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REVIEW ARTICLE

The impact of neoadjuvant immune checkpoint inhibitors on kidney cancer and bladder cancer surgeries: a systematic review

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ABSTRACT

Background: the neoadjuvant use of immune checkpoint inhibitors (ICIs) in patients with kidney cancer and bladder cancer is controversial, and there are reports suggesting increased difficulties in surgeries in these settings.

Aims: we performed a systematic review using PRISMA guidelines methodology to analyze pertinent literature available up to January 05, 2024 in PubMed, updating our previously published systematic review on the subject.

Results: we have selected 25 publications for the neoadjuvant use of different immune checkpoint inhibitors before nephrectomies for kidney cancer and seven publications concerning the neoadjuvant use of immune checkpoint inhibitors before cystectomies for bladder cancer. Reports of additional surgical difficulties were noted in 6/25 reports for kidney cancer and 0/7 reports for bladder cancer.

Conclusions: in the setting of neoadjuvant immune checkpoint inhibitors, a minority of cases of nephrectomies may be challenging due to inflammatory changes to the surrounding tissues, which may require more experienced surgeons. Neoadjuvant immune checkpoint inhibitors do not seem to pose additional surgical difficulties in cystectomies for the treatment of bladder cancer.

Introduction

Usually cured by surgery when diagnosed and treated in its early stages, kidney and bladder tumors until recently responded poorly to systemic therapies in advanced and metastatic disease. The development of immunotherapy has altered significantly the treatment of these tumors, especially in the metastatic setting. Immune checkpoint inhibitors (ICIs) are biologic drugs that block T-cell inhibitory proteins, such as CTLA-4 (cytotoxic T-lymphocyte associated antigen 4) and PD-1 (programmed death-1)¹. These drugs allow for the recognition of the tumor by the immune system, leading to phagocytosis and lysis of the cancerous cells². ICIs, alone or in combination with other drugs, are becoming the primary treatment approach for patients with advanced/metastatic renal or bladder cancers³.

These drugs have also been increasingly used in the preoperative scenario, as neoadjuvant treatments, or as primary treatments in the setting of metastatic disease, with surgery often indicated in responders to systemic treatment. However, preoperative therapy could alter the surgical dynamics, as there are reports of treatment associated changes, such as fibrosis and adhesions of surrounding tissues leading to a greater rate of surgical complications and even increased recovery time^{4,5}.

Some authors have hypothesized that neoadjuvant ICIs could complicate renal and bladder surgical procedures. Pignot et al⁶ reported that in a series of 11 patients treated with neoadjuvant ICIs prior to cytoreductive nephrectomies (CNs), surgeons were challenged to find dissection planes, which resulted in increased difficulties. On the other hand, there are studies that do not indicate an increased

difficulty during the procedures, such as the report by Singla et al⁷. These authors described a series of 11 patients who underwent CNs after nivolumab treatment in which there was no increased difficulty during the nephrectomies.

The impact of upfront systemic therapy on surgical complications remains uncertain. Drugs such as nivolumab, pembrolizumab, ipilimumab, atezolizumab, avelumab, and durvalumab block different proteins, potentializing the immune system response against cancer cells, which can retract or decelerate the growth of some tumors, but can also create significant surgical challenges⁸.

Due to the scarce and controversial literature in this regard, we performed a systematic review to analyze the relation between the administration of neoadjuvant immunotherapy and unexpected surgical outcomes, updating our previous publication on the theme⁹.

Materials and Methods

Search strategy

We conducted a systematic search of the PubMed database. The search was conducted to identify studies up to January 05, 2024. The studies were included in the Rayyan platform¹⁰ for recording decisions. The search and selection process adhered to the requirements of PRISMA guidelines, and the review is registered in the PROSPERO platform with the coding CRD42024537305¹¹. Details of the search and selection process are presented in Figure-1.

On PubMed, we used association descriptions with three mesh terms, in the model: drug AND disease AND complication. In the "drug" field, the following terms were used: Pembrolizumab, Atezolizumab, Ipilimumab, Nivolumab,

Avelumab, Durvalumab, ICIs and Immune checkpoint inhibitors. In the "disease" field, the terms: kidney cancer and bladder cancer were used. In the "complications" field, the following terms were used: surgical complications or surgery complications.

