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Current Problems in Cancer

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The impact of preoperative immune checkpoint inhibitors on kidney and bladder cancer surgeries: a systematic review[☆]

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A B S T R A C T

Therapies based on the use of immune checkpoint inhibitors (ICIs), such as nivolumab, pembrolizumab, ipilimumab, atezolizumab, avelumab, and durvalumab, have proven effective in the treatment of metastatic urological neoplasms. Recently, it has been hypothesized that the use of this type of treatment prior to surgery could lead to an increased difficulty in renal and bladder surgeries. The literature concerning this topic, however, is still scarce and non-consensual. In our systematic review, we used the PRISMA guidelines methodology to search the pertinent literature available up to June 18, 2020 in PubMed. Additionally, we searched the related grey literature in the abstracts of the meetings of the American Society of Clinical Oncology (ASCO), American Society of Clinical Oncology Genitourinary (ASCO-GU), European Society of Medical Oncology (ESMO), and American Urological Association (AUA) from 2015 to 2020. We were able to find only 16 publications that addressed the use of ICIs prior to surgery in kidney and bladder neoplasms. The results were conflicting, and usually the issue of surgical difficulties after the use of ICIs was not di-

[☆] Impact of preoperative ICIs on kidney and bladder surgeries.

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rectly approached. We hope that our publication may raise the awareness towards the need to further investigate the effects of neoadjuvant ICIs on surgical outcomes in urologic cancers.

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ARTICLE INFO

Kidney cancer, Bladder cancer, Immune checkpoint inhibitors, Surgery, Complications.

Introduction

Excluding prostate cancers, of the urological neoplasms, kidney and bladder cancers are the most prevalent. Usually cured by surgery when diagnosed and treated in early stages, these tumours until recently responded poorly to systemic therapies. Immune checkpoint inhibitors (ICIs) are biologic drugs that block the T-cell inhibitory proteins, such as CTLA-4 (cytotoxic T-lymphocyte associated antigen 4) and PD-1 (programmed death-1)¹. These drugs allow the recognition of the tumour cells by the immune system, leading to the phagocytosis and lysis of the cancerous cell². Therefore, immune checkpoint blockade can unleash the power of naturally occurring T cells by eliminating the negative signals that block T-cell function. In the last few years, since the approval of nivolumab and ipilimumab for the treatment of metastatic kidney cancer in 2015, various ICIs have assumed a prominent role as second line and, more recently, as first line therapies for advanced and metastatic kidney and 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 treatment⁴. Although chemotherapy has been the standard treatment for metastatic urological cancers for many years, metastases of kidney cancers do not respond well to this type of treatment, and many patients with metastatic bladder cancers are not eligible for chemotherapy^{5,6}. In addition, ICIs tend to present a significantly lower incidence of clinically relevant toxicities compared to chemotherapy^{5,7,8}. Thus, the role of ICIs in the treatment of kidney and bladder cancers is increasingly prominent, and they will probably be considered the standards of care in the metastatic setting. 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 tumours⁹.

In this recent scenario, some have hypothesized that neoadjuvant ICIs could complicate renal and bladder surgical procedures due to the increase of adhesions and fibrosis in the surroundings of the affected organs. Pignot et al¹⁰ 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 difficulties¹⁰. On the other hand, there are studies that do not indicate an increased difficulty during the procedures, such as the report by Singla et al¹¹. These authors described a series of 11 patients who underwent CNs after nivolumab treatment in which there was no increased difficulty during the nephrectomies¹¹. Due to the scarce and controversial literature in this regard, we performed a systematic review to analyse the possible relation between unexpected surgical outcomes and the previous use of ICIs, and, therefore, to produce a more solid foundation for future studies.

Materials and methods

The development of this study was based on the review writing methods of the PRISMA statement¹².

Eligibility criteria

We included 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 with preoperative use of immune checkpoint inhibitors such as atezolizumab, ipilimumab, pembrolizumab, nivolumab, avelumab or durvalumab, and subjected to subsequent surgery. There was no time or language restriction for the studies selection. 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 were excluded. We also excluded all articles in which references to surgical complications were not available or mentioned. In the case of serial publications from the same institution, we only included the most recent. Additionally, we excluded articles characterized as double publishing.

Information sources

The electronic database chosen to carry out the research was the Medline/PubMed, with the last survey on June 18, 2020. No filter was used in this search in order to expand it to its maximum. The references of the included articles were also checked. We also searched the grey literature in abstracts presented at urological and oncological congresses, such as ASCO, ASCO-GU, ESMO e AUA, from 2015 to 2020, with the last search on July 9, 2020.

