Review
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Contemporary Trends in Adjuvant and Neoadjuvant Treatment for Renal Cell Carcinoma

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Abstract

Renal cell carcinoma is an increasingly significant cancer in which surgical resection is still the sole curative approach. There is a risk of recurrence in one-third of patients after surgery. Successful experiences with some solid organ cancers and effective treatment response to targeted agents in metastatic cases have suggested a similar adjuvant approach for renal cell carcinoma. Consequently, placebo-controlled adjuvant trials have been reported and the Food and Drug Administration approved sunutinib as an adjuvant treatment after nephrectomy in high-risk patients, with the risk of treatment-related side effects. Several clinical series have indicated that neoadjuvant application can provide significant downsizing of the cancer mass in complex cases and enable radical surgery. Similarly, neoadjuvant therapy could enable nephron-sparing surgery for certain patients. Both adjuvant and neoadjuvant approaches for renal cell carcinoma require further trials with larger patient numbers. This review presents contemporary experience on adjuvant and neoadjuvant treatment for renal cell carcinoma.
Keywords: Renal cell carcinoma, adjuvant, neoadjuvant, targeted therapy

Adjuvant Therapy

Renal cell carcinoma has an important place among adult cancers. Although its overall incidence is reported as 2-3%, significant differences have been observed between countries (1). It is also important to note that its incidence is showing an upward trend. Its incidence has risen by more than 30% over the past 15 years (2). This clearly indicates that the significance of renal cell carcinoma will continue to grow. Early incidental diagnosis increases the rate of local disease and enables curative surgical treatment. However, a substantial proportion of patients, about 1 in 3, may develop metastatic disease within 5 years of curative surgery (3,4). Recurrence after curative surgery can involve metastatic disease, and mortality may be unavoidable (5). This shows that a significant proportion of patients who receive curative treatment will experience recurrence during follow-up, and raises the need to prevent recurrence by detecting patients at risk and providing adjuvant therapy in advance. Indeed, favorable results of adjuvant systemic therapies in breast and gastrointestinal tract cancers suggest a similar approach may be applicable in renal cell carcinoma (6). This gives rise to the need to at least identify and provide adjuvant systemic therapy to high-risk patients, and there is a growing body of research in pursuit of these ends.

For many years, it was accepted as a general rule that adjuvant therapy had no place in the treatment of renal cell carcinomas (7). However, this appears to be changing due to recent developments. This section discusses the current state of postoperative adjuvant systemic therapies in renal cell carcinomas.

Early Adjuvant Therapy Studies

Renal cell carcinoma is generally a chemoresistant cancer. Therefore, before the availability of agents targeting the vascular endothelial growth factor receptor (VEGF-R) system, two classic immunotherapy molecules widely used in metastatic disease,

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interferon (IFN-α) and interleukin (IL)-2, were tried as adjuvant therapy. In particular, IFN-α and IL-2 alone, in combination, and even combined with various chemotherapeutics were tried as adjuvant therapy, but none provided a significant advantage in terms of disease-free or overall survival (8,9,10,11). Despite being an old and costly study, the data demonstrating a significant extension of disease-free survival in renal cell carcinoma were reported in a trial of a vaccine obtained from autologous tumor cells in a series of 558 patients (12). However, the study faced serious criticism due to the high risk of bias, poor explanation of the criteria used in patient selection, the significant number of non-clear cell cancer cases included, the nonhomogeneity of the groups (even in numbers), and the drop-out rate. Besides these concerns, commercial production of the vaccine also proved impossible.

In a meta-analysis done in 2013, data from 14 clinical trials were examined and a detailed evaluation of 3380 patients treated with various agents (mostly IFN and IL, but 1 trial included adjuvant radiotherapy) revealed no survival advantage (13). Conversely, an unfavorable effect on 5-year disease-free survival was observed in patients who received adjuvant cytokines. It light of these data, it can be concluded that there is no evidence supporting the adjuvant use of non-targeted therapeutic agents and that clinical trials evaluating them ended at this stage.

Recent Adjuvant Therapy Studies

Identifying the von Hippel-Lindau gene mutation in the molecular pathogenesis of renal cell carcinoma and understanding its role in angiogenesis gave rise to the concept of "targeted" therapy. Similarly, the role of the phosphatidylinositol-3-kinase-Akt-mammalian target of rapamycin (mTOR) system in renal cell carcinoma was determined. Thus, angiogenesis (VEGF-R system) and mTOR inhibitors soon began to be used effectively for metastatic renal cell carcinoma and were clearly shown to confer advantages in both disease-free and overall survival. They are currently in standard use as first-line and even second-line therapies for systemic disease. Therefore, it is imperative to evaluate the use of these agents in the adjuvant setting.

