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REVIEW

New Targets, New Agents, and Radiotherapy in Genitourinary System Cancers: A Course Summary

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SUMMARY

The use of Stereotactic Ablative Radiotherapy (SABR) in the treatment of genitourinary system cancers has increased, supported by studies showing a survival benefit, particularly in oligometastatic disease. However, as an increasing number of patients receive novel systemic therapies concurrently, the toxic effects of these interactions require careful evaluation. This review aims to examine the efficacy and toxicity outcomes of combining radiotherapy (especially SABR) with novel systemic agents in Prostate, Bladder, and Renal Cell Cancers (RCC), based on current evidence and the EORTC-ESTRO OligoCare consortium guidelines. Systemic Agent Risk Categorization: Combining SABR with systemic therapy classified as high-risk when showed a significant increase in Grade ≥3 toxicity, whereas no such increase was observed with low-risk agents. Prostate Cancer (PCa): New-generation hormonal agents (Abiraterone, Enzalutamide, Apalutamide) can be used safely concurrently with radiotherapy. Applying SABR to oligoprogressive lesions in Metastatic Castration Resistant PCa (mCRPC) can extend the duration of the current hormonal treatment duration. Bladder Cancer (BCa): The use of immunotherapy and Antibody-Drug Conjugates is increasing, with nearly all of these agents falling into the high-risk drug category. Evidence in this area is low, and experience is limited. A 1 to 2 week break between RT and systemic treatment is recommended to mitigate toxicity risk. RCC: TKIs and immunotherapies are widely used and are mostly in the high-risk drug category. Despite this, SABR (with immunotherapy or TKI) in oligoprogressive RCC lesions has shown good tolerability with high local control rates (over 90% 2-year LC) and can extend the time before switching systemic therapy (NEST) by a median of 12.6 to 15.2 months. A 1 to 2 week break between RT and systemic treatment is recommended to mitigate toxicity risk. The combination of RT and novel systemic agents in genitourinary system cancers is promising in terms of efficacy and prolonging the time to switch systemic therapy, especially in oligometastatic disease. As agents other than those for prostate cancer are often high-risk, careful consideration of optimal treatment timing and individualized decisions made through a multidisciplinary approach are vital.

Keywords: Bladder cancer; oligometastasis; prostate cancer; renal cell carcinoma; SABR; systemic therapy; toxicity.

INTRODUCTION

The Role of Stereotactic Ablative Radiotherapy (SABR)

The use of Stereotactic Ablative Radiotherapy (SABR) in oligometastatic cancer was prominently introduced by the SABR-COMET Phase II Randomized Trial. This trial suggested a survival advantage for SABR in oligometastatic disease.[1] The long-term results of SABR-COMET showed significantly improved Overall Survival (OS) (p=0.006) and Progression-Free Survival (PFS) (p=0.001) in the SABR arm compared to the control arm. The original toxicity profile indicated an acceptable safety margin, with the incidence of Grade

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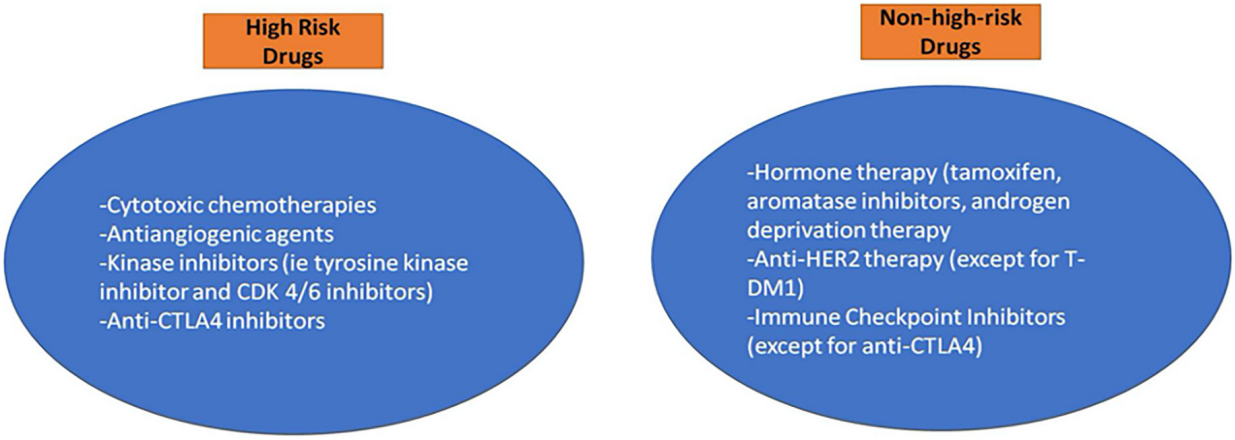

Fig. 1. Categorization of systemic therapies, based on their interaction risk with SABR.
CDK: Cyclin dependent kinase; HER2: Human epidermal growth factor receptor 2; T-DM1: Trastuzumab drug maytansinoid 1.