All possible combinations between terms were performed, for example, when using "Pembrolizumab" in the drug field: "Pembrolizumab AND bladder cancer AND surgical complications"; "Pembrolizumab AND kidney cancer AND surgical complications"; "Pembrolizumab AND bladder cancer AND surgical complications"; "Pembrolizumab AND kidney cancer AND surgical complications". The articles resulting from the search were grouped and duplicate studies were excluded.

In phase two – the screening phase – we read only the title and abstract of the articles retrieved, and based on the previously established eligibility criteria selected the manuscripts for complete evaluation.

Inclusion and Exclusion Criteria

We included in the review clinical trials performed on humans, retrospective studies, cohort studies, case reports and letters to the editor, in which patients who presented with renal or bladder cancer were treated preoperatively with immune checkpoint inhibitors such as atezolizumab, ipilimumab, pembrolizumab, nivolumab, avelumab or durvalumab. All the selected studies were in English.

We excluded from the review experimental studies with animals, articles presenting treatment with only chemotherapy or radiotherapy, studies in which the surgery subsequently performed was a transplant, or

manuscripts that did not meet the inclusion criteria. We also excluded all articles in which references to surgical complications were not available or mentioned. Gray literature also was excluded.

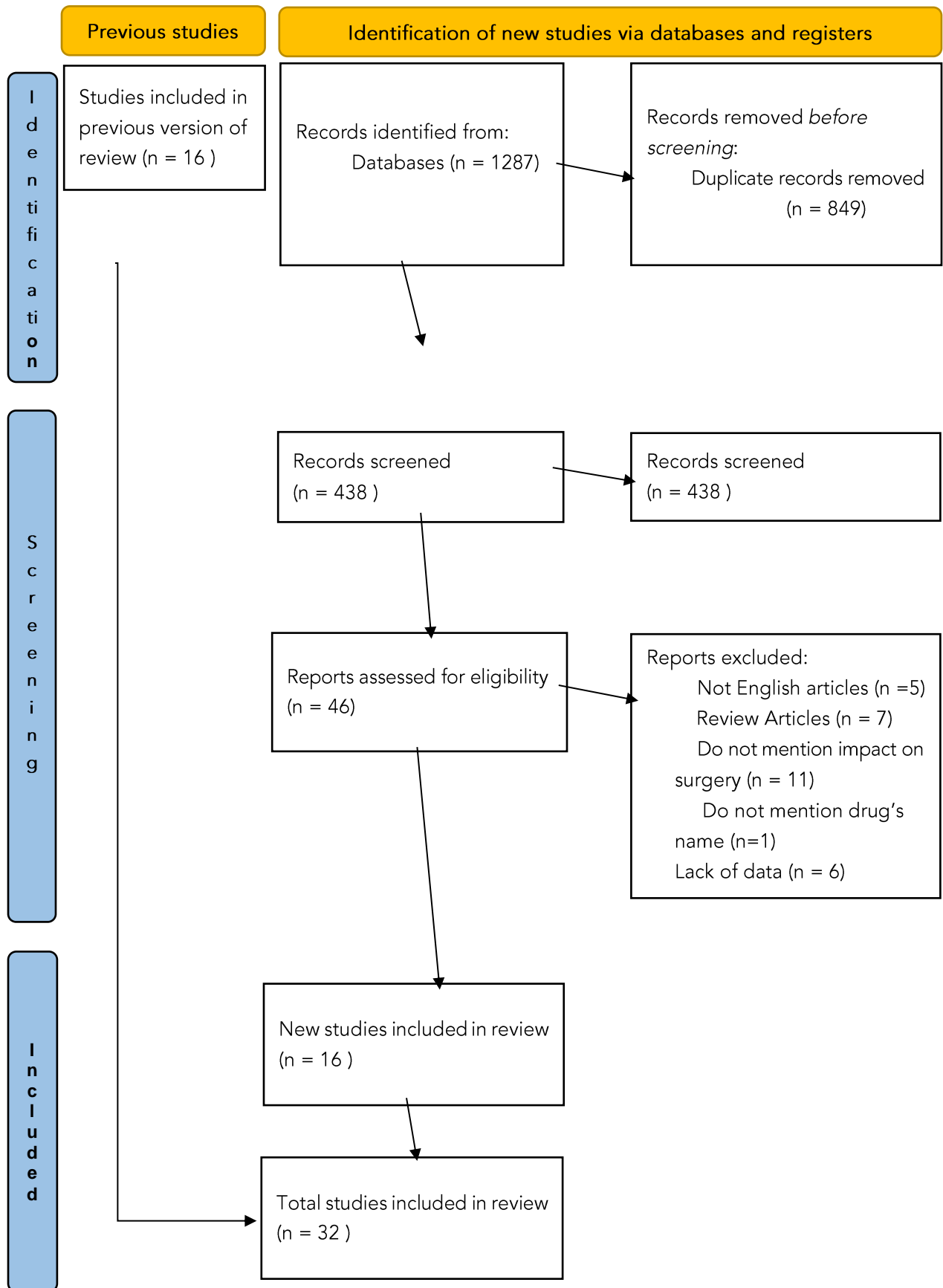
Literature Analysis

In phase three we thoroughly read the complete versions of the manuscripts and analyzed if they fitted into our inclusion criteria. Thus, we analyzed if they actually contained information about the effects of preoperative use of ICIs in patients with bladder or kidney cancer that were submitted to subsequent surgery. In this phase, we have included 16 articles, leaving us with a total of 32 publications.

Results

As illustrated in the flow diagram below (Fig. 1), according to PRISMA methodology, 1,287 publications were retrieved from the literature; of these, 849 duplicate records were removed. Forty-six reports were selected for eligibility by reading abstracts, and of these manuscripts, 30 were excluded for the following reasons: the articles were not in English, the design of the study was a review; the study was an experiment in animals; the