This section focuses on targeted agents that are used in metastatic disease and shown to induce an objective clinical response in recent adjuvant therapy trials (i.e. agents with proven efficacy). Accordingly, sorafenib and sunitinib, which target the VEGF-R system, were the first targeted molecules to be investigated for adjuvant use. The studies for which results have been published to date and their findings can be summarized as follows.

ASSURE: A randomized prospective trial including a large number of patients (14). The study initially included 1943 nephrectomy cases and pathological stages ranging from T1b (high grade) to T4 (all grades). Both lymph node positive and negative patients were included. Patients were stratified based on parameters such as intermediate/high or very high risk, clear or non-clear cell type, performance status, and type of resection. They were then randomly assigned to receive sunitinib daily for 4 weeks/no treatment for 2 weeks (n=647), sorafenib daily (n=649), or placebo (n=647). One year of treatment was planned. An increase in disease-free survival from 5.8 years to 7.7 years was initially anticipated. However, dose adjustments were necessary due to adverse events. The report of an initial interim analysis stated that neither arm of the study yielded significant differences in disease-free survival or overall survival compared to the placebo group (14). It was noted that dose adjustments increased treatment adherence. Nevertheless, severe adverse effects were reported in the treatment arms. These preliminary results laid the foundation for a strong opinion against adjuvant therapy.

STRAC: The second prospective, randomized, placebo-controlled trial investigating adjuvant therapy (15). This study included 615 high-risk patients with clear-cell renal carcinoma who underwent nephrectomy. Treatment with sunitinib 50 mg daily (4 weeks treatment/2 weeks off) versus placebo for 1 year was planned. According to the results of an initial evaluation, median disease-free survival was 6.8 years in the treatment group and 5.6 years in the placebo group. Disease-free survival rates were also significantly higher in the treatment arm based on 3- and 5-year data (59.5% for placebo versus 64.9% for sunitinib at 3 years, 51.3% for placebo versus 59.3% for sunitinib at 5 years). Dosage titration was required in approximately one-third of patients in the treatment arm due to adverse events. Treatment discontinuation was reported at a rate of 28% in the treatment arm versus 5.6% in the placebo arm. Preliminary data indicated a disease-free survival advantage despite the high incidence of adverse events. According to these data, adjuvant sunitinib provided a 14-month disease-free survival advantage and a 24% risk reduction. Thus, contrary to the first study, a significant disease-free survival advantage was reported. It is noteworthy that despite the potential patient overlap with ASSURE, STRAC included relatively higher risk patients and involved a central radiological evaluation. However, STRAC had a shorter follow-up period and included fewer patients. Considering these possible limitations, a "small" meta-analysis including the STRAC data challenged the statistical significance of the increase in disease-free survival (7). Although patients treated with sunitinib were evaluated as a meta-analysis, it deserves mention that the patients were heterogeneous and the majority comprised ASSURE patients. Essentially, the results of the STRAC trial are striking and support the view that adjuvant therapy is necessary at least for high-risk patients, but it is clear that there is a significant adverse event profile. It was recently published that adjuvant sunitinib therapy also showed a disease-free survival advantage in subgroup analyses of the STRAC trial (16). Based on STRAC data demonstrating this survival advantage, sunitinib was recently approved by the Food and Drug Administration (FDA) for adjuvant use in high-risk patients (17).

Comparison of ASSURE and STRAC: The discrepancy in disease-free survival reported in these two studies may be attributed to various factors. We believe the most important of these, which was mentioned briefly above, was that STRAC included more homogenous and, more importantly, relatively higher risk patients; in other words, patients with the greatest need for adjuvant therapy. Another noteworthy issue is the heterogeneous group included in the ASSURE trial. At least one-fifth of the patients in ASSURE had non-clear cell renal cancer and approximately 10% of those had sarcomatoid changes. In contrast, all of the patients in STRAC had clear cell carcinoma.