3 or higher toxic effects less than 5%. In the phase II SABR-5 trial, rates of Grade 2 or higher toxic effects were lower than previously published for SABR-COMET (18.6% vs. 29%).[2] Finally, the same investigators presented a secondary analysis of the SABR-5 trial at last year's ASTRO. This study investigated the toxicity rates associated with the combined use of SABR and various systemic therapies (classified as high-risk or non-high-risk), particularly focusing on whether administering high-risk drugs concurrently with SABR increases the risk of severe side effects (Grade 3+).[3]

INTERACTION WITH SYSTEMIC THERAPY AND TOXICITY

A critical consideration is the concurrent use of systemic therapy with SABR, as many patients receive both. The EORTC-ESTRO OligoCare consortium provided consensus recommendations based on a systematic review of the toxicity and interaction outcomes of combining systemic therapy and SABR.[4] Systemic therapies are categorized based on their interaction risk with SABR (Fig. 1):

High-risk drugs: Combining these with SABR leads to a significantly increased rate of Grade ≥3 toxicity (p=0.009).[3] Examples include cytotoxic chemotherapies and Anti-CTLA4 inhibitors. Tyrosine Kinase Inhibitors (TKIs) for RCC are considered in this category.

Non-high-risk drugs: Combining these with SABR showed no significantly increased toxicity (p=0.884).[3] Examples include Hormone therapy (e.g., tamoxifen, aromatase inhibitors, new-generation hormonal therapies for prostate cancer), anti-angiogenic agents, and certain checkpoint inhibitors (excluding anti-CTLA4).

Caution on timing: SABR-related toxicity can be observed with a delay of 2 to 7 months after treatment.

PROSTATE CANCER (PCA)

Radiotherapy finds its place across the spectrum of prostate cancer treatment: Definitive, salvage, metastasis-directed therapy (MDT) in the oligometastatic setting, and palliative care. Hormone therapy for prostate cancer began its antiandrogen phase in the 1960s with the introduction of steroidal antiandrogens (Cyproterone acetate), which were subsequently largely replaced by the development of non-steroidal antiandrogens starting in the 1970s and 1980s. The development of third generation non-steroidal antiandrogens has significantly improved survival outcomes since the 2000s.[5]

Androgen Receptor Pathway Inhibitors (ARPIs):

- **Third generation nonsteroidal antiandrogens: enzalutamide, apalutamide, and darolutamide:** These are potent selective androgen receptor (AR) antagonists with high receptor affinity. Their primary actions include inhibiting AR binding to androgens, inhibiting the translocation of the AR-hormone complex to the nucleus, and inhibiting AR binding to DNA and tumor gene expression.
- **Biosynthesis inhibitors: abiraterone acetate:** Abiteron Acetate is an inhibitor of the CYP17 enzyme. It suppresses androgen production from all three sources: The testes, the adrenals, and the tumor tissue itself, unlike conventional hormone therapies that only suppress testicular production. It is used in metastatic and non-metastatic settings.

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- **Evidence for RT and ARPIs in PCa:** Primary RT in Metastatic PCa (on Abiraterone): A study on Metastatic Castration Resistant PCa (mCRPC) patients with ≤5 metastases receiving abiraterone found that local RT to the primary tumor was associated with a longer median OS (24.1 vs. 21.4 months), although this was of borderline significance (p=0.08). Crucially, local RT significantly diminished the local recurrence rate (5% vs. 31%) and led to a longer duration of abiraterone treatment.[6]
- **SABR for oligoprogression (on abiraterone/enzalutamide):** Applying SABR to oligoprogressive lesions in mCRPC patients on Abiraterone or Enzalutamide extended the median duration of ARPIs treatment by 8.6 months.[7]
- **Salvage RT+ADT+enzalutamide (STREAM trial):** This phase II trial for high-risk PSA recurrent PCa showed a promising 3-year PFS of 53%.[8] However, the study was criticized for using conventional staging instead of PSMA PET, a low RT dose (66 Gy), and a higher-than-expected Grade 3 toxicity rate (29%).[9]
- **ARPIs in high-risk non-metastatic PCa (STAMPEDE):** A meta-analysis showed that combination therapy (Abiraterone acetate and prednisolone with or without Enzalutamide) in high-risk non-metastatic PCa was associated with significantly higher rates of metastasis-free survival compared with ADT alone.[10]
- The ATLAS study is a Phase III, randomized, double-blind, placebo-controlled trial evaluating the addition of apalutamide to standard therapy for patients with high-risk localized or locally advanced prostate cancer receiving primary radiation therapy.[11] The study is fully enrolled (approximately 1,503 patients) but is ongoing. The primary efficacy and safety results of the ATLAS study have not yet been published.
- **Summary for PCa:** New-generation hormonal agents are generally classified as non-high-risk drugs and can be used safely concurrent with radiotherapy.

