the proportion of individuals in each group with cancer was compared. For the secondary aim, we also carried out single variable cox proportional survival analysis to calculate hazard ratio (HR) for cancer and Kaplan Meier curve was constructed for the comparison between exposed and unexposed groups. Time to event started from the year of comorbid disease diagnosis to cancer diagnosis. Individuals who were lost to follow up are included until that time in analysis. All statistical work was done using SPSS v26.0.

RESULTS

Part 1: Presence of a comorbid inflammatory condition and proportion of patients who develop cancer in HNPCC

64 HNPCC patients including 21 cases with a CID and 43 controls without CID were analyzed. Of the 14 patients with LS, MMRPV included MLH1 (23.8%), MSH2 (14.3%), MSH6 (9.5%) and PMS2 (19.6%). Seven (33%) did not have a MMRPV. Age at last follow up, gender, race, smoking history and family history of cancer did not differ between cases and controls (Table 1). CID in the 21 patients included CD (23.8%), UC (9.5%), inflammatory/rheumatoid arthritis (33.3%), psoriasis (14.3%), and one case each of psoriatic arthritis, dermatomyositis, ankylosing spondylitis, and sarcoidosis. The mean age at CID diagnosis was 39 ± 13 years.

The proportion of patients who had a history of cancer diagnosis at the time of their last follow up was 84.2% in cases and 76.7% in controls (P = 0.74). Age at first cancer diagnosis was 45.5 ± 14.6 years for cases and 43.8 ± 7.1 years for controls (P = 0.67). The proportion of patients who had developed cancer after diagnosis of CID in cases was 57.1% with a 10 year (6.0-16.5) median duration of follow-up and 46.5% in controls (P = 0.42) when also followed for 10 years prior to last follow up or death. Approximately half of the cancers were HNPCC-specific: 52.4% of cases *vs* 44.2% of controls (P = 0.54) (Table 2). The distribution of cancers based on MMRPV is presented in Table 3.

Median total surveillance colonoscopies after HNPCC diagnosis were 5 (IQR 3.0-6.0) for cases and 4 (IQR 2.0-6.0, P = 0.19) for controls with a median 1 year interval for both groups. 42.9% of cases *vs* 46.5% of controls had partial colectomy and 33.3% of cases compared to 7.0% controls had total proctocolectomy. Overall, 83% of female cases and 76% of female controls had a history of total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO[MSF1]). 50.0% of cases and 28.0% of controls had the procedure prophylactically while the others had TAH-BSO for endometrial cancer. 1 (4.7%) female in case group had prophylactic TAH-BSO prior to the diagnosis of CID.

In a sub-group analysis, we compared the 7 individuals with IBD (5 CD and 2 UC) to the control group (n = 43) for the proportion of patients who developed specifically CRC. One CD individual had stricturing ileitis and no colonic disease or prior colon surgery and another developed CD in an ileal pouch following proctocolectomy and ileal pouch anal anastomosis for resection of a cecal adenocarcinoma. Both individuals were exposed to monoclonal antibodies/immunomodulators for treatment of CD. Of the other three CD patients, two had ileitis and one had mild segmental colitis. They did not receive monoclonal antibodies/immunomodulators for treatment. One UC patient had moderate pancolitis and received monoclonal antibodies/immunomodulator. The other UC patient had moderate left sided colitis and did not receive above mentioned immunosuppressive treatment. Mean duration of follow up for IBD in the exposed group was 19.2 ± 12.1 years compared to the unexposed group 16.0 ± 12.6 years, P = 0.64. All cases had intact colons at the time of CID diagnosis except the one CD individual mentioned above.

Four (57.1%) cases developed colorectal (CRC) cancer (P = 0.86) over a median 10-years (IQR 5-18) from IBD diagnosis compared to 53.5% of controls when followed for 10 years. Both UC and 2/5 CD (40%) patients developed CRC at a median age of 41.8 years (IQR 19-57) compared to 46.0 year (IQR 41-52) in the control group. Median stage of CRC cancer at the time of diagnosis was II in both groups.

Part 2: Monoclonal antibody and/or immunomodulator exposure and the proportion of patients who develop cancer in HNPCC

For the secondary aim, we compared the proportion of individuals who developed cancer after diagnosis of a CID in the 9/21 (39.5%) individuals exposed to monoclonal antibodies and/or immunomodulators to the 12/21 (61.5%) unexposed. Mean age at end of follow-up for the exposed group was 54.2 ± 20.0 years compared to 53.7 ± 12.4

Table 1 Demographics, genetic diagnosis, surveillance, surgical history, and cancer in hereditary non-polyposis colorectal cancer

	Inflammatory disease present, *n* = 21	Controls, *n* = 43	*P* value
Current age (yr), mean ± SD	53.9 ± 15.7	53.8 ± 7.8	0.97
Gender, *n* (%)			
Female	12 (57.1)	25 (58.1)	0.94
Race, *n* (%)			
White	17 (81.0)	40 (93.0)	0.34
Black	1 (4.8)	1 (2.3)	
Others	3 (14.3)	2 (4.6)	
Smoking Status, *n* (%)			
Former/current	9 (42.9)	20 (46.5)	
Never Smoker	12 (57.1)	23 (53.5)	0.72
Family History of Cancer, *n* (%)			
Colon	13 (61.9)	33 (78.6)	0.16
LS Cancer	11 (52.4)	24 (57.1)	0.72
Other cancers	12 (57.1)	25 (58.1)	0.94
LS MMRPV, *n* (%)	14 (66.7)	21 (67.4)	1
MLH1	5 (23.8)	10 (23.3)	
MSH2	3 (14.3)	7 (16.3)	
MSH6	2 (9.5)	4 (9.3)	
PMS2	4 (19.0)	8 (18.6)	
No MMRPV	7 (33.3)	14 (32.6)	
Age of HNPCC diagnosis, mean ± SD			
LS	43.6 ± 14.0	45.4 ± 7.6	0.66
No MMRPV	49.0 ± 5.4	46.3 ± 2.2	0.59
Screening colonoscopies			
Median total number	5 (IQR 3.0-6.0)	4 (IQR 2.0-6.0)	0.19
Median years between colonoscopies	1.0 (IQR 1.0-1.5)	1.0 (IQR 1.0-1.6)	0.87
History of complete or partial colectomy	15 (76.2)	23 (53.5)	0.08
TAH-BSO (% of females in each group)	10 (83.3)	19 (76.0)	0.8
History of Prophylactic TAH-BSO (% of females in each group)	6 (50.0)	7 (28.0)	0.27
Proportion of patients with any cancer, *n* (%)	16 (84.2)	33 (76.7)	0.74
Cancer Incidence-10 yr follow up	12 (57.1)	20 (46.5)	0.42
Age at Diagnosis of first cancer (yr), mean ± SD	45.5 ± 14.6	43.8 ± 7.1	0.67

HNPCC: Hereditary non-polyposis colorectal cancer; LS: Lynch syndrome; MMRPV: Mismatch repair pathogenic variant; TAH- BSO: Total abdominal hysterectomy-bilateral salpingo-oophorectomy.

years for the unexposed group (P = 0.70). The exposed and unexposed groups were followed for a median 10 and 8.5 years, respectively.