Information searching process

All research was conducted individually. The articles and abstracts obtained from the searches were analysed by six researchers and, in case of doubt or disagreement amongst them, a senior researcher would evaluate the study and decide whether it would be included in the review or not. No contact has been made with the authors of the articles and abstracts selected once the information needed for the study was obtained by reading the texts.

Search items

Data referring to the post-operative state of patients who had previously undergone treatment for bladder and kidney cancer with immunotherapy through the use of ICIs.

Search strategy

On PubMed, the search included the following descriptors: "Pembrolizumab AND bladder cancer AND surgery complications"; "Pembrolizumab AND kidney cancer AND surgery complications"; "Atezolizumab AND bladder cancer AND surgery complications"; "Atezolizumab AND kidney cancer AND surgery complications"; "Ipilimumab AND bladder cancer AND surgery complications"; "Ipilimumab AND kidney cancer AND surgery complications"; "Nivolumab AND bladder cancer AND surgery complications"; "Nivolumab AND kidney cancer AND surgery complications"; "Avelumab AND bladder cancer AND surgery complications"; "Avelumab AND kidney cancer AND surgery complications"; "Durvalumab AND bladder cancer AND surgery complications"; "Durvalumab AND kidney cancer AND surgery complications"; "ICIs AND bladder cancer AND surgery complications"; "ICIs AND kidney cancer AND surgery complications"; "Immune

checkpoint inhibitors AND bladder cancer AND surgery complications"; "Immune checkpoint inhibitors AND kidney cancer AND surgery complications"; "Nephrectomy AND immune checkpoint inhibitors"; "Pembrolizumab AND bladder cancer AND surgical complications"; "Pembrolizumab AND kidney cancer AND surgical complications"; "Atezolizumab AND bladder cancer AND surgical complications"; "Atezolizumab AND kidney cancer AND surgical complications"; "Ipilimumab AND bladder cancer AND surgical complications"; "Ipilimumab AND kidney cancer AND surgical complications"; "Nivolumab AND bladder cancer AND surgical complications"; "Nivolumab AND kidney cancer AND surgical complications"; "Avelumab AND bladder cancer AND surgical complications"; "Avelumab AND kidney cancer AND surgical complications"; "Durvalumab AND bladder cancer AND surgical complications"; "Durvalumab AND kidney cancer AND surgical complications"; "ICIs AND bladder cancer AND surgical complications"; "ICIs AND kidney cancer AND surgical complications"; "Immune checkpoint inhibitors AND bladder cancer AND surgical complications"; "Immune checkpoint inhibitors AND kidney cancer AND surgical complications"; "Nephrectomy AND immune checkpoint inhibitors";

On the ASCO website, the search was carried out by using the following filters: for the "track" category it was selected "genitourinary cancer - kidney and bladder" and for "type" it was selected "poster session". On the ASCO-GU website, we selected "renal cell cancer" and "urothelial carcinoma" for "track", "poster session" for "type" and "oncology" and "treatment" for "topic", within which we selected "immunotherapy". On the AUA website, "immunotherapy" was searched in "advanced research" filtered by "abstract" and the years of "2015 to 2020". At last, on the ESMO website, articles published in the 2015-2019 ESMO congresses and in the 2017-2019 ESMO immuno-oncology congresses were reviewed. In order to carry out the research, we selected "immunotherapy" and "genitourinary" for "topic" and "abstracts" for "format".

In phase one of selecting the studies – the identification phase – we found 272 manuscripts on PubMed, of which we excluded only the ones that were duplicates (144), leaving us with 128 articles. Additionally, we found five studies through references of other articles, and five studies from the grey literature searched. Thus, we ended up with 138 studies to analyse.

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, included the ones that fit into the inclusion criteria and excluded those that fit into the exclusion criteria. Therefore, of the 138 manuscripts we excluded 106, leaving us with 32 articles.

In phase three of selecting the studies – the eligibility phase –, we thoroughly read the complete versions of the manuscripts and analysed if they framed into our inclusion criteria. Thus, we analysed 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 excluded 16 articles, leaving us with the 16 articles that were included in the review and analysed in detail.

Results

As illustrated in the flow diagram below (Fig. 1), according to PRISMA methodology, 138 publications were retrieved from the literature. Of these manuscripts, 122 were excluded for the following reasons: 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; or the surgery in question was a transplant. In the end, our review included 16 studies.

Kidney cancer

Table 1 summarizes the findings of 11 manuscripts in which ICIs were used in the treatment of patients with renal cancers before radical nephrectomy. Of these, six were case reports,

Table 1
Nephrectomies after the use of ICIs.