Approximately 10% of the patients in ASSURE had stage T1 disease, while all patients in STRAC were stage T3 and/or lymph node-positive. Furthermore, the trials included very different patient numbers. The sunitinib arms of ASSURE and STRAC included 647 and 309 patients, respectively. Dose titrations due to adverse events resulted in 25 mg and 37.5 mg doses in ASSURE and STRAC, respectively. Thus, higher doses of the drug were administered in the STRAC trial. Central radiological evaluation in the STRAC trial is another important difference. Both of these studies suggest that adjuvant sunitinib may be effective, at least in a well selected and high-risk patient group. Therefore, because STRAC included a more homogenous, higher risk patient group and the probability of micrometastasis is higher in these patients, it seems valid to believe that it conferred a disease-free survival advantage (18). In fact, even within the STRAC trial, it was reported that adjuvant therapy provided a significant disease-free survival advantage of 6.2 years versus 4 years in the "very high risk" subgroup. However, the fact that overall survival data have not been released fuels continued debate regarding adjuvant therapy. Due to both the lack of overall survival data and the high incidence of adverse events, adjuvant therapy is not recommended in the latest version of the European Urology Guidelines (7). It was stated that available evidence regarding adjuvant therapy is inadequate for various reasons such as the need for longer follow-up, the potential presence of radiologically undetectable micrometastases in high-risk patients, and the possibility that in the STRAC study, sunitinib stabilized these micrometastases, resulting in the extended time to detectable recurrence (i.e. disease-free survival). Adverse effects and the importance of quality of life were emphasized. One of the major arguments presented was that guidelines should be based on evaluation of the results of meta-analyses, as has been done with other cancers, rather than data from a single study. For example, a definitive conclusion regarding adjuvant therapy for rectal cancer and the subsequent creation of guidelines could only be achieved with meta-analysis data (19). The same must be done for renal cancer. Currently, a "small" and limited meta-analysis including the ASSURE and STRAC trials, with their limited patient numbers and follow-up periods, reports a conclusion against adjuvant therapy (7).

PROTECT: This is the latest phase 3 placebo-controlled randomized trial to publish results. A total of 1538 patients with high-grade stage T2 and T3 clear cell renal cancer were randomized to receive pazopanib or placebo for 1 year after nephrectomy. The initial dose of 800 mg administered to 403 patients was lowered to 600 mg, and disease-free survival was evaluated. A one-third reduction in hazard ratio for disease-free survival was reported in patients who started at 800 mg, while no statistically significant improvement in disease-free survival was detected in those treated with 600 mg (20). In a subanalysis supporting these findings, early (3 or 5 weeks) drug concentrations of 311 patients and late (16 or 20 weeks) drug concentrations of 250 patients were compared with disease-free survival and adverse event profile (21). The study showed that an early high drug dose prolonged disease-free survival with no change in the incidence of adverse events (except hypertension). Similarly, it was reported that those with a pazopanib concentration above 20.5 µg/mL in the early or late period had a significant disease-free survival advantage. However, it is clear that long-term follow-up of this study is needed.

Ongoing studies: Results from phase 3 placebo-controlled trials of other adjuvant targeted agents are being awaited. Of these, the results of studies of sorafenib (SORCE), axitinib (ATLAS), and everolimus (EVEREST) will be of interest.

The Future

In relation to STRAC in particular, there are no other large series/long follow-up data that show a disease-free survival advantage in favor of adjuvant therapy (22). Only an autologous vaccine trial which included a limited number of patients and was determined unfeasible due to cost reported an increase in survival (12). Long-term follow-up results are also expected for pazopanib. As results from trials of new targeted agents become available, adjuvant therapy approaches will continue to increase.

On the other hand, the optimal duration of adjuvant therapy with targeted agents is also unknown. In current studies, treatment usually continues for 1 year. It is known that in metastatic disease, resistance is acquired after response to targeted agents. Unnecessarily prolonged adjuvant therapy can lead to recurrence with a more resistant tumor population. Therefore, studies should also focus on determining optimal adjuvant treatment durations. It has yet to be determined whether adjuvant therapy should continue for 1 year, 5 years, or a lifetime. Adverse events and high cost are other barriers.