No significant difference in age, gender, race, smoking, or family cancer history was observed between the groups (Table 4). 22.2% (2/9) of exposed and 16.7% (2/12) of the unexposed group had a history of cancer prior to CID diagnosis. One individual in the exposed group had a history of breast cancer while the other had a history of both pancreatic and colon cancer. In the unexposed group, one individual had history of colon cancer while the other had a history of both endometrial and colon cancer. Median duration of exposure to monoclonal antibodies and immunomodulators was

Table 2 Cancers observed based on presence or absence of a comorbid inflammatory condition over 10 yr of follow up, *n* (%)

Number of patients who developed a cancer	CID present, *n* = 21	No CID, *n* = 43
	12 (57.1)	20 (46.5)
Lynch syndrome specific cancers		
Colorectal	9 (42.9)	12 (27.9)
Endometrial	2 (9.5)	8 (18.6)
Small Bowel	0 (0)	1 (2.3)
Urothelial	1 (4.8)	1 (2.3)
Non-Lynch Syndrome-specific cancers		
Breast	1 (4.8)	0 (0)
Nasopharynx	1 (4.8)	0 (0)
Prostate	1 (4.8)	0 (0)
Ovarian	0 (0)	1 (2.3)
B-Cell Lymphoma	1 (4.8)	0 (0)

CID: Comorbid inflammatory condition.

Table 3 Distribution of cancers based on genetic diagnosis by comorbid inflammatory condition status

	CID present			CID non present		
	CRC	LS specific[1]	All other	CRC	LS specific	All other
MLH1	2 (40.0)	2 (40.0)	1 (20.0)	2 (20.0)	2 (20.0)	0 (0)
MSH2	2 (66.7)	0 (0)	1 (33.3)	2 (28.6)	4 (57.1)	1 (14.3)
MSH6	0 (0)	0 (0)	0 (0)	2 (50.0)	1 (25.0)	0 (0)
PMS2	2 (50.0)	0 (0)	1 (25.0)	0 (0)	2 (25.0)	0 (0)
No MMRPV	3 (42.9)	1 (14.3)	1 (14.3)	6 (42.9)	1 (7.1)	0 (0)

[1]LS Specific cancers other than colorectal cancer. These include endometrial, small bowel and urothelial.
CRC: Colorectal cancer; LS: Lynch syndrome; CID: Comorbid inflammatory condition.

5.7 (3.4-8.3) years and 2.5 (0.8-8.0) years, respectively. Four patients on biologics also received combination therapy with an immunomodulator (Table 5).

Seven of nine (77.8%) exposed compared to 5/12 (41.7%) unexposed patients developed any cancer after diagnosis of a CID (P = 0.18). The hazard ratio for cancer with medication exposure was calculated to be 1.59 (P = 0.43, 95%CI: 0.5-5.1). Figure 1 shows the Kaplan-Meier curve for cancer after diagnosis of CID. Median time to cancer after IBD or rheumatic disease diagnosis was 5.0 years (P = 0.64) in both groups. All 7 (77.8%) exposed individuals developed a LS-specific cancer compared to 3 (25%) unexposed. 9 total cancers developed in the 7 exposed individuals, including CRC (n = 6), and one each of breast, renal and endometrial cancer. The five unexposed individuals developed seven cancers in total, including CRC (n = 3) and one each of prostate, endometrial, nasopharynx and B cell lymphoma.

In individuals with IBD, 71.4% developed malignancy. All three (60.0%) exposed individuals with IBD developed cancer compared to two (40.0%) unexposed (P = 0.43). Fifty percent of rheumatic disease patients developed cancer. Four (57.1%) were exposed to immunosuppressive medications compared to three unexposed (42.9%). We found no significant difference in the proportion of individuals with cancer based on type of CID[MSF2] (IBD *vs* rheumatic disease) (P = 0.64). Mean age of diagnosis of CID was also similar in individuals who developed cancer (37.8 ± 14 years) compared to those who did not (40.3 ± 13.4 years, P = 0.39). The duration of CID was not associated with cancer incidence, 10.0 years (IQR 6.5-18.0) in those who developed cancer compared to 10.5 years (IQR 4-14.5) in those who did not develop cancer (P =

Table 4 Characteristics of individuals with a comorbid inflammatory condition based on medication exposure

Characteristic	Exposed	Unexposed	*P* value
	n = 9 (39.5)	*n* = 12 (60.5)	
Current age (yr), mean ± SD	54.2 ± 20	53.6 ± 12.4	0.7
Gender, *n* (%)			
Female	4 (44.4)	8 (66.7)	0.4
Race, *n* (%)			
Caucasian	7 (77.8)	10 (83.3)	1
Others	2 (22.2)	2(16.7)	
Smoking Status, *n* (%)			
Former/current	4 (44.4)	5 (41.7)	1
Never smoked	4 (55.6)	7 (58.3)	
Previous history of cancer, *n* (%)	2 (22.2)	2 (16.7)	1
Family history of cancer, *n* (%)			
LS specific cancer	6 (66.7)	5 (41.7)	0.39
All other cancers	6 (44.4)	8 (66.7)	0.4
Duration of Follow up, (yr), median (IQR)	10.0 (9.0-22.0)	8.5 (5.3-17.3)	0.38
Comorbid disease, *n* (%)	3 (33.3)	4 (33.3)	1
Crohn's disease	2 (22.2)	3 (25.0)	
Ulcerative colitis	1 (11.1)	1 (8.3)	
Rheumatic disease, *n* (%)	6 (66.7)	8 (66.7)	1
Pathogenic variant			
MLH1	2 (22.2)	3 (25.0)	
MSH2	2 (22.2)	1 (8.3)	
MSH6	0 (0)	2 (16.7)	0.68
PMS2	2 (22.2)	2 (16.7)	
MSI-H	3 (33.3)	4 (33.3)	
Cancer after CID diagnosis	7 (77.8)	5 (41.7)	0.18
Time to Cancer After Diagnosis of CID, (yr), median (IQR)	5.0 (2.0-16.0)	5.0 (1.0-10.5)	0.64
Age at Diagnosis of first cancer (yr), median (IQR)	49 (23.0-54.0)	48 (44.0-50.0)	0.99

HNPCC: Hereditary non-polyposis colorectal cancer; LS: Lynch syndrome; MMRPV: Mismatch repair pathogenic variant; CID: Comorbid inflammatory disease.

0.66).