Nephrectomies after the use of ICIs							
Publication Year	Reference	Design	Journal/ Congress	Number of patients	Type of surgery	Drug used	Complications
2018	Woldu, S L <i>et al.</i> ¹³	Case Report	Urology Case Report	1	Cytoreductive nephrectomy	Nivolumab	Treatment did not seem to complicate surgery.
2018	Ikarashi, D <i>et al.</i> ¹⁴	Case Report	International Journal of Urology	1	Radical nephrectomy	Nivolumab	Treatment did not seem to complicate surgery.
2019	Fallah, J <i>et al.</i> ¹⁵	Clinical trial	ASCO-GU	18	Not reported	Durvalumab +/- tremelimumab or durvalumab	One patient had sudden death 9 days after receiving combination therapy prior to surgery.
2019	Labbate, C <i>et al.</i> ¹⁶	Case Report	Immunotherapy of Cancer	1	Left radical nephrectomy	Nivolumab and ipilimumab	There were dense adhesions near the renal hilum and bulky lymphadenopathy and a thrombus adherent to the endothelium.
2019	Singla, N <i>et al.</i> ¹¹	Retrospective Study	Urologic Oncology	11	Nephrectomy	Nivolumab or nivolumab and ipilimumab	Treatment did not seem to complicate surgery.
2019	Shepherd, A R H <i>et al.</i> ¹⁷	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	Pignot, G <i>et al.</i> ¹⁰	Retrospective Study	European Association of Urology	11	Nephrectomy	Nivolumab+ ipilimumab, nivolumab+ tivozanib, or nivolumab alone	Inflammatory infiltration after long exposure to ICI results in challenging surgery.
2020	Okada, T <i>et al.</i> ¹⁸	Case Report	International Cancer Conference Journal	1	Radical nephrectomy	Nivolumab + ipilimumab	Intraoperative findings indicated that the adhesions around the tumour were tight.
2020	Singla, N <i>et al.</i> ¹⁹	Cohort	Urologic Oncology	391	Cytoreductive nephrectomy	Not reported	Treatment did not seem to complicate surgery.
2020	Shapiro, D <i>et al.</i> ²⁰	Cohort	AUA	53	Cytoreductive nephrectomy	anti-PD1, anti-CTLA4, and anti-PD1+ anti-CTLA4	Treatment did not seem to complicate surgery.
2020	de Joode, K <i>et al.</i> ²¹	Letter to the Editor	Urologic Oncology	1	Open radical nephrectomy	Nivolumab and ipilimumab	ICIs facilitate nephrectomy by transforming unresectable to resectable primary RCC.

