



Understanding and Treating Upper Tract Urothelial Carcinomas (UTUCs)

MODERATED BY DR. GARY STEINBERG

WITH EXPERT PANEL: DRS. ALON WEIZER, SETH LERNER, AHMAD SHABSIGH, SURENA MATIN, JENNIFER LINEHAN AND SUMANTA (MONTY) PAL.

Dr. Weizer: Okay. I can only hope. Thanks for having me. It was great to hear Dr. Shabsigh, and I'm glad to be with all of you, even if it's virtual.

I'm going to pick up where he left off and talk to you a little bit about surgical options. There's a little overlap here, because I think Dr. Shabsigh already kind of mentioned.

The goals are really to achieve cancer control in patients with localized disease. This is