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ABSTRACT

Up to one third of patients with renal cell carcinoma will present with metastatic disease, and 20 to 40% of those with clinically localized disease will eventually be found to have metastatic involvement. Prognosis continues to be guarded for this population, with a 2-year survival of only 10 to 30%. Although advances are being made in the medical management of renal cell carcinoma, the role of surgery in the treatment algorithm is also being additionally refined. Palliative surgery either via nephrectomy or metastasectomy has a role in certain well-selected patients. There are also data to support total metastasectomy at the time of either nephrectomy or recurrence in a small subset of patients with minimal, resectable metastases. More controversial is the idea of cytoreductive nephrectomy as an adjunct to immunotherapy. Recent phase III trials indicate that nephrectomy may play an important role in management of metastatic renal cell carcinoma in conjunction with cytokine-based immunotherapy. Nephrectomy is also an essential component of tumor-based vaccine and adoptive immunotherapy protocols and may play a role in other novel therapies.

INTRODUCTION

To date, the most effective systemic treatment for metastatic renal cell carcinoma is cytokine-based immunotherapy. The role of nephrectomy in this treatment paradigm, either before or after immunotherapy, remains a controversial topic. Because most data on this topic are related to cytoreduction before nephrectomy, this article will concentrate solely on this subject. We now have two randomized prospective trials that suggest an advantage to preimmunotherapy cytoreductive nephrectomy in appropriately selected patients. Therefore, the role of cytoreduction after immunotherapy will not be discussed in detail.

BIOLOGICAL RATIONALE

The rationale for cytoreduction can be better understood by examining the tumor biology of renal cell carcinoma. Beginning with the phenomenon of spontaneous regression of metastatic disease, the ability of renal cell carcinoma to manipulate and suppress the body's natural immunity has been recognized for many years and studied extensively. Because nearly all foci of spontaneous metastatic regression occur in the lung and only after the primary tumor has been extirpated, Freed (1) speculated that the lung, with its rich supply of macrophages, lymphocytes, and immunoglobulin, might suppress the metastases through host immune mechanisms and that the primary tumor suppresses this antitumor effect. He cited animal data that revealed that cell-mediated cytotoxicity is diminished with continuing growth of the primary tumor. In a sense, the primary tumor may act as an immunologic sink by diverting circulating antibodies and lymphocytes away from distant metastases (2, 3).

Our knowledge of lymphocyte cellular signaling and regulation pathways has continued to advance, resulting in a much greater appreciation of the immune dysfunction caused by renal cell carcinoma. Renal cell carcinoma (along with some other solid malignancies) continue to progress despite significant tumor-infiltrating lymphocytes (TILs), implying that there may be host immune dysfunction and poor tumor antigen recognition and/or presentation (4). Lymphocytes from patients with metastatic renal cell carcinoma have been shown to have defective T-cell receptors (5), increased apoptosis (6, 7), and defective signal transduction (4, 8), with TILs often showing greater dysfunction than peripheral blood lymphocytes. Renal cell carcinoma has also been shown to produce high levels of proinflammatory and T-cell inhibitory cytokines such as interleukin 8 (IL-8), IL-6, granulocyte-macrophage colony-stimulating factor, tumor necrosis factor α, IL-10, and transforming growth factor β, which also may actively suppress immunologic responses (9, 10).

It has also been documented that the primary lesion in metastatic renal cell carcinoma rarely responds to systemic immunotherapy, even when there is significant regression of distant metastases. The National Cancer Institute reported on a series of 51 patients who were not candidates for nephrectomy before the initiation of IL-2–based systemic therapy and noted a response rate of only 6%, with no significant responses seen in the primary tumor (11). Similarly, Sella *et al.* (12) reported that of 17 patients who underwent IFN-α immunotherapy, 15 patients (88%) had viable tumor present in the nephrectomy specimens. This lack of response of the primary tumor to immunotherapy has been reported by others and is additional evidence that the primary tumor causes immune dysfunction and implies a benefit to preimmunotherapy cytoreductive nephrectomy (13).

Other potential benefits of nephrectomy before biological response modifier therapy include the prevention of additional shedding of tumor cells, which might produce new metastases, and palliation of complications of locally advanced disease or paraneoplastic syndromes, which might have an impact on immunotherapy.