DISCUSSION

When an inflammatory condition coexists with HNPCC, the clinician must evaluate the risk of cancer associated with the inflammatory disease itself, and any immunosuppressive medications used to treat the inflammatory condition, since the immune system detects and destroys tumor specific antigens produced by MSI-H cancers[11,12]. Our objective was to first evaluate the impact of a CID on the proportion of patients who develop cancer in HNPCC and additionally the risk based on immunosuppressive medication exposure for treatment of the CID. In patients prospectively followed in a hereditary cancer registry, we found no difference in the proportion of HNPCC individuals with cancer based on CID status. The age at comorbid disease diagnosis, type of disease, and disease duration did not correlate

Table 5 Details of exposure for each patient with type of cancer and age at diagnosis of cancer

Disease	Genetic Diagnosis	Medication	Duration /mo	Dose/mg	Cancer type and stage	Age at diagnosis of cancer
Ulcerative colitis	PMS2	Ustekinumab,	12		Colon II	19
		Golimumab	6			
		Vedolizumab	24			
Crohn's disease	MLH1	6MP	24	50	Colon I	57
Crohn's disease	PMS2	Adalimumab	18		Colon III	17
		Golimumab	6			
		Vedolizumab	12			
Sarcoidosis	MLH1	MTX	60	15	Renal I	49
Rheumatoid arthritis	LLS	Etanercept	120		Breast I, Colon IV	76
		Tofacitinib	9			
		MTX	35	15		
		Azathioprine	72	50		
Rheumatoid arthritis	MSH2	MTX	4	20	Colon II	51
		Rituximab	72			
Psoriatic arthritis	MSI-H	Adalimumab	36		Colon III	44
		Ustekinumab	10			
		MTX	36	15		
Dermatomyositis	MSH2	MTX	12	15	NA	NA
Rheumatoid arthritis	MSI-H	MTX	120	10	NA	NA

MSI-H: High microsatellite instability; MTX: Methotrexate; 6MP: 6-mercaptopurine, NA: Not applicable (no cancer seen during duration of the study).

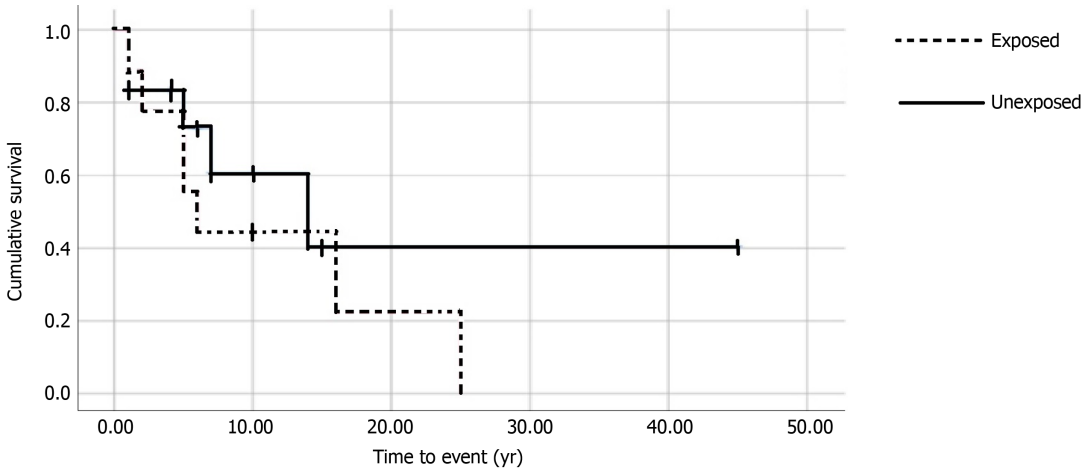

Figure 1 Kaplan Meier curve for cancer free survival between individuals exposed and unexposed to immunosuppressive medications.

with cancer development.

Epidemiological studies in the general population demonstrate that inflammatory diseases are associated with increased cancer risks. The standardized incidence ratio for CRC ranges from 1.1 to 7.0 in IBD and correlates with disease duration, anatomical extent, and severity[13]. A 10%-15% increased risk of cancer is observed in rheumatoid arthritis, particularly for lung cancer and lymphom[14]. Derikx *et al*[15] found that the incidence rate (4/15) of cancer in LS individuals with IBD was similar to LS without IBD, though they developed cancer at a younger age. Individuals were followed for 7 years and the impact of treatment was not evaluated. Another case series of 12 LS individuals with IBD found that 4 developed CRC between the ages of 32-47 years

[16]. We also found a younger median age of cancer diagnosis at 42 years in the four of seven (57.1%) IBD patients but did not observe a difference in the overall cancer risk between those with IBD compared to controls. Interestingly, in the above quoted studies, most CRC cases occurred in those with UC, as both UC patients developed CRC in our study. However, we also found that two of five with colon-predominant CD developed CRC. We hypothesize that a colon-predominant inflammatory process in HNPCC individuals further compounds the risk of colon cancer as observed in IBD. This is further supported by the observation that MLH1 and MSH2 deficient mice who have experimentally induced colonic inflammation develop CRC at faster rates and younger ages than MMR-proficient mice[17,18].

Inflammatory diseases are associated with significant morbidity and poor quality of life if left untreated[19,20]. Therefore, professional societies recommend the use monoclonal antibodies and immunomodulators to treat moderate to severe disease[21-23]. A logical conclusion is that the treatment of an inflammatory disease decreases any associated cancer incidence. However, monoclonal antibodies and immunomodulators have been associated with increased cancer risk in the general population. Wolfe demonstrated increased risks of lymphoma OR 1.7 (95%CI: 1.3-2.2), melanoma OR 2.3 (95%CI: 0.9-5.4), and non-melanotic skin cancer (OR 1.5, 95%CI: 1.2-1.8) in individuals exposed to an anti-TNFs compared to the general population[24]. A meta-analysis from nine clinical trials that compared the cancer risk in rheumatoid arthritis patients exposed to TNF-α inhibitors *vs* placebo found an elevated OR for cancer of 3.3 (95%CI: 1.2-9.1) in the exposed group[25]. This risk was dose dependent. Similarly, a US Food and Drug Administration analysis from 1998 to 2008 demonstrated higher incidence rates of lymphomas and solid tumors in children and adolescents who received TNF-alpha inhibitors for IBD and juvenile rheumatoid arthritis[26]. The combination of a TNF-alpha inhibitor with a thiopurine immunomodulator further increased this cancer risk and was associated with an increased risk of non-melanoma skin cancer as well [27,28]. In addition, methotrexate has been implicated in lymphoproliferative disorders[29], and azathioprine and 6-mercaptopurine have been implicated in skin cancers and lymphomas[30].

Given the lack of difference in the proportion of cancer cases between HNPCC with and without CID, our secondary aim was to evaluate if medication exposure had any effect on the proportion of individuals who develop cancer. It has been described that TNF-alpha inhibitors play a major role by regulating the TNF Related Apoptosis Inducing Ligand, an important mediator in immune surveillance[31]. In addition, murine models demonstrate that immune suppression results in an increased risk of sporadic breast, lung, small intestine and colon cancers[32]. Suppression of the immune system's antineoplastic role in MSI-H cancers could further compound these risks. Interestingly, we found that, though non-significant, there was an increased proportion of LS-specific cancers in the exposed group. The near doubling of LS-specific cancers (78% *vs* 42%) was primarily attributed to CRC cancer (66.6% *vs* 25%). Individuals with a colon-predominant IBD may benefit from medication sparing therapies and colonic resection may mitigate the elevated cancer risk as well.

The risk of CRC in IBD has historically been associated with severity and duration of the disease[33]. From this standpoint, immunosuppressive medications can potentially decrease CRC incidence in patients with IBD. In a metanalysis, Lu *et al*[34] describe an antineoplastic effect of thiopurines on colorectal neoplasia in patients with IBD, particularly amongst the patients with ulcerative colitis. However, these studies did not directly address individuals with LS. Genetic susceptibility to malignancy in LS adds another layer of complexity given the intricacy of balancing immunosuppression which decreases malignancy risk in inflammation but may also theoretically decrease immune surveillance.