patients did not make use of immunotherapy prior to surgery or the drugs used were not atezolizumab, nivolumab, ipilimumab, pembrolizumab, avelumab and durvalumab; the article did not mention the drug's name or its impact on surgery; or the surgery in question was a transplant. Finally, our review included 16 new studies, which were listed together with the 16 studies from our previous review, totalling 32 studies.

Figure 1. PRISMA flow diagram.



Kidney Cancer

Table 1 summarizes the findings of 25 manuscripts in which ICIs were used in the treatment of patients with renal cancers before radical nephrectomy. Of these, thirteen were case reports, six were retrospective studies, one was a letter to the editor, and two were cohort studies. In relation to the number of patients, a total of 828 patients were included for kidney cancer neoadjuvant therapy.

Among the studies, one did not mention the drug used, eight used nivolumab and ipilimumab, eight used just nivolumab, one used

durvalumab +/- tremelimumab or durvalumab and one used not only the combination of nivolumab and ipilimumab, but also nivolumab alone. Other therapies, such as the combination of ipilimumab and nivolumab, cabozantinib and nivolumab, bevacizumab and atezolizumab, pembrolizumab and axitinib, pembrolizumab and lenvatinib, were conducted in one trial with no surgical complications. One case report evinced the regression of a caval thrombus with pazopanib after the administration of nivolumab + ipilimumab, however the thrombus was firmly adherent to the vein.

Table 1. Nephrectomies after the use of ICIs.

Nephrectomies after the use of ICIs							
Publication year	Reference	Design	Journal	Number of patients	Type of surgery	Drugs used	Complications
2018	Woldu, SL et al ¹²	Case report	Urology case report	1	Cytoreductive nephrectomy	Nivolumab	Treatment did not seem to complicate surgery
2018	Ikarashi, D et al ¹³	Case report	International journal of urology	1	Radical nephrectomy	Nivolumab	Treatment did not seem to complicate surgery
2019	Fallah, j et al ¹⁴	Clinical trial	ASCO-GU	18	Not reported	Durvalumab, Tremelimumab	One patient had sudden death 9 days after receiving combination therapy prior to surgery.
2019	Labbate, C et al ¹⁵	Case report	Immunotherapy of cancer	1	Radical nephrectomy	Nivolumab, Ipilimumab	Dense adhesions near the hilum, bulky lymphadenopathy and thrombus adherent to the endothelium.