Multiple retrospective reports of immunotherapy for renal cell carcinoma have shown prior nephrectomy to be a positive

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Table 1 Cytoreductive nephrectomy in preparation for immunotherapy: retrospective studies

Source	No. of patients	Surgical mortality, no. (%)	Unable to receive postoperative BMR therapy, no. (%)	Overall response, no. (%)	Complete response, no. (%)	Partial response, no. (%)
Rackley *et al.* (13)	37	1 (2.7)	8 (21.6)	3 (8.1)	0 (0.0)	3 (8.1)
Wolf *et al.* (20)	23	0 (0.0)	6 (26.1)	3 (13.0)	2 (8.7)	1 (4.3)
Bennett *et al.* (21)	30	5 (17)	23 (76.6)	4 (13.3)	3 (10.0)	1 (3.3)
Fallick *et al.* (22)	28	1 (3.6)	2 (7.1)	11 (39.3)	5 (17.9)	6 (21.4)
Walther *et al.* (23)	195	2 (1.0)	74 (37.9)	19 (17.8)	4 (3.7)	15 (14.0)
Figlin *et al.* (24)	62	0 (0.0)	7 (11.3)	19 (34.5)	5 (9.1)	14 (25.5)
Levy *et al.* (25)	66	2 (3.0)	12 (18.1)			
Total	441	11/441 (2.5)	132/441 (29.9)	59/375 (15.7)	19/375 (5.1)	40/375 (10.7)

prognostic factor independent of other well-recognized factors such as performance status and site or burden of disease (14–19). In 670 patients, who were treated with immunotherapy and chemotherapy, described by Motzer *et al.* (14), the median survival was 10 months. Pretreatment features associated with shorter survival in the multivariate analysis were absence of nephrectomy, low Karnofsky performance status (<80%), lactate dehydrogenase level > 1.5 times normal, hemoglobin level lower than normal, and corrected serum calcium level > 10 mg/dL

Finally, it is postulated that cytokines and growth factors released by the primary tumor (*e.g.,* vascular endothelial growth factor) may promote growth of metastases. If this is true, removal of this cytokine release by cytoreductive nephrectomy might benefit the patient and allow for improved therapeutic response to growth factor inhibitors (*e.g.,* vascular endothelial growth factor inhibitors)

RETROSPECTIVE STUDIES

A number of retrospective series have examined preimmunotherapy cytoreductive nephrectomy (Table 1; refs. 13, 20–25). Unfortunately, these studies all are subject to the selection bias inherent in retrospective reviews, making analysis of their conclusions difficult. The largest series reported is from the National Cancer Institute and included 195 patients who underwent nephrectomy with resection of adjacent or contiguous metastases before undergoing IL-2 therapy (23). The overall response rate in this series was 18% (including 4% complete responses and 14% partial responses), which is similar to what one would expect from immunotherapy alone. In this series, 38% of patients were unable to undergo treatment with IL-2 secondary to progression of tumor, postoperative complications, or a debilitated state. There was a 1% mortality rate in this series. Other smaller series have reported mixed results with cytoreductive nephrectomy (Table 1), with response rates varying between 8 and 35%. The number of patients unable to receive systemic therapy after nephrectomy varies as well from 7 to 77% and mortality rates are 0 to 17%. Variability in patient selection, including the distribution of those with good *versus* poor performance status, limited *versus* extensive metastases, location of metastases, and long *versus* short metastasis-free interval, most likely accounts for these conflicting results.

Bennett *et al.* (21) reported the poorest outcomes regarding surgical morbidity, mortality, and the inability to receive postoperative systemic therapy. They reported a 17% mortality rate, and 77% of patients were unable to receive systemic immunotherapy after surgery. Certainly patient selection was at least partially the cause of these poor outcomes. In this series, almost one third of patients had brain metastases, 43% had bony metastases, and 37% had hepatic metastases. Of the 30 patients, only 2 were Eastern Cooperative Oncology Group (ECOG) status 0, 24 were ECOG status 1, and 4 were ECOG status 2. This study reinforces the dangers of poor patient selection when considering cytoreductive nephrectomy and the importance of preoperative evaluation by the urologic surgeon and medical oncologist.