There are limitations to our series worth mentioning, most of which are related to the inherent limitations seen in a retrospective study. Given the small subset of HNPCC patients with CID, we may not have captured a difference in cancer incidence between the exposed and unexposed groups when indeed there is one. However, this is the largest group of patients described with a length of follow up of at least 10 years. Furthermore, we are not able to specifically comment on the impact of each inflammatory disease based on severity and duration of illness. Moreover, the degree of immunosuppression was highly variable based on type, dose and duration of treatment which is described but not accounted for in the results. In our clinical experience, medications may be prescribed based on the severity of the inflammatory disease and personal history of malignancy. Though there is no data to guide specific management, the average duration of medication exposure exceeded one year. Drug trials also exclude patients with hereditary cancer syndromes, and it is unlikely that there will be a large enough population to evaluate each medication for each inflam-

matory condition. This study is the first to evaluate the impact of biologics and immunomodulators on cancer risk in HNPCC. Our study population was primarily Caucasian, however the malignancy risk associated with these medications have not been correlated with race. We also included individuals with HNPCC but without a MMRPV potentially masquerading a significant difference between exposed and unexposed groups, if any. However, these patients had MSI-H tumors and were followed in a similar fashion as those with LS due to an increased incidence of malignancy. The number of individuals without a MMRPV was also similar in both groups. Future studies should report cancer specific survival rates.

In our small cohort, CID does not appear to add any additional cancer risk to patients with HNPCC regardless of MMRPV status. The decision to start a biologic or immunomodulator in this cohort is understandably complex and should be individualized with consideration given to any colonic inflammatory disease.

CONCLUSION

In our small cohort, CID does not appear to add any additional cancer risk to patients with HNPCC regardless of MMRPV status. The decision to start a biologic or immunomodulator in this cohort is understandably complex and should be individualized with consideration given to any colonic inflammatory disease.

ARTICLE HIGHLIGHTS

Research background

Patients with Lynch Syndrome and hereditary non polyposis colorectal cancer (HNPCC) have an increased cumulative lifetime risk of developing colorectal, endometrial, ovarian, stomach, small bowel, hepatobiliary, urothelial, and brain cancers. These individuals may have co-existent systemic inflammatory conditions such as inflammatory bowel disease (IBD) and rheumatic diseases. Treatment of moderate to severe inflammatory disease generally involves modulating the immune system with systemic immunosuppressive medications, in particular monoclonal antibodies and immunomodulators alone or in combination. Interaction of the inflammatory disease and immunosuppressive medications in individuals at increased risk of malignancy due to baseline genetic diagnosis is unknown.

Research motivation

The immune system is known to protect against cancer by detecting neoantigens presented by cancer cells, so clinicians may be hesitant to prescribe these medications in patients with HNPCC due to concern of an elevated cancer risk. This leads to significant morbidity for these individuals. Moreover, treatment with immunosuppressive medications might theretically place them at higher risk for cancer. There is limited existing data to guide clinicians in this regards.

Research objectives

The primary aim was to compare the proportion of individuals with Lynch syndrome and HNPCC who develop cancer based on comorbid inflammatory disease status. Lynch syndrome and HNPCC individuals with comorbid inflammatory disease (cases) were matched to controls (Lynch syndrome and HNPCC without comorbid inflammatory disease) in a 1:2 ratio. Our secondary aim was to compare the proportion of comorbid inflammatory disease patients (n = 21) who developed cancer with and without exposure to a monoclonal antibody and/or immunomodulator therapy in Lynch syndrome and HNPCC population.

Research methods

Lynch Syndrome and HNPCC individuals enrolled in the David G. Jagelman Hereditary Colorectal Cancer Registries at the Sanford R. M.D. Center for Hereditary Colorectal Neoplasia at the Cleveland Clinic from 1979 to 2019 who met inclusion criteria were included in the study. Individuals with comorbid IBD including ulcerative colitis (UC) and Crohn's disease (CD), and rheumatic diseases were included. For our primary aim, controls were randomly chosen from the registry after matching for presence and type of mismatch repair gene pathogenic variant, age at last

follow up, and gender. We compared the proportion of patients who had developed any cancer up to last follow up or death between the two groups. For our secondary aim, patients were divided into two groups based on any exposure to these medications. Duration of exposure was determined through the electronic medical record or paper chart review by duration of prescription length and provider notes. The proportion of individuals who developed a cancer was calculated from the year of diagnosis of comorbid disease until last follow up or death.

Research results

64 HNPCC patients including 21 cases with a comorbid inflammatory disease and 43 controls without comorbid inflammatory disease were analyzed. The proportion of patients who had developed cancer after diagnosis of comorbid inflammatory disease in cases was 57.1% with a 10 year (6.0-16.5) median duration of follow-up and 46.5% in controls (P = 0.42) when also followed for 10 years prior to last follow up or death. Approximately half of the cancers were HNPCC-specific: 52.4% of cases *vs* 44.2% of controls (P = 0.54). For the secondary aim, we compared the proportion of individuals who developed cancer after diagnosis of a comorbid inflammatory disease in the 9/21 (39.5%) individuals exposed to monoclonal antibodies and/or immunomodulators to the 12/21 (61.5%) unexposed. Seven of nine (77.8%) exposed compared to 5/12 (41.7%) unexposed patients developed any cancer after diagnosis of a CID (P = 0.18). The hazard ratio for cancer with medication exposure was calculated to be 1.59 (P = 0.43, 95%CI: 0.5-5.1). This is the first study of its kind, attempting to address the interaction between genetic predisposition to cancer, inflammatory disease and immunosuppression. It remains to be seen whether these results are reproduced in larger multicenter studies.

Research conclusions

In our small cohort, comorbid inflammatory disease does not appear to add any additional cancer risk to patients with HNPCC regardless of MMRPV status. The decision to start a biologic or immunomodulator in this cohort is understandably complex and should be individualized with consideration given to any colonic inflammatory disease.

Research perspectives

We propose collaborative research to assess the risk of malignancy in lynch syndrome and HNPCC individuals on immunosuppressive medications. The risk of colorectal cancer in IBD has historically been associated with severity and duration of the disease. From this standpoint, immunosuppressive medications can potentially decrease colorectal incidence in patients with IBD. However, there are no studies that directly address individuals with genetic predisposition to cancer. Genetic susceptibility to malignancy adds another layer of complexity given the intricacy of balancing immunosuppression which decreases malignancy risk in inflammation but may also theoretically decrease immune surveillance.

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CASE REPORT

Late recurrence of localized pure seminoma in prostate gland: A case report

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Abstract

BACKGROUND

Late relapses of early-stage germ cell tumors are rare. Most patients (~85%) with stage I seminoma are cured by radical orchiectomy. The detection of late relapse is challenging given the relative rarity of this phenomenon, and the fact that patients who have completed surveillance are usually not undergoing regular oncologic workup nor imaging. While many treatment options do exist for a patient with late relapse of seminoma, surgery is typically the mainstay as these tumors are generally thought to be more chemo-resistant.