2019	Singla, N et al ⁷	Retrospective study	Urologic oncology	11	Nephrectomy	Nivolumab, Ipilimumab	Treatment didn't complicate surgery.
2019	Shepherd, ARH et al ¹⁶	Case report	ANZ journal of surgery	1	Radical nephrectomy	Nivolumab, Ipilimumab	The caval thrombus was densely adherent to the intima and could not be completely excised
2020	Pingnot, G et al ⁶	Retrospective study	European association of urology	11	Nephrectomy	Nivolumab, Ipilimumab, Tivozanib.	Inflammatory infiltration after long exposure to ICI results in challenging surgery.
2020	Okada, T et al ¹⁷	Case report	International cancer conference journal	1	Radical nephrectomy	Nivolumab, Ipilimumab	Intraoperative findings that the adhesions around the tumor were tight.
2020	Singla, T et al ¹⁸	Cohort	Urologic oncology	391	Cytoreductive nephrectomy	Not reported	Treatment did not seem to complicate surgery
2020	Shapiro, D et al ¹⁹	Cohort	AUA	53	Cytoreductive nephrectomy	anti-PD1, anti-CTLA4	Treatment did not seem to complicate surgery
2020	De Joode, K et al ²⁰	Letter to the editor	Urologic oncology	1	Radical nephrectomy	Nivolumab, Ipilimumab	ICIs facilitate nephrectomy by transforming unresectable to resectable primary RCC.
2021	Nishimura, K et al ²¹	Case report	BMC Urology	1	Cytoreductive nephrectomy	Nivolumab, Ipilimumab, Pazopanib	The caval thrombus was firmly adherent
2021	Sazuka, T et al ²²	Case Report	IJU Case Reports	2	Cytoreductive nephrectomy	Nivolumab, Ipilimumab	The tumor strongly adhered to its surroundings.

2022	Zhuang, TZ et al ²³	Case Report	Frontiers in Oncology	1	Cytoreductive nephrectomy	Nivolumab, Ipilimumab	The patient tolerated his procedure well
2022	Uematsu, T et al ²⁴	Case Report	Urology Case Reports	1	Robotic Cytoreductive Partial Nephrectomy	Avelumab, Axitinib	Treatment did not seem to complicate surgery
2022	Mebroukine, S et al ²⁵	Case Report	Journal of Surgical Case Reports	1	Robotic-assisted double partial nephrectomy	Nivolumab	Operating time was 5 h, estimated blood loss was 1000 ml.
2022	Yoshino, M et al ²⁶	Retrospective study	Japanese Journal of Clinical Oncology	41	Cytoreductive nephrectomy	Nivolumab, Ipilimumab	Treatment did not seem to complicate surgery
2022	Yoshida, K et al ²⁷	Retrospective Study	In vivo	3	Radical nephrectomy	Nivolumab, Ipilimumab, Pembrolizumab, Axitinib	Presurgical treatment may facilitate the control of bleeding during surgery
2022	Pignot, G et al ²⁸	Retrospective study	European Urology Oncology	30	Radical nephrectomy	Nivolumab, Ipilimumab	Surgeons described inflammatory changes. Difficulties in finding dissection planes.
2022	Otsuka, H et al ²⁹	Case Report	Urology Case Reports	1	Radical nephrectomy	Ipilimumab, Nivolumab	There were no complications during surgery
2022	Carlo, M et al ³⁰	Clinical Trial	European Urology	18	Radical nephrectomy	Nivolumab	In this pilot study, no related intraoperative complications or readmissions were observed.
2023	Karam, J et al ³¹	Clinical Trial	Nature communication	17	Radical nephrectomy	Sitravatinib, Nivolumab	There were no complications during surgery.
2023	Machida, A et al ³²	Case Report	Cancer Diagnosis & Prognosis	1	Radical nephrectomy	Nivolumab, Cabozantinib	There were no complications during surgery