In 1997, Fallick and McDermott (22) identified several criteria believed to be predictive of good outcome after cytoreductive nephrectomy and applied these to all patients in the series with metastatic renal cell carcinoma. The criteria included the absence of central nervous system, bone, or liver metastases, an ECOG performance status of 0 or 1, the possibility of >75% tumor debulking, and predominantly clear cell histologic findings on any biopsy specimens of the tumor. Using these criteria, only 28 patients of a total of 85 were believed to be candidates for cytoreductive nephrectomy. There were, however, no perioperative deaths or complications that prevented additional systemic therapy, and only a single patient had progression of disease that required withholding of systemic therapy in this series. The overall response rate was 39%, including five complete and six partial responses, with a median survival of 20.5 months in the entire group.

Because of the morbidity involved with nephrectomy and the possibility of disease progression while recovering, some groups have investigated laparoscopic cytoreductive nephrectomy with tissue morcellation (26). In one series, the median time to immunotherapy in 19 patients undergoing open nephrectomy was 67 days (range, 50 to 151 days) compared with 60 days (range, 47 to 63 days) in 5 patients who underwent hand-assisted laparoscopic nephrectomy and only 37 days (range, 34 to 57 days) in 6 patients who underwent pure laparoscopic nephrectomy. The morbidity of laparoscopic nephrectomy was comparable with traditional open nephrectomy, and the procedure, including tissue morcellation, was feasible even for large tumors. In a larger subsequent report of 31 patients undergoing attempted laparoscopic nephrectomy; however, the same group showed the potential difficulties of this operation (27). Eleven cases required open conversion, and blood loss was much higher

(750 to 3000 mL) than is typically expected from laparoscopic nephrectomy. Only 18 patients (58%) proceeded to immunotherapy postoperatively. Local invasion, obliteration of tissue planes, and enhanced vascularity increase the difficulty of this procedure. Although the role of laparoscopy is still being refined in cytoreductive nephrectomy, it seems clear that this will be reserved for centers with extensive laparoscopic experience and for patients who are properly selected and counseled.

Cytoreductive nephrectomy has also been studied in the setting of locally advanced renal cell carcinoma, including extension to the renal vein and inferior vena cava and distant metastases. Slaton *et al.* (28) retrospectively reviewed 15 patients who underwent nephrectomy and caval thrombectomy with concurrent metastases. There were two re-explorations for postoperative hemorrhage, but no perioperative deaths were reported. Median time to initiation of postoperative immunotherapy was 48 days for the six patients for whom it was planned (other patients had preoperative and postoperative immunotherapy or resection of metastases only as adjuvant therapy). Excellent performance status is critical for success with these extensive resections. Careful screening for cardiovascular and cerebrovascular disease is recommended, particularly if cardiopulmonary bypass and hypothermic cardiac arrest will be required for the operation (29).

PROGNOSTIC FACTORS FOR CYTOREDUCTIVE NEPHRECTOMY

Because of the variable response to cytoreductive nephrectomy and immunotherapy, several investigators have tried to identify pretherapy characteristics that predict good response to therapy. Wood *et al.* (30) evaluated 126 consecutive patients undergoing cytoreductive nephrectomy and found that length of stay after nephrectomy, tumor grade, preoperative white blood cell count, and partial thromboplastin time were significant predictors of survival after cytoreductive nephrectomy. In addition, the authors thought that pretherapy biopsy may be warranted to rule out high-grade tumors such as sarcomatoid variants, collecting duct tumors, and other nonconventional tumors that may display a poor prognosis (31). Slaton *et al.* (32) have reported that patients with metastatic renal cell carcinoma involving multiple organs, particularly the liver or central nervous system, are at high risk for death during the first 6 months after nephrectomy and are less likely to be palliated by the surgery. Han *et al.* (33) also retrospectively analyzed factors that predict outcome after cytoreductive nephrectomy and found that patients with lung-only or bone-only metastases who underwent cytoreductive nephrectomy followed by immunotherapy had a median survival of 31 months compared with a 13-month median survival ($P = 0.001$) in patients with multiple metastatic sites undergoing nephrectomy and immunotherapy. They concluded that patients with bone-only metastases, although less common than those with lung-only or multiple metastatic sites, fare relatively well with cytoreductive nephrectomy followed by immunotherapy and that those with multiple metastatic sites do poorly overall.