BLADDER CANCER (BCA)

The standard of care for muscle-invasive bladder cancer (MIBC) is Radical Cystectomy (RC). However, multimodal bladder-sparing treatment including chemoradiotherapy (CRT), is a reasonable option for certain patients.

New Agents and the Role of Immunotherapy

Novel systemic agents are mainly used in the adjuvant, maintenance, and metastatic settings.

- **Adjuvant Immunotherapy (Nivolumab):** In patients' post-neoadjuvant chemotherapy (NAC), or those ineligible for cisplatin-based therapy who did not receive NAC, adjuvant immunotherapy (Nivolumab) is used, often based on PD-L1 status.[12] The Checkmate-274 trial showed that Nivolumab significantly improved disease-free survival (DFS) versus placebo in the adjuvant setting.[13]
- **Maintenance Immunotherapy (Avelumab):** In the Bladder Javelin study, for advanced or metastatic urothelial carcinoma, Avelumab maintenance therapy has shown a survival advantage.[14]
- **Antibody Drug Conjugates (ADC):** Antibody-Drug Conjugate (ADC) is an innovative class of biopharmaceutical drugs primarily designed as targeted therapy, most notably for cancer treatment. This complex molecule functions like a "SABR" in precise radiation treatment. This ADC mechanism allows for the precise delivery of a highly toxic agent to the tumor site, thereby maximizing the cancer-killing effect while simultaneously minimizing systemic exposure and damage to surrounding healthy tissues.

Agents like Enfortumab Vedotin and Sacituzumab Govitecan deliver a cytotoxic payload directly to cancer cells via an antibody. While they have good response rates (Enfortumab Vedotin ORR: 40.6% vs 17.9% for chemotherapy), their high side effect profiles necessitate careful consideration when combined with RT.[12,15]

Radiotherapy in Metastatic BCa

The evidence for SABR in oligometastatic bladder cancer is currently limited to low-level retrospective studies and reviews.[16–18]

Summary for BCa: Experience is limited, evidence is low, and nearly all commonly used new agents are in the high-risk drug category. Therefore, for patients planned for RT, a treatment break of 1 to 2 weeks between systemic therapy and RT is recommended for safety.

RENAL CELL CARCINOMA (RCC)

The systemic treatment of RCC relies heavily on Tyrosine Kinase Inhibitors (TKI) and Immunotherapies instead of classic chemotherapies.[19] RT has a broad role from local treatment for unresectable primary tumors to MDT and palliation.

Local treatment of metastases: MDT (surgery, SABR, or other ablative techniques) for oligometastatic RCC is recommended in contemporary NCCN guidelines. Systemic reviews suggest that local treat-

ments for metastases are associated with better survival outcomes and palliation.[20–22]

SABR and immunotherapy (RAPPORT trial): This trial combined SABR with short-course Pembrolizumab in oligometastatic RCC. OS at 2 years was 74%. Local control (LC) at 2 years was 92%, demonstrating SABR'S efficacy even in known radioresistant RCC. [23] The regimen was well-tolerated, with Grade ≥3 toxicity reported at 13%.

SABR and TKI (oligoprogression): A prospective study of SABR for oligoprogression in metastatic RCC patients receiving TKI therapy showed good OS (1-year OS 92%) and LC (1-year LC 93%).[24] The SABR to the progressing lesion allowed patients to continue the same TKI agent for a median of 12.6 months longer (NEST increase).

Another study investigating the role of SABR in switching systemic therapy for extracranial oligometastatic RCC showed that 27.2% of patients had a median NEST change of 15.2 months after MDT completion, with no significant difference in OS or PFS compared to those who did not have a NEST change.[25]

Summary for RCC: The majority of targeted agents used here (especially TKIs) are classified as high-risk drugs. By paying close attention to treatment timing, excellent results can be achieved even in this historically radioresistant tumor type.

CONCLUSION

The combination of RT and novel systemic agents in genitourinary system cancers is promising in terms of efficacy and prolonging the time to switch systemic therapy, especially in oligometastatic disease. As agents other than those for prostate cancer are often high-risk, careful consideration of optimal treatment timing and individualized decisions made through a multidisciplinary approach are vital.

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