2023	Reeses, W et al ³³	Retrospective study	Urologic oncology	220	Cytoreductive nephrectomy	Ipilimumab, Nivolumab, Cabozantini b, Bevacizumab, Atezolizumab, Pembrolizumab, Axitinib, Lenvatinib	Treatment did not seem to complicate surgery
2023	Bhanjy, Y et al ³⁴	Case Report	Kidney Cancer Journal	1	Cytoreductive nephrectomy	Nivolumab, Ipilimumab	Treatment did not seem to complicate surgery

Moreover, in one study the monotherapy of anti-CTLA4 and anti-PD 1 drugs and their combination was used, whereas another study used the combination of nivolumab and ipilimumab, nivolumab and tivozanib and nivolumab alone. In the majority of articles, the number of cycles of immunotherapy ranged from one to four; however, one study reported sixteen cycles and other four studies didn't describe the number of cycles. In most of the studies a radical nephrectomy or a cytoreductive nephrectomy was performed after the treatment with ICIs, except for two studies which performed a robotic-assisted cytoreductive partial nephrectomy and a double partial nephrectomy; in these case reports, the nephron sparing surgery was possible due to the downsizing of the tumor, and in both reports the pathological findings were compatible with R0 resections.

Regarding complications, nine studies denied the relation between the previous use of ICIs and increased complication rates during or after surgery, one stated that there was a certain facilitation in the execution of the surgical procedure and five suggested an increased difficulty in performing the nephrectomy. Most of the studies that mentioned complications

associated them with increased adherences in the tumoral zone or the adherence of a thrombus to the intimal layer of the inferior vena cava. Regarding pathological findings, only three studies didn't include data, and in the remaining articles necrosis and infiltration with inflammatory cells were uniformly reported.

Bladder Cancer

Table 2 indicates the findings of seven manuscripts in which patients were treated with ICIs before radical cystectomy. Of these manuscripts, six were clinical trials and one was a letter to the editor. In this section, 401 patients were included among the reports. The drug that most often appeared in the studies was pembrolizumab, which was present in three of them; atezolizumab was reported in two studies, durvalumab and tremelimumab in one trial and durvalumab + olaparib in one manuscript. The cycles of preoperative immunotherapy varied from one to five, but most studies made use of three.

In all articles, the surgery performed was a radical cystectomy. As for the possible relationship between unexpected surgical outcomes and prior use of ICIs, in only one of

the trials, which used the combination of durvalumab + olaparib, one patient developed a wound dehiscence and one patient had a

fatal outcome. None of the analyzed studies presented any relevant pathological findings.

Table 2. Cystectomies after the use of ICIs.

Cystectomies after the use of ICIs							
Publication year	Reference	Design	Journal	Number of patients	Type of surgery	Drugs used	Complications
2019	Scuderi, S et al ³⁵	Clinical Trial	AUA	51	Cystectomy	Pembrolizumab	Treatment did not seem to complicate surgery
2019	Gao, J et al ³⁶	Clinical Trial	2019 ASCO Annual Meeting	28	Cystectomy	Durvalumab and Tremelimumab	Treatment did not seem to complicate surgery
2019	Powles, T et al ³⁷	Letter	Nature	95	Cystectomy	Atezolizumab	Treatment did not seem to complicate surgery
2020	Briganti, A et al ³⁸	Clinical Trial	European Association of Urology	109	Cystectomy	Pembrolizumab	Treatment did not seem to complicate surgery
2020	Truong, H et al ³⁹	Clinical Trial	Official Journal of the American Urological Association	11	Cystectomy	Pembrolizumab	Treatment did not seem to complicate surgery
2020	Moreno, J et al ⁴⁰	Clinical Trial	Journal of Clinical Oncology	12	Cystectomy	Durvalumab, Olaparib	Wound dehiscence and one death
2020	Szabados, B et al ⁴¹	Clinical Trial	European Urology oncology	95	Cystectomy	Atezolizumab	Treatment did not seem to complicate surgery

Discussion

Immune checkpoint inhibitors (ICIs) have revolutionized the management of patients with kidney and bladder cancers, and the indications for the use of these drugs have been expanding. In 2015, nivolumab and ipilimumab were approved for clinical use in patients with metastatic kidney cancer, and in 2016 the use of ICIs was approved for metastatic bladder cancer as well⁴².