In another analysis of the University of California at Los Angeles database, 236 patients with metastatic disease and no lymphadenopathy (N0 M1) were compared with 86 patients with distant metastases and concomitant lymph node disease ($n + M1$; ref. 34). Of those who underwent postnephrectomy immunotherapy, objective response rates were 30% for the N0 M1 group and only 11% for the $n + M1$ group. The patients with $n + M1$ disease who were not undergoing immunotherapy had the worst prognosis, with an overall median survival of 4.5 months, which was not significantly different ($P = 0.18$) from patients with $n + M1$ disease who did undergo immunotherapy (overall median survival, 10.8 months). In an analysis of 154 patients with metastatic renal cell carcinoma at the National Cancer Institute undergoing nephrectomy before IL-2–based therapy, median survival in lymph node-positive patients (8.5 months) was also found to be significantly inferior to that of lymph node-negative patients (15 months; ref. 35).

Others have analyzed serum immunologic markers such as C-reactive protein in an attempt to predict response to cytoreductive nephrectomy (36). In patients with a normal preoperative C-reactive protein level, the levels of serum immunosuppressive acidic protein and natural killer cell activity did not differ significantly before and after nephrectomy. In contrast, those with an elevated C-reactive protein level preoperatively had significantly elevated serum immunosuppressive acidic protein levels, which decreased significantly postoperatively, and also significantly decreased natural killer cell activity preoperatively, which increased significantly postoperatively. They concluded that those patients with elevated C-reactive protein levels preoperatively may benefit most from cytoreductive nephrectomy followed by immunotherapy.

PROSPECTIVE PHASE III TRIALS

The variable results found from multiple retrospective trials of cytoreductive nephrectomy made a randomized prospective trial vital to advancing our knowledge of treatment of metastatic renal cell carcinoma. Recently, the Southwest Oncology Group (SWOG) trial 8949 and the European Organization for the Research and Treatment of Cancer trial 30947 were reported (37–39). Using an identical treatment protocol (designed by SWOG), these trials provide the best information to date regarding the use of cytoreductive nephrectomy. The eligibility criteria for these trials included a histologically confirmed diagnosis of metastatic renal cancer (biopsy of the primary tumor or metastatic foci was allowed), a primary tumor that was considered resectable by the attending physician (inferior vena cava thrombus below the hepatic veins and regional lymphadenopathy were allowed), an ECOG performance status of 0 or 1, and no history of prior treatment with chemotherapy, hormonal therapy, IL-2, IFN, lymphokine-activated killer cells, or other biological response modifiers. In addition, prior or concomitant radiation therapy to the primary tumor or to metastatic sites was not allowed, and a serum bilirubin level no higher than three times the upper limit of normal and a serum creatinine level no higher than 3.0 mg/dL were required. Patients were randomly assigned to nephrectomy followed by IFN-α2b or IFN-α2b alone. The results for the two trials and a combined analysis are shown in Table 2 (37–39). Both trials demonstrated significantly longer overall survival in the groups randomized to nephrectomy before immunotherapy, and this benefit persisted across all study stratifications, including per-

Table 2 Phase III trials of IFN-α-2b *versus* IFN-α-2b with nephrectomy

Trial	No. of patients	Median survival, mo			Response to therapy, %			Unable to receive postsurgery immunotherapy. no. (%)	Operative mortality, no. (%)
		Interferon	Surgery + Interferon	*P*	IFN	Surgery + IFN	*P*		
SWOG 8949 (37)	241	8.1	11.1	0.05	3.3	3.6	NS	NR	1 (0.8)
European Organization for Research and Treatment of Cancer 30947 (38)	85	7	17	0.03	12	19	0.38	NR	1 (2.4)
Combined analysis (39)	331	7.8	13.6	0.002	5.7	6.9	0.60	9 (5.6)	2 (1.4)

NS, not significant; NR, not reported.

formance status, site of metastasis, and measurable *versus* nonmeasurable disease. There was a single perioperative death in each of the series after nephrectomy, and overall, <6% of patients did not receive immunotherapy in the group randomized to nephrectomy plus IFN. Despite the increased survival, there were no differences in response rates between the two groups. Patients with a performance status of 0 had a significantly longer survival than patients with a performance status of 1. Both studies demonstrated that nephrectomy can be performed safely with little chance of interfering with the subsequent ability to receive immunotherapy. Unfortunately, the overall median survival was only 13.6 months, with a benefit of only 5.8 months for the nephrectomy group. Although it seems likely based on retrospective studies that the use of IL-2 will enhance survival in this population over IFN alone, we will have to wait for prospective studies to answer this question definitively.