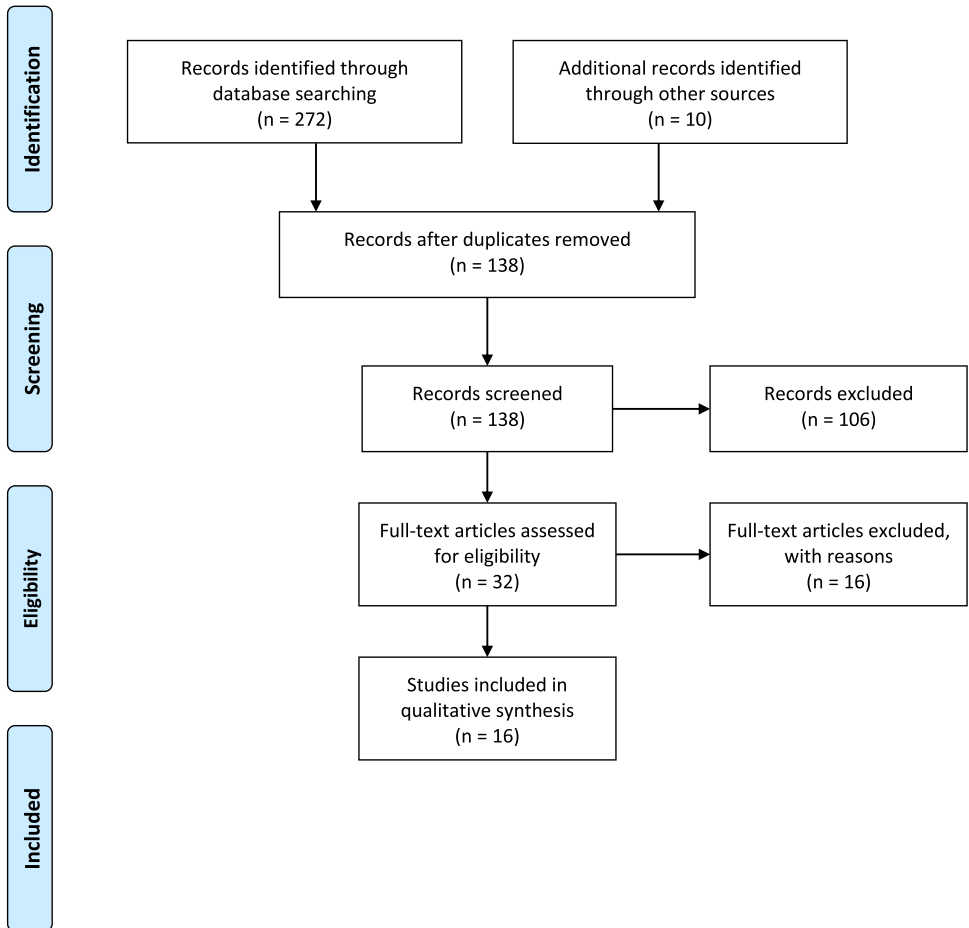


Fig. 1. PRISMA flow diagram. (Color version of figure is available online.)

two were retrospective studies, one was a letter to the editor, and two were cohort studies. In relation to the number of patients, six studies included one patient, two eleven patients, one eighteen patients, one 53 patients, and then, one study included 391 patients. Among the studies, one did not mention the drug used, four used nivolumab and ipilimumab, two used just nivolumab, one used durvalumab +/- tremelimumab or durvalumab and one used not only the combination of nivolumab and ipilimumab, but also nivolumab alone. Moreover, in one study the monotherapy of anti-CTLA4 and anti-PD1 drugs and their combination were used, whereas one study used the combination of nivolumab and ipilimumab, nivolumab and tivozanib and nivolumab alone. In the majority of articles, the number of cycles 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 was performed after the treatment with ICIs, except for three studies in which was executed a cytoreductive nephrectomy and for one that didn't specify the type of surgery. Regarding complications, five studies denied the relation between the previous use of ICIs and increased complications during surgery, one stated that there was a certain facilitation in the execution of the surgical procedure and five suggested an increased difficulty. Most of the studies that mentioned complications associated them with increased adherences in the tumoral zone. Regarding pathological findings, only three studies

didn't include data, and in the other eight articles, necrosis and infiltration with inflammatory cells were reported.

Bladder cancer

Table 2 indicates the findings of five manuscripts in which patients were treated with ICIs before radical cystectomy. Of these manuscripts, four were clinical trials and one was a letter to the editor. Most of them had a significant number of patients; the least number of patients observed were 11, in one study, and 28 in another one, and all the other manuscripts included more than 50 patients - the largest one 95 patients. The drug that most often appeared in the studies was pembrolizumab, which was present in three of them; atezolizumab was reported in one study, and durvalumab and tremelimumab in another one. The cycles 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 relation between unexpected surgical outcomes and prior use of ICIs, all studies found that treatment did not seem to complicate surgery. None of the analysed studies presented any relevant pathological findings.

Discussion

Summary of evidence

Not much is reported in the searched literature concerning the possible relation between unexpected surgical outcomes and the previous use of ICIs in patients with kidney or bladder cancer, even though a lot has been published about immunotherapy, which shows that this topic is underrated. The reason for the scarceness in literature could be the fact that the approval of these drugs for the treatment of kidney and bladder cancers is very recent. Among the few existing studies, the findings are still controversial. Considering that most of the publications on this matter were case reports, the strength of evidence is still low and, therefore, studies with higher impact are needed.

As of the studies that discussed the use of ICIs previously to surgery in kidney cancer patients, 54.5% did not show any surgical complications related to the treatment. The largest study was the cohort by, Singla et al¹⁹ with 391 patients, which stated that performing CNs after prior ICIs appears to be safe, with pathologically favourable tumour characteristics. However, Pignot et al¹⁰ responded to Singla's study¹¹ reuniting a series of 11 cases which showed that in 81.8% of the patients, surgeons experienced difficulties in finding dissection planes because of adhesions and inflammatory reactions at the kidney and the surrounding tissue, which resulted in a challenging surgery. Another cohort study conducted by Shapiro et al²⁰ with 53 patients asserted that preoperative therapy with ICIs was not associated with high grade surgical complications. Sharing the same outcome, a retrospective study¹¹ affirms that there were no untoward intraoperative challenges encountered that could definitely be attributed to ICI exposure. Exceptionally, de Joode et al²¹, in a letter to the editor, mention that ICIs could even facilitate nephrectomy by transforming unresectable into operable RCCs. Additionally, two^{13,14} out of the five case reports selected in our systematic review claim that there was no relation between prior ICIs' therapy and unexpected surgical outcomes. Nevertheless, the other three^{16,17,18} cases reported complications. Labbate et al¹⁶ stated that there were dense adhesions near the renal hilum and bulky lymphadenopathy and a thrombus adherent to the endothelium. Shepherd et al¹⁷ reported that, in the radical nephrectomy associated with the cavotomy, after nivolumab and ipilimumab treatment, the caval thrombus was densely adherent to the intima and could not be completely excised. Okada et al¹⁸ also mentioned that intraoperative findings indicated that the adhesions around the tumour were tight. Therefore, due to the increased adhesion and fibrosis verified, these three cases required more complex surgical techniques, which may demand an experienced surgeon in order to perform the procedure.