CASE SUMMARY

In this article, we describe the management of a patient with an early-stage pure seminoma who was subsequently identified to have a recurrence two decades later. We provide a review of the literature not only focused on clinical factors and biology, but also the management of late recurrences specifically in pure seminoma and in prostate gland.

CONCLUSION

There is a paucity of data and treatment recommendations for this clinical entity, and a multidisciplinary approach emphasizing subspecialty expert consultation and patient education is imperative.

Key Words: Late recurrence of pure seminoma; Pure seminoma; Seminoma; Primary prostatic seminoma; Germ cell tumor relapse; Treatment of relapsed seminoma; Biology of pure seminoma; Seminoma tumor markers; Case report

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Grade C (Good): C
Grade D (Fair): 0
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Core Tip: This case report describes of a patient with early-stage pure seminoma subsequently identified to have a recurrence within the prostate over two decades later. We provide a robust review of the literature focused on clinical factors, biology, and management of late recurrences specifically in pure seminoma and in prostate gland. There remains a lack of consensus data on treatment recommendations for this clinical disease. As such, a multidisciplinary approach emphasizing subspecialty expert consultation and patient education is imperative.

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INTRODUCTION

Late relapses of early-stage germ cell tumors (GCTs) [both seminomatous and non-seminomatous GCTs (NSGCTs)] are rare and are typically defined as recurrence at least two years after completion of successful primary treatment[1]. Notably, most patients (-85%) with stage I seminoma are cured by radical orchiectomy[2]. As such, the detection of late relapse is challenging given the relative rarity of this phenomenon, and the fact that patients who have completed surveillance are usually not undergoing regular oncological workup nor imaging. While many treatment options do exist for a patient with late relapse of seminoma, surgery is typically the mainstay as these tumors are generally thought to be more chemo-resistant[1,11].

The purpose of this report is to describe the management of a patient with an early-stage pure seminoma who was subsequently identified to have a recurrence two decades later. A majority of the reports studying late relapse combine a mixed patient population of seminoma and NSGCTs, and focus more on clinical characteristics that may be associated with the late relapse. As such, we aim to provide a brief review of the literature not only focused on clinical factors and biology, but also the management of late recurrences specifically in pure seminoma. There is a paucity of data and treatment recommendations for this clinical entity, and a multidisciplinary approach emphasizing subspecialty expert consultation and patient education is imperative.

CASE PRESENTATION

Chief complaints

The patient complained of urinary frequency, nocturia and intermittent urinary stream 20 years after his initial diagnosis of stage I pure seminoma.

History of present illness

The patient is a 60 years old man who originally presented in 1998 to a different facility and underwent a right radical orchiectomy for a testicular mass. Pathology showed a stage I (pT1 N0 M0) pure seminoma. He received adjuvant radiation therapy to the periaortic fields and subsequently did well with no evidence of disease recurrence.

Twenty years later, he developed frequency of urination, nocturia, and intermittent urinary stream. He was found to have an abnormal digital rectal exam and underwent a trans-rectal ultrasound which showed an irregular prostate gland. He ultimately underwent a prostate biopsy which revealed pure seminoma in 10 out of 12 cores bilaterally (Figures 1-3).

History of past illness

Tumor markers after diagnosis of recurrence were as follows: Alpha fetoprotein (AFP) 3.4 and human chorionic gonadotropin (HCG) < 2. A left testicular ultrasound showed a spermatocele, but no obvious masses. Staging computed tomography (CT) scans of the chest, abdomen and pelvis demonstrated an enlarged prostate with extracapsular

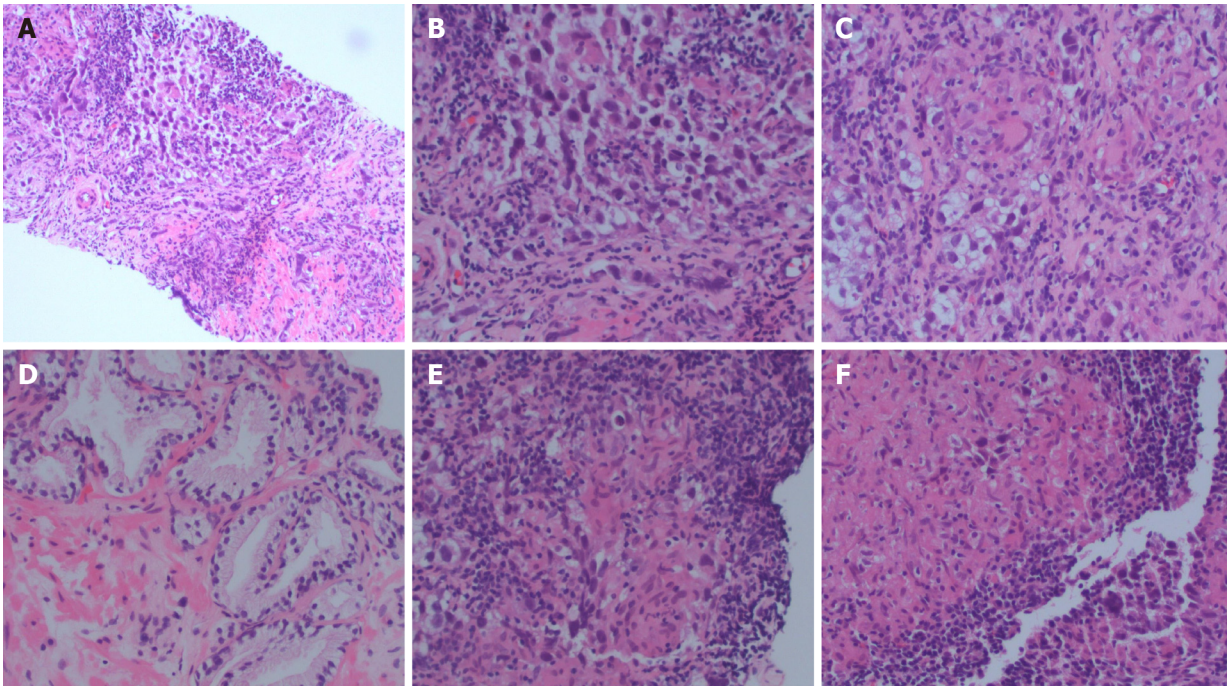

Figure 1 Representative hematoxylin and eosin sections. A: Tumor section; B: Tumor section; C: Granuloma; D: Benign prostate; E: Granuloma and lymphocytes; F: Granuloma.