As stated previously, no improved response rate in the nephrectomy arms of these two trials was found, whereas a survival advantage was demonstrated. How might this be explained? One interesting theory is that the enhanced survival of patients after cytoreductive nephrectomy could be attributable to postoperative azotemia from resection of the kidney not related to an immune system basis (40). Mathematical models of malignant invasion based on tumor-induced toxic effects in adjacent normal tissue have been proposed. These models suggest that mild systemic acidosis caused by resection of functioning nephrons can alter the microenvironment in the tumor and peritumoral normal tissue sufficiently to reduce tumor growth rate and prolong survival. This hypothesis was tested by retrospectively reviewing the patient data from the SWOG 8949 trial. In patients with no postoperative renal dysfunction, the median survival was only 4 months compared with 17 months in those with a postoperative elevation of blood urea nitrogen and creatinine levels. Unfortunately, information regarding systemic pH, serum electrolytes, and other clinical data were unavailable because of the retrospective nature of the review, limiting the conclusions that can be drawn. Obviously, if these results can be confirmed, they suggest a broad new range of therapies for tumors beyond just renal cell carcinoma.

NEPHRECTOMY AS A COMPONENT OF ADOPTIVE IMMUNOTHERAPY

Adoptive immunotherapy involves the transfer of antitumor cells into the host to mediate tumor regression. In renal cancer patients, nephrectomy is typically a requirement for these protocols as a source for tumor antigens or TILs. University of California at Los Angeles investigators have reported the most encouraging results with this therapy (41). In this protocol, TILs were harvested from the nephrectomy specimens, expanded *ex vivo*, and reinfused along with IL-2. Many patients also received preoperative cytokines to improve the yield of TILs, and in some cases, CD8+ cytotoxic lymphocytes were enriched to enhance responses. Sixty-two patients were enrolled, and 55 eventually underwent treatment after nephrectomy. A 25.5% overall partial response rate with a 9.1% complete response rate was reported. On the basis of these encouraging results, a prospective, randomized trial comparing standard low-dose IL-2 therapy given with and without TILs was undertaken (42). The overall response rate was 9.9% in the IL-2 and TIL group and 11.4% in the IL-2–only group ($P = 0.753$). Median survival was 12.8 months in the TIL and IL-2 group and 11.5 months in the IL-2 alone group. Although these results are disappointing, nephrectomy may continue to be a part of adoptive immunotherapy and tumor-based vaccine protocols in the context of informed consent at facilities that can support these highly technical procedures.

DISCUSSION

The role of surgery in the management of metastatic renal cell carcinoma is still being defined, but certain conclusions can be made. Surgery for palliation of symptoms related to the primary tumor or metastases is justified, but only in rare circumstances when angioinfarction or other strategies cannot adequately control the symptoms. Resection of the primary tumor along with complete resection of solitary or limited metastases can occasionally lead to long-term survival, but it is an unusual patient who satisfies the criteria for this type of surgery. Nephrectomy before immunotherapy has been shown in phase III trials to result in a survival benefit in patients with good performance status and limited burden of disease, although the overall improvement in survival is modest. Whether nephrectomy performed after a response to immunotherapy will provide a benefit similar to preimmunotherapy, nephrectomy remains to be seen. Additional randomized, prospective trials need to be completed to additionally elucidate the role of nephrectomy in metastatic renal cell carcinoma, particularly in the context of antiangiogenic and molecularly targeted therapies. Nephrectomy will continue to play a role in adoptive immunotherapy

strategies. It is hoped that additional research into novel therapies, such as dendritic cell therapy, gene therapy, or other agents, will further advance the management of patients with metastatic renal cell carcinoma.

OPEN DISCUSSION

Dr. Andrew Novick: Are there any situations today where you would recommend deferring an initial or preliminary cytoreductive nephrectomy by treating the patient first with systemic therapy and then revisiting the issue of nephrectomy later?

Dr. Robert Flanigan: Absolutely, let me give you one recent example from our practice. We saw an 18-year-old man who had massive disease in the abdominal area but had a pretty good performance status; however, from his X-rays, it looked like his superior mesenteric artery and vein went right through the middle of the mass. We reviewed the case very carefully and decided that, in this circumstance, cytoreductive nephrectomy was not the right thing to do. In general, we also use performance status as an indicator. If the patient does not have very good performance status, we think the patient is probably not going to benefit substantially. Our studies have shown that although there was a statistically significant increased survival, even in the patients who had performance status 1, that difference in terms of absolute survival was really modest. Other important selection factors are site and volume of metastases.

Dr. Robert Motzer: Is the clinical stage of the primary tumor a factor?