Essentially, treating micrometastases with targeted agents that suppress angiogenesis (at least in theory) may also be considered suspect. This is because the degree to which micrometastases are associated with angiogenesis must be further elucidated and investigated. New molecules are also needed in this respect. However, recent studies have demonstrated the efficacy of several new immunotherapeutics in advanced bladder and renal cancers. The most recent of these is nivolumab, a monoclonal antibody targeting the programmed death 1 receptor. Nivolumab and everolimus were compared in a study of 821 patients who had previously received systemic therapy with standard primary targeted agents, and nivolumab was reported to provide a survival advantage (21.8 months versus 19.6 months) with a milder adverse event profile (23). These findings in metastatic disease also suggested the possibility of its use in the adjuvant setting. Indeed, there is an example of favorable outcomes after the postoperative adjuvant use of these agents in melanoma (24). However, a major drawback to approaches using these agents is the theory that since the primary focus is removed with surgery, treatment targeting the immune checkpoints in question may fail in the absence of antigens (25). Therefore, prospective studies have also been designed to investigate the perioperative (neoadjuvant/adjuvant) use of such immune agents. For example, the PROSPER trial is evaluating nivolumab (2 cycles preoperatively + postoperatively until toxicity or progression) versus a placebo in 766 high-risk renal cell carcinoma patients. The IMmotion010 trial is investigating the adjuvant use of atezolizumab after

surgery. The results of these and similar studies will open new horizons for adjuvant therapy.

The need for risk evaluation in the planning of adjuvant therapy and its suitability for high-risk patients are apparent even in light of data from available studies. Different classification methods have also been described for this purpose. These methods aim to classify patients according to clinical stage and pathological features. The University of California, Los Angeles integrated staging system divided patients into 5 classes based on their T and N stages, Fuhrman grade, and Eastern Cooperative Oncology Group performance status (26). On the other hand, in an evaluation of 1671 patients using the Leibovich score or stage, size, grade, and necrosis (SSIGN), stage, tumor size, nuclear grade, and necrosis were used to predict "low, moderate, and high risk of recurrence" (27). For example, progression risk of 42% and 63% were reported at 1 year and 3 years, respectively, in the high-risk group. Therefore, patients in this at-risk group can be considered candidates for adjuvant treatment. There is also a striking recent publication recommending the use of the SSIGN classification (28). In fact, it was stated that the calculated SSIGN score can be used to predict recurrence during 20-year follow-up after surgery. High scores were found to correlate with disease-related mortality. However, it should be kept in mind that classifications based on such clinical and pathological criteria may show significant intra- and inter-observer variations for reasons such as standardization differences in pathological evaluation.

As in other cancers, an individualized or tumor-specific risk estimation and treatment plan based on various genetic and molecular properties will be the most realistic approach both in theory and practice. This type of approach is currently used in clinical practice for breast cancer (29). There is no reason this cannot be done in renal cell carcinoma. Indeed, a study reported that analysis of 16 genes is valuable in prediction of recurrence in renal cell carcinoma (30). The patients in STRAC were evaluated based on data from this 16-gene assay and a "16-gene recurrence score" was developed for clinical use (31). As in breast cancer, providing personalized treatment using such genetic risk calculations also seems possible for renal cell carcinoma in the future.

Neoadjuvant Therapy

The most effective curative treatment currently available for renal cell carcinoma is surgery. Therefore, surgical treatment is initially considered for all eligible patients. This is also the case for patients with tumor thrombosis or locally advanced disease, and even metastatic patients with a single focus. In some patients, however, the excision of large masses invading surrounding tissues may not be surgically possible or may be highly risky. These cases may require an alternative to extensive surgery requiring adjacent organ resection or vascular graft, or a mass-reducing approach to make surgery more feasible. Similarly, alternative approaches that enable patients with a mass in their only kidney or patients with bilateral renal masses to avoid dialysis must also be considered. For example, a nephron-sparing approach may be possible for these patients if the mass can be reduced. Considering the fact that renal cell carcinoma is a radioresistant disease, effective systemic therapy is also needed for this purpose. Essentially, neoadjuvant systemic therapy is needed for two important reasons: to enable the removal of difficult and complex masses, and for mass reduction in order to facilitate nephron-sparing surgery.

Although questionable for angiogenesis inhibitors, one of the potential benefits of neoadjuvant therapy is the possibility of early control of micrometastases. Another potential benefit, however, is that it may offer the possibility of safe surgery for high-risk patients and reduce the likelihood of recurrence with systemic therapy. In addition, it may be possible to prevent disease progression while the patient is awaiting surgery, at least in theory.