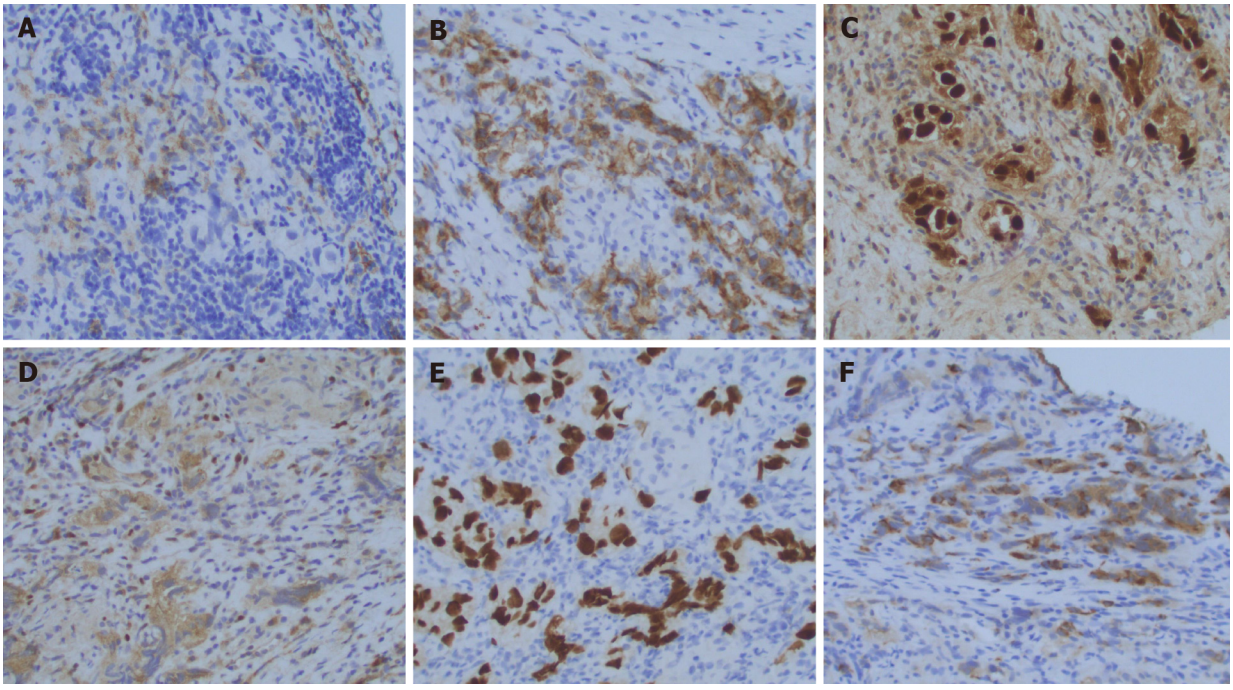

Figure 2 Representative immuno-stains. A: OCT4; B: PLAP; C: SALL4; D: EMA; E: Keratin; F: EMA.

extension, seminal vesicle invasion, possible tumor invasion into the rectal wall, an enhancing 1 cm periprostatic lymph node, and a 6 mm right pelvic sidewall lymph node. He was then referred to our tertiary care center for further management. His case was presented at a multidisciplinary genitourinary tumor board where further imaging was recommended.

He underwent a positron emission tomography (PET) scan which showed an fluorodeoxyglucose (FDG)- avid mass replacing the prostate gland with invasion into the right seminal vesicle, loss of the normal fat planes between the prostate, bladder and rectum concerning for extracapsular invasion, and an FDG-avid prominent right mesenteric lymph node consistent with nodal metastasis (Figure 4A).

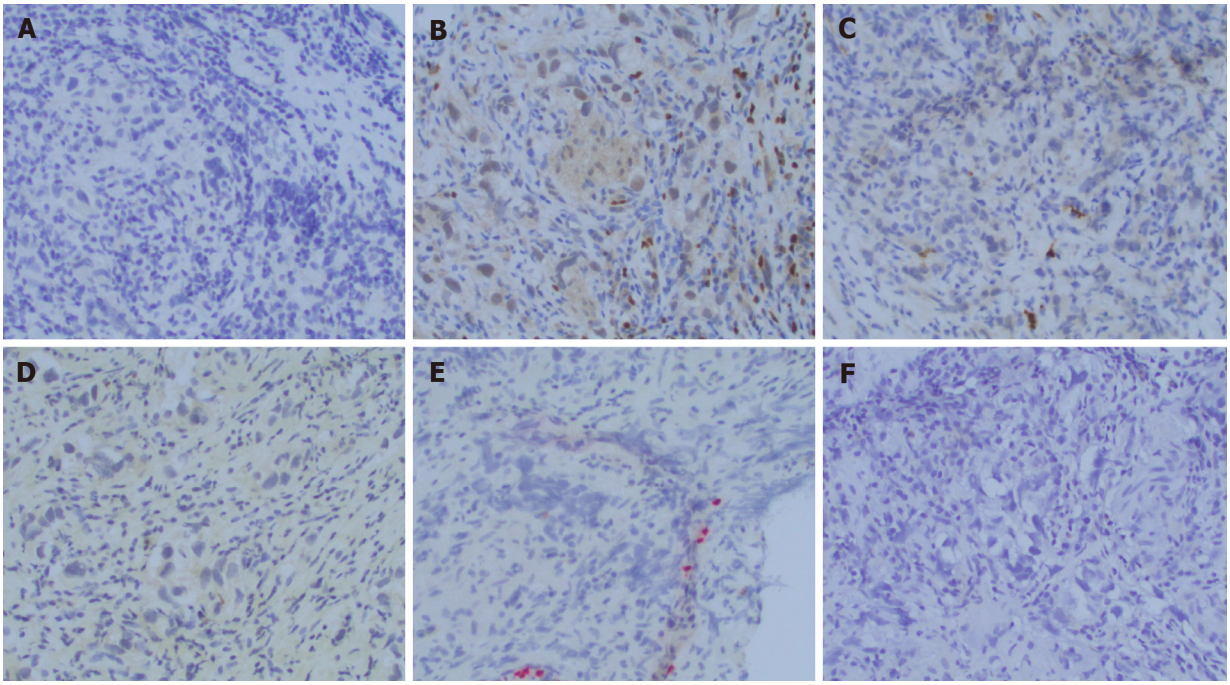

Figure 3 Representative immuno-stains. A: PAX8; B: PIN4; C: PSA; D: PSAP; E: S100; F: SOX10.

Personal and family history

Past medical history: Gastroesophageal reflux disease; post-nasal drip/recurrent sinusitis; hyperlipidemia - diet controlled; low testosterone; B12 deficiency.

Past surgical history: Left inguinal hernia repair - 2014; right orchiectomy - 1998; tonsillectomy - age 3.

Allergies: No known drug allergies.

Family history: Mother - lymphoma at age 94; maternal uncle - prostate cancer in his 80 s.

Social history: Patient denied history of smoking, alcohol or drug use. He currently lives with his wife. He has 3 children. He is a pilot.

Physical examination

Electrocorticography performance status: 0; pain score: 0/10; general: Alert and oriented to place, self, time, in no acute distress well-appearing; head, ears, eyes, nose, and throat: Normocephalic, atraumatic, anicteric sclera, moist mucous membranes, no oral lesions or thrush; chest: Chemotherapy port site clean; cardiovascular: Normal S1, S2, regular rate and rhythm, no murmurs/rubs/gallops; pulmonary: Clear to auscultation bilaterally, no crackles/wheezing/rales; abdomen: Soft, non-distended, non-tender, normal bowel sounds, no rebound/guarding, no hepatosplenomegaly; back: No costovertebral angle tenderness. No tenderness along the spine. Extremities: Warm, well perfused, no joint deformities. No cyanosis, clubbing, or edema.

Laboratory examinations

Tumor markers after diagnosis of recurrence were as follows: AFP 3.4 and HCG < 2.