Dr. Flanigan: I don't think the stage of the primary tumor itself has any real relationship, except that, obviously, if the patient has disease that extends into the inferior vena cava, you have to make a judgment call.

Dr. Motzer: What about associated retroperitoneal adenopathy?

Dr. Flanigan: We looked at the SWOG data to see whether lymphadenopathy in our study was also a very poor prognostic finding, but we couldn't make that conclusion. However, I am convinced that bulky disease in the retroperitoneum is a poor prognostic finding, but everything is a matter of degree.

Dr. Daniel George: What do you do for the patient who has a relatively small primary tumor with fairly bulky metastatic disease?

Dr. Flanigan: If it is feasible, we will treat them laparoscopically.

Dr. W. Marston Linehan: Our approach is a little different and really hasn't changed since 1984 when we first started doing these. In small tumors, if there is more tumor outside the kidney than inside the kidney, we recommend systemic therapy. We recommend treatment up front. We have published that there is a worse prognosis with patients who have bulky retroperitoneal nodes (35). In this case, our surgical approach is often to remove the disease in the retroperitoneum. That is the approach we have been most successful with for 20 years. When we first started seeing people, we would treat them with IL-2 with their kidney in place; however, they could not tolerate therapy. So we started debulking these people before systemic therapy and started to see some real responses. Then we said, "We do not have the volume to do a randomized trial but that is going to be the approach we will take." All these years, we have still never seen a response in the primary tumors; the patients who are doing the best are the ones who have been debulked.

Dr. Flanigan: If we see tremendous volume of disease outside the kidney, other than in the retroperitoneum, our approach would be to do systemic therapy first also, but for bulky disease outside the kidney in the retroperitoneum, if we felt it was surgically amenable to treatment, we would go after that first and then use systemic therapy.

Dr. Robert Figlin: Have you and the European group ever gone back to see whether papillary tumors did the same as clear cell tumors?

Dr. Flanigan: We looked at that in our group, and the number of papillary tumors, given the varied criteria used for the diagnosis of papillary renal cancer in those days, was very small. So, we couldn't make that conclusion.

Dr. Michael Atkins: If you knew that a patient had a papillary tumor or had a chromophobe tumor ahead of time, would you still recommend a debulking nephrectomy?

Dr. Flanigan: Yes, if our medical oncologist felt that he was going to treat the patient with some agent that was applicable to the metastatic disease.

Dr. Atkins: Let's say we can identify 50% of the population as very unlikely to respond to IFN or IL-2. Would that be justification for doing a biopsy of the primary tumor before subjecting the patient to a debulking nephrectomy?

Dr. Flanigan: Absolutely. I think whatever technology would predict who would respond to therapy would influence whether surgery would be the thing to do.

Dr. Ronald Bukowski: I think it's dangerous just to do a biopsy in the general community. We have all seen patients who have had a needle biopsy interpreted as consistent with renal cell carcinoma, and on surgical removal of the primary tumor, it has turned out to be a nonepithelial renal tumor such as transitional cell carcinoma. I think we have to be cautious at this point in time.

Dr. Flanigan: Even in the SWOG data, there was a small percentage of patients who did not have renal epithelial tumors even though a biopsy was required.

Dr. Atkins: Is there any benefit to palliative nephrectomy in patients presenting with systemic symptoms related to disease burden?

Dr. Flanigan: Although I do think you're right that some patients may benefit, particularly patients who have a strong paraneoplastic syndrome component of hypercalcemia, statistically it's hard to show that there is any benefit to just a palliative nephrectomy.

Dr. Michael Gordon: If it was proven, based on the UCLA data, that CA-IX was a predictor of response, I think the biopsy you need to do is of the metastatic disease to make sure that there have not been epigenetic (methylation) or other changes that have silenced it. You're going to take out a primary tumor that expresses CA-IX and be left with metastases that don't. If this turns out to be the issue, I don't think you want to biopsy the primary but rather biopsy and stain the metastases, and if the metastatic lesion is CA-IX positive or similarly predictive then you want to perform a nephrectomy regardless of what the primary lesion shows.

Dr. Atkins: Those are speculative issues that we should talk about in the future. It would be useful to make an appeal to the urology community that in patients who are having a debulking nephrectomy that we make an effort to have frozen tissue stored because those are patients who are going to get treated for stage IV disease, and it would be great to have tumor tissue available that could be analyzed in those patients.

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