For all of these reasons, targeted agents that are proven effective and have become standard in metastatic disease are being increasingly used in the neoadjuvant setting. Neoadjuvant applications, especially with targeted agents, appear in the literature first as case reports, then as small series. A review was also published recently (32).

On the other hand, the potential unfavorable consequences of neoadjuvant therapy should not be ignored. Targeted agents are known to cause serious adverse events. Developing some of these adverse events, such as cardiac toxicity, during the course of neoadjuvant therapy may result in a patient becoming ineligible for surgery, which offers a real chance at curative treatment. There may be progression while under neoadjuvant therapy and the patient may, for example, jump to the metastatic stage. Another drawback is the increased risk of perioperative morbidity after neoadjuvant therapy (33).

One of the possible theoretical benefits of neoadjuvant therapy is for metastatic patients. Although this application in metastatic patients is actually considered "pseudo-neoadjuvant", such an approach may become widespread in the future as a more rational method. Cytoreductive nephrectomy may be more meaningful for patients who respond to this type of (pseudo-) neoadjuvant therapy, and an unnecessary and risky surgical treatment with nephrectomy, for instance in a metastatic patient not responding to systemic therapy, can be avoided (34).

Which drug to use and for what duration have yet to be determined for neoadjuvant therapy. This section summarizes the current state of neoadjuvant applications.

Pre-nephrectomy Systemic Therapy Studies

In the first study to demonstrate the downsizing effect of sunitinib on primary tumors, treatment responses were reported for 17 patients with available abdominal tomography scans from a series of 22 patients (35). The Response Evaluation Criteria in Solid Tumors were used to measure treatment efficacy. According to these criteria, only 1 patient showed progression, 12 patients (71%) had stable disease, and 4 patients (24%) showed partial response. The authors reported a median tumor volume reduction of 31% and a median increase in mass necrosis volume of 39%. A total of 3 patients underwent nephrectomy and extensive necrosis was reported. Soon after, a more definitive series regarding the neoadjuvant use of sunitinib was published (36). In a series of 19 patients

who were initially ineligible for nephrectomy due to locally advanced disease or metastatic load, 9 patients (47%) had progression, 7 patients (37%) had stable disease, and 3 patients (16%) showed partial response. Reduction in primary tumor volume was seen in 8 patients (42%), with an average decrease of 24%. However, nephrectomy was possible in 4 of the 19 patients. No perioperative morbidity was reported. In a series of 28 patients in the same center, it was reported that neoadjuvant sunitinib resulted in a median tumor reduction of 28%, and nearly half of the patients were able to undergo nephrectomy (37). Similarly, another study reported decreased tumor diameter (mean reduction of 12%) in 17 (85%) of 20 patients treated with neoadjuvant sunitinib (38).

In a phase 2 trial on the neoadjuvant use of sorafenib, a mean reduction in tumor size of 10% was observed in 77% of patients (39). In a prospective, randomized, placebo-controlled trial of the same agent, a tumor volume reduction of 29% was reported in stage T1-3 patients in the sorafenib arm (40). There was no difference in survival during the 2-year follow-up period, and it was suggested that the tumor gained heterogeneity during treatment and that resistance to treatment may develop.

Different results have been reported for neoadjuvant targeted therapy in patients with inferior vena cava thrombosis. In a series of 5 patients with vena cava thrombosis who received sorafenib, tumor downsizing/downstaging was observed in 4 patients (41). On the other hand, in another series of 25 patients, regression of the thrombosis level was reported in only 3 patients treated with sunitinib (42). Similarly, in 14 patients with tumor thrombosis, neoadjuvant therapy resulted in thrombosis regression in only 1 patient (43). Therefore, there is not enough scientific evidence on the efficacy of neoadjuvant therapy in those with vena cava thrombosis.

Studies on Systemic Therapy for Nephron-sparing Surgery

One of the main reasons neoadjuvant therapy is needed is that it may enable the downsizing of large masses and thus facilitate nephron-sparing surgery. This approach may be necessary to allow patients with a mass in their only kidney or with bilateral renal masses to avoid hemodialysis.