Imaging examinations

Staging CT scans of the chest, abdomen and pelvis demonstrated an enlarged prostate with extracapsular extension, seminal vesicle invasion, possible tumor invasion into the rectal wall, an enhancing 1 cm periprostatic lymph node, and a 6 mm right pelvic sidewall lymph node.

Literature review: Late recurrences of early stage GCTs remains a rare clinical entity. This applies to both pure seminoma and NSGCTs. Studies detailed below have shed light on additional clinical factors associated with late recurrences aside from the clinical stage. In particular, there is an observation that NSGCTs have a higher

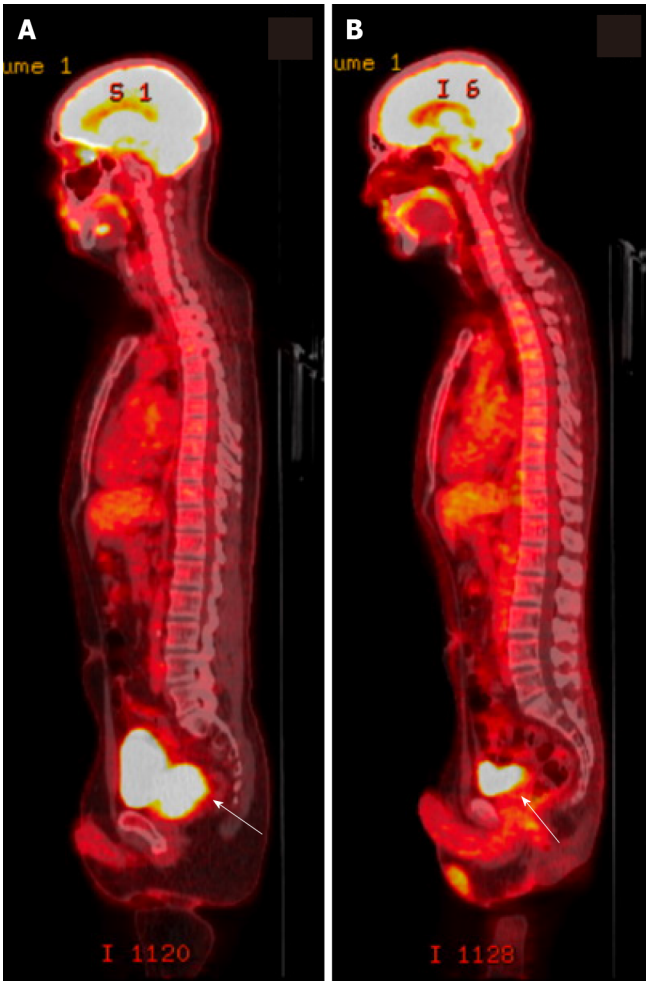

Figure 4 Representative positron emission tomography/computed tomography scans. A: Positron emission tomography/computed tomography (PET/CT) scan at diagnosis of relapse of pure seminoma. An fluorodeoxyglucose (FDG)-avid mass is shown (white arrow) replacing the prostate gland with invasion of the right seminal vesicle. Loss of the normal fat planes between the prostate, bladder and rectum is concerning for extracapsular invasion. An FDG-avid prominent right mesenteric lymph node consistent with nodal metastasis. B: PET/CT scan after completion of 4 cycles of etoposide and cisplatin. Significant decrease in size and activity of prostate mass and resolution of FDG-avid right mesenteric lymph node consistent with response to therapy (white arrow).

propensity to recur late than do pure seminomatous tumors[3]. While the treatment of a germ cell tumor recurrence can generally involve surgery or chemotherapy[2,3], a thorough assessment of tumor locality, patient functional status and prior treatments must be taken into account in detailing a personalized approach especially for curative intent.

A study of 1263 patients with late recurrence of GCTs has demonstrated that positive tumor markers at initial presentation and the presence of differentiated teratoma in post-chemotherapy surgical specimens are predictors of late recurrence. Additionally, late recurrences more than 5 years from initial therapy occurred mainly in patients with metastatic NSGCTs, whereas late recurrence was only seen in one case of metastatic seminoma and in one case of stage I NSGCT managed by surveillance. In patients with stage I seminoma treated with adjuvant radiation, the latest recurrence in this study was seen at 21 mo[3]. Interestingly, very late recurrences after 5 years in stage I and II seminoma treated with post- operative radiotherapy have been reported and were more common in bulky stage II disease[4].

The possibility of a new extra-gonadal primary tumor rather than a recurrence of the initial primary tumor for these patients must be seriously considered. Although ionizing radiation can have late effects mediating new tumorigenesis, the recurrence we have described has occurred outside of the radiated field, or "landing zone". As such, it is important to note that there have been very few cases reported of primary seminoma of the prostate. To our knowledge, this entity has only been described in at least 5 circumstances. Hashimoto *et al*[12] recently reported the case of a 54-year old man with difficulty urinating who was found to have an enlarged and irregular prostate, as in our patient. Core biopsy demonstrated cells positive for placental

alkaline phosphatase, CD117, periodic acid-Schiff, and negative for cytokeratin 7, leukocyte common antigen, vimentin, S100 protein, CD30, and prostate-specific antigen. The pathological exam was therefore consistent with seminoma. Notably, this patient had completely normal testes on ultrasound and physical exam with no other distant disease on imaging by chest and abdominal CT scan. He was treated with three cycles of bleomycin, etoposide, and cisplatin (BEP) chemotherapy and has responded well with complete remission of disease. Hence, although rarely described, the notion of an extra-gonadal germ cell tumor is certainly plausible and data does point towards platinum-sensitivity of these particular tumors[12,13].

A population based study by Oldenburg *et al*[5] evaluated 1123 patients with seminoma and 826 patients with non-seminoma, identifying twenty-five patients who developed a late relapse. Of note, four of ten initial seminoma patients relapsed with non-seminomatous pathology, one non-seminoma patient relapsed as a seminoma, and three relapses were noted to have undifferentiated carcinomas. This observation implies the significance of biological heterogeneity within these relapses, which necessitates a comprehensive multidisciplinary approach to their management. All ten of the seminoma patients in this study and seven of the eight non-seminoma patients received salvage chemotherapy regimens. The authors caution regarding the use of salvage chemotherapy in patients considered to have a late germ cell tumor relapse. Indeed, the role for surgical resection can lead to cure, as it did for eight of their non-seminoma patients. A suggested treatment strategy includes cisplatin-based chemotherapy followed by a complete resection of residual masses, if needed.

A descriptive analysis of 122 cases of malignant GCTs assessed the characteristics of late relapse in 50 patients with pure seminoma and 72 patients with non-seminoma. The time course to late relapse was 42 mo (range 25 to 276 mo) in seminoma and 64.5 mo (range 28 to 216 mo) in non-seminoma[6]. The wide ranges seen for both disease states are intriguing and implies that specific biological factors are at play to mediate relapses such as the one presented above. Another intriguing observation from the authors was that for late recurring seminoma, 80% of cases developed from stage 1 disease while for non-seminoma, 75% of late relapses developed from primary systemic disease.