Table 2
Cystectomies after the use of ICIs.

Cystectomies after the use of ICIs							
Publication Year	Reference	Design	Journal/ Congress	Number of patients	Type of surgery	Drug Used	Complications
2019	Scuderi, S <i>et al.</i> ²²	Clinical Trial	AUA	51	Cystectomy	Pembrolizumab	Treatment did not seem to complicate surgery.
2019	Gao, J <i>et al.</i> ²³	Clinical Trial	2019 ASCO Annual Meeting	28	Cystectomy	Durvalumab and Tremelimumab	Treatment did not seem to complicate surgery.
2019	Powles, T <i>et al.</i> ²⁴	Letter	Nature	95	Cystectomy	Atezolizumab	Treatment did not seem to complicate surgery.
2020	Briganti, A <i>et al.</i> ²⁵	Clinical Trial	European Association of Urology	109	Cystectomy	Pembrolizumab	Treatment did not seem to complicate surgery.
2020	Truong, H <i>et al.</i> ²⁶	Clinical Trial	Official Journal of the American Urological Association	11	Cystectomy	Pembrolizumab	Treatment did not seem to complicate surgery.

Since the first approval of an ICI for the treatment of patients with bladder cancer occurred in 2016²⁷, one year later than its approval for kidney cancer, there are fewer studies published on this topic. Therefore, the majority (80%) of the manuscripts about this matter selected in our systematic review are abstracts of congress presentations. Of the five selected studies, not one reported significant complication in surgery due to the previous use of ICIs. Briganti et al²⁵, in a clinical trial with 109 patients, supports the surgical safety of radical cystectomy after neoadjuvant immunotherapy, as the complications appeared to be in line with what was previously seen with chemotherapy. Powles et al²⁴, in a letter published in Nature, mentioned a pathological complete response rate of 31% in a cohort of 95 patients, reporting no new safety issues associated with immunotherapy. Scuderi et al²², in a clinical trial performed in 51 patients, affirmed that neoadjuvant immunotherapy did not impact blood loss, surgical time, the number of nodes removed, in-hospital length of stay and readmission rates. Another clinical trial with 28 patients conducted by Gao et al²³ indicated that Durvalumab plus Tremelimumab is an effective and safe therapy for patients with muscle invasive bladder carcinoma. Furthermore, Troung et al²⁶, in a clinical trial with 11 patients, did not associate preoperative pembrolizumab treatment with increased length of stay, estimated blood loss, transfusions or readmissions rate. Thus, these five articles suggest that prior treatment with ICIs doesn't seem to complicate surgery in cases of bladder cancer, but it is worthy to note that this conclusion may be premature and not represent reality since the literature addressing this subject is still very scarce.

Limitations

We must highlight the possibilities of publication and selection bias in our systematic review. Since ICIs are very new drugs, several studies regarding this topic are still in progress, with a scarce literature on the connection between ICIs and surgical complications; this increases the risk of publication bias. Considering the fact that we used only one database, we may not have had access to articles on the subject published in other platforms, which leads to a selection bias. In addition, there is a risk that we have not used all the necessary keywords or that we have failed to include in the study a useful article for our project, increasing the risks of bias.

Conclusions

Our systematic review allowed us to conclude that the possible relation between use of ICIs before surgical procedures in kidney or bladder cancer patients and their outcomes is still a rare and very controversial topic. Evidence shows many cases in which surgeries were more challenging due to the previous use of ICIs, but also reports various cases in which these unexpected outcomes did not occur or were not considered significant.

Further studies analysing a larger number of patients, prospectively assessing the variable of surgical difficulty are needed. With the increasing use of ICIs as both first-and second-line therapies in kidney and bladder cancers, it is likely that more clinical trials will be developed addressing this new and controversial topic.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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