On this topic, a 12-patient experience with sunitinib was reported in the first series presenting nephron-sparing surgery after neoadjuvant therapy (44). All of the patients had large or central masses. A mean reduction in tumor volume of 21% was observed and all of the patients were able to undergo nephron-sparing surgery. Surgical margins were tumor-negative in all cases. In another study, nephron-sparing surgery was planned after pazopanib therapy in 25 patients with large and central masses, 92% of the patients showed a reduction in tumor volume, and 20 were able to undergo nephron-preserving surgery (45). In addition, it was reported that neoadjuvant therapy enabled the preservation of a significant amount of renal parenchymal tissue. In a multicenter retrospective analysis, neoadjuvant sunitinib in 72 patients (78 kidneys) reduced tumor size by a mean of 32% and enabled nephron-preserving surgery in 63% of the kidneys (46).

These data show that neoadjuvant therapy has a place in the treatment of complex/central masses, especially if nephron-sparing surgery is needed.

Adverse Events and Complications

One of the main problems with neoadjuvant therapy is the side effects of the agents used. As mentioned in the previous section, large adjuvant therapy trials have demonstrated that patients can develop serious adverse events which can result in discontinuation of treatment. Hypertension and cardiac adverse effects are the most important. The ASSURE trial reported a potential adverse effect on left ventricular ejection fraction (47). Therefore, patients with limited cardiac reserve, for example, require a more cautious approach; the risk of being ineligible for surgery due to cardiac reasons after neoadjuvant therapy must be weighed, and it may even be necessary to perform surgery first.

It is also argued that the anti-angiogenic effect of targeted agents that suppress the VEGF system increase surgical morbidity (48). Due to the role of angiogenesis in wound healing, it has been claimed that there may be an increased risk of surgical site infection or urinary tract leakage due to neoadjuvant agents, but that the rate of serious complications (Clavien ≥3) remains unchanged (49). However, a significant increase (up to 25%) in the incidence of urinary leakage has also been reported (45).

Studies are needed to determine the necessary duration of neoadjuvant therapy. Available data suggest that tumor shrinkage usually occurs within the first 3-5 months. In this case, a presurgical 3-course treatment may be adequate for sunitinib, for example (33). The timing of treatment discontinuation prior to surgery is also important to ensure a minimum impact on wound healing. Authors stating that such complications do not change with neoadjuvant therapy suggest that discontinuation 24 hours before surgery is sufficient for sunitinib, although agents with a long half-life, such as bevacizumab, should undoubtedly be discontinued earlier (50). Some authors state that it is safer to discontinue treatment at least 2 weeks preoperatively (51). Based on the half-life of the drug being used, it may also be safe to discontinue therapy 2-3 times the half-life before surgery (52). This may in theory enable a low-risk approach in terms of disease progression by avoiding a long drug-free period. According to this, since the half-life of sorafenib is 1-2 days and the half-life of the active metabolite of sunitinib is about 4 days, it may be safer and more reasonable to discontinue sorafenib 3-4 days before surgery and discontinue sunitinib at least 1 week before surgery. This problem will be solved as agents with short half-lives become available.

Conclusion

Considering the FDA approval for high-risk patients based on STRAC data, an appropriate approach in current practice is to present adjuvant therapy to the patient as an alternative in light of clinical and pathological evaluations but also taking into account the possibility of adverse events. In the meantime, patients should definitely be informed about the high risk of adverse events and impaired quality of life. However, it should also be noted that the drug in question is not licensed for

adjuvant use in our country and is therefore not covered by social security reimbursement for this indication.

Neoadjuvant therapy utilizing more effective agents with safer adverse event profiles and short half-lives may be used more widely in the future. On the other hand, recent developments have prompted the initiation of clinical trials evaluating the neoadjuvant use of immunomodulatory agents in renal cell carcinoma. There is still a need for prospective, randomized, large-scale series to elucidate this topic.

Questions

1. Which targeted therapy agent has been approved by the Food and Drug Administration for adjuvant therapy following nephrectomy in renal cell carcinoma?

Sunitinib.

2. Which trial resulted in Food and Drug Administration approval of adjuvant therapy after nephrectomy in renal cell carcinoma?

STRAC.

3. Adjuvant therapy with which targeted agent was shown to confer an overall survival advantage in renal cell carcinoma?

There is no agent with a demonstrated overall survival advantage, prolonged disease-free survival was observed with sunitinib and pazopanib.

4. Neoadjuvant angiogenesis inhibitors may be associated with which surgical complications in particular?

Surgical site infection, impaired wound healing, and urinary leakage.

5. Considering the half-life of neoadjuvant sunitinib, discontinuing treatment at least how long before surgery may be safer in terms of surgical side effects?

One week.

Ethics

Peer-review: Externally peer-reviewed.

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