Hence, in regards to pure seminoma relapse we postulate that cellular and molecular mechanisms governing self-renewal, senescence and even extracellular contacts could play a viable role. Factors that may be at play in the evolution of a late relapse include a derangement in genes regulating these processes, thereby resulting in a persistence of seminoma cancer stem cells. Gene expression studies have clearly documented that the human embryonic stem cell genes OCT4, NANOG, STELLAR, and GDF3 are expressed in seminoma, supporting the role for such a mechanistic evolution of late relapse[7]. Whether these cancer progenitor cells can maintain a long-term quiescence followed by transformation to a more mitogenic phenotype is a matter of debate, but is certainly possible given rare but notable reports of pure seminoma late relapses.

Importantly, in comparing the pattern of relapses in pure seminoma, it is noted that both early (< 2 years) and late (> 2 years) relapses harbor similar anatomical distributions with few distinctions. In one retrospective review of 1060 stage I seminoma patients, it was observed that a single site of relapse with isolated para-aortic or pelvic nodes were the most predominant distributions. However, all late relapses after adjuvant radiotherapy occurred in the mediastinum, whereas early relapse sites were inguinal, supraclavicular and lung. There were no significant differences between the times to late relapse between patients who were managed with adjuvant radiation *vs* active surveillance[1]. This supports, to some degree, a similar biology in both early and late seminoma patients. While studies may be limited into understanding these mechanistic factors due to the small number of relapses, treatment decisions for late relapse can be made in similar fashion to early relapse. Guidance is provided in the National Comprehensive Cancer Network guidelines, with surgical excision preferred for solitary localized relapses as well as for early (< 2 years) relapses and systemic chemotherapy preferred for late (> 2 years) relapses where surgery is not feasible.

It is not well established what the ideal modality of therapy is for relapse after adjuvant radiotherapy, but as these tumors may be chemo-sensitive it is reasonable to consider systemic and localized approaches with a preference for surgery where possible. In the study previously mentioned, among 294 stage I pure seminoma patients treated with adjuvant radiotherapy after orchiectomy, 14 (5%) had a relapse after a median time of 15 mo (range 5-72 mo). Specifically, later relapses were noted after adjuvant radiotherapy in three patients, representing 1% of the entire adjuvant radiotherapy group (3/294) and 21% of the relapsed patients after adjuvant radiation (3/14). To date, our case is the only known report of relapsed stage I pure seminoma

occurring approximately 20 years after adjuvant radiation.

Nine of the patients in the review by Hosni *et al*[1] who relapsed after adjuvant radiation went on to receive salvage chemotherapy with platinum based regimens such as etoposide and cisplatin (EP). One patient with late relapse in the mediastinum received both chemotherapy and salvage radiation, whereas four patients with isolated inguinal early relapse either received salvage radiation (3 patients) or inguinal lymph node dissection (1 patient). Importantly, none of the patients in the adjuvant radiotherapy group developed a second relapse. Similarly, among patients with relapse of seminoma managed with active surveillance, none of the patients in the late relapse group developed a second relapse after either salvage radiotherapy or chemotherapy. Although not conclusive, this suggests a similar chemo-sensitivity profile for relapsed seminoma originally managed with active surveillance or adjuvant radiation.

While treatment of these relapses has curative potential, the outcomes for seminoma tend to be better than for non-seminoma. In the retrospective study by Dieckmann *et al* [6], thirty-seven out of 72 (51.3%) patients with non-seminoma failed to be cured in contrast to only 6 out of 48 (12.5%) patients with seminoma who failed to be cured. The use of surgery increased the chance of cure for these patients. This again supports a distinct and perhaps more chemo-resistant tumor biology for late relapses, more-so for patients who have previously received chemotherapy. Hence, while seminomas and other chemotherapy-naive cases may respond to chemotherapy, inclusion of experienced urological surgeons in care of these patients is crucial to determine the appropriate intervention for best possible outcomes.

FINAL DIAGNOSIS

Pure seminoma localized to prostate gland.

TREATMENT

The patient mentioned in this review subsequently was consented for treatment with EP and completed 4 cycles of therapy.

OUTCOME AND FOLLOW-UP

Response assessment with CT chest, abdomen and pelvis scans showed reduction in the size of the dominant prostate mass and resolution of the pelvic adenopathy. A restaging PET scan showed no FDG-avid lesions (Figure 4B). His case was again reviewed at the multidisciplinary tumor board, where review of imaging confirmed response to chemotherapy.

Subsequent scans continued to show complete response to therapy. At this point, the patient is over two years from completion of cancer-directed treatment for his recurrence of pure seminoma. Clinically, he is doing well without major functional limitations.

DISCUSSION

Our case represents an anomaly of late relapsed stage I pure seminoma due to its discovery after approximately 20 years since completion of adjuvant postoperative radiation therapy. He has maintained remission successfully after receipt of platinum-based chemotherapy. This observation sparks an intriguing discussion into the clinical factors, biological mechanisms, and treatment modalities surrounding this rare clinical entity. While a lack of concrete evidence for management is marred by the small number of late relapsed cases in pure seminoma, a few retrospective studies have shed light on patient outcomes after varied approaches inclusive of surgery, platinum-based chemotherapy and radiation.

The clinical vignette presented in our paper is also unique in that he has achieved a complete response to treatment with a less intensive chemotherapy regimen. Although the standard of therapy for non- pulmonary metastasis from testicular cancer generally

includes 4 cycles of BEP or etoposide, ifosfamide and cisplatin, this patient has received less than that and has been cured. Factors that may help explain this include the fact that his disease was managed with adjuvant radiation alone after orchiectomy, implying chemo-sensitive disease at relapse. Nonetheless, it remains unknown whether there are chemosensitivity differences between early and late relapsed seminomas managed with adjuvant radiation.

Studies suggested that serum levels of microRNA (miR)-371a-3p (the so-called M371 test) have a much higher sensitivity and specificity than the classic markers of testicular GCTs and are applicable toward both seminoma and non-seminoma. The M371 test outperforms the classic markers of GCT with both a sensitivity and a specificity greater than 90%. All histologic subgroups, except teratoma, express this marker. If validated, M371 can be used for detection of late recurrence without concern for excess radiation exposure over time[14]. Furthermore, in a case like ours, M371 can help to detect residual disease after completion of chemotherapy and offer early salvage surgery.

CONCLUSION

Whether his recurrence was a manifestation of true relapse from his original seminoma or a completely new primary is also unclear and not likely to be proven with the present scope of our knowledge. We have presented a literature review that details findings by other groups in regards to primary seminoma of the prostate. This clinical entity has demonstrated chemosensitivity to platinum-containing regimens and remains a plausible diagnosis to consider. Whether pure seminoma can manifest with a late relapse into the prostate is not known, but the theory of an extra-gonadal second primary tumor should be considered in this regard. Given our patient's pure seminomatous pathology and the fact that he has responded well to chemotherapy, the biology of his initial and relapsed disease states may share a common evolutionary tumorigenesis.

In summary, further research will be required to identify the ideal follow-up strategy to detect late relapses in pure seminoma and prognostic factors including more specific biological characteristics. The identification of patients at risk for late relapse is limited by its rarity and a lack of large-scale data[1,2]. The surveillance schedule for stage I seminoma patients has generated some controversy. While some experts suggest lifelong follow-up in contrast to 5-10 years of follow-up[8-10], a more personalized approach taking into account patient characteristics with risk-adapted projections can be considered.

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