Immunotherapy is currently first line therapy for patients with metastatic kidney cancers⁴³ and recently an important randomized trial suggested a significant role for pembrolizumab and axitinib as adjuvant therapies for high risk renal cell carcinomas, showing for the first time a survival benefit for an adjuvant therapy in patients with this disease⁴⁴. In patients with bladder cancers, another randomized trial has shown survival benefit in metastatic urothelial cancers treated with pembrolizumab plus

enfortumab vedotin versus the standard chemotherapy regimen of gemcitabine plus cisplatin/carboplatin⁴⁵. There is still controversy about preoperative (neoadjuvant) use of these drugs in patients with renal and bladder cancers, however. There is concern that the inflammatory effects caused by ICIs in the primary tumors may render resections more difficult, and increase the rates of perioperative complications in surgeries performed after immunotherapy.

In our previous systematic review on the subject, most series/studies did not report additional difficulties during nephrectomies after the use of ICIs. However, it was reported in a few reports. The most compelling was the manuscript by Pignot et al, in which in most cases (81.8%) surgeons reported difficulties in finding dissection planes due to fibrosis of the tissues surrounding the kidney, suggesting that nephrectomies in these settings should be performed by more experienced surgeons¹⁶. In our current update of the literature, we reviewed additional 14 publications in excess of the 11 previously reported on the subject for kidney cancer surgeries after the use of ICIs. Of these, in 3/14 reports nephrectomies were considered to be more difficult than usual due to inflammatory reactions in the surgical field.^{21,22,28} In a few case reports with preoperative ICIs in situation of vena caval thrombus, in two reports the surgery was considered easier due to the reduction of the thrombus^{27,32}, but in one report the thrombus seemed to be more adherent to the caval wall, making the surgery more challenging²¹. Overall, in 6/25 (24.4%) reports (one is from the same group), it was stated that neoadjuvant ICIs posed additional difficulties to renal surgeries. Although the results concerning the use of preoperative ICIs in kidney cancers are

controversial, it seems clear to us that this phenomenon may occur. It is not clear, however, if there may be an association of this finding to a specific drug.

Published literature is more limited concerning the neoadjuvant use of ICSs in radical cystectomies. We have found two additional articles regarding our previous systematic review, and none reported additional difficulties during surgery^{40,41}. It seems that for radical cystectomies neoadjuvant immunotherapy does not pose any additional problem for the surgeon. This finding is important, since in view of the recent publication on the superiority of pembrolizumab associated with enfortumab vedotin in comparison to gemcitabine and cisplatin for metastatic urothelial carcinoma we expect an increasing number of trials with these drugs in the neoadjuvant setting. It is an auspicious finding that apparently neoadjuvant pembrolizumab does not impact the quality of radical cystectomies.

Our systematic review has some relevant limitations - we have only accessed the Pubmed database, and included only English literature, which may have left out of our review important publications. Additionally, although we have used a number of pertinent keywords, some useful studies on neoadjuvant ICIs may not have been included due to selection biases.

Immune checkpoint inhibitors are new drugs in the urologic oncology armamentarium, and apparently the neoadjuvant use of these medications may pose additional surgical difficulties in some nephrectomies, but not in radical cystectomies. The novelty of the current immunotherapy regimens does not allow for definitive conclusions about its use in the neoadjuvant setting, but the surgeon must be

aware of possible surgical difficulties, especially in kidney cancer. Our conclusions have many caveats, however. Most series are quite small, and from different centers around the world, which could make surgical expertise and case volumes different across studies. There was not a standardization in the amount of immunotherapy cycles before surgery. It was also not possible to ascertain if surgical difficulties were present more frequently with a specific ICI or not. Nevertheless, we believe that this comprehensive review may add to the scant literature published so far on the subject, and hope that future studies may allow for the prediction of a more challenging surgery or not with preoperative use of ICIs.

Conclusion

Apparently, in a minority of cases of nephrectomies, there may be inflammatory changes to the surrounding tissues which may render surgeries more challenging, requiring more experienced surgeons, in the setting of neoadjuvant ICIs. Neoadjuvant ICIs do not seem to pose additional surgical difficulties in cystectomies for the treatment of bladder cancer.

Conflict of Interest Statement:

The authors have no conflict of interest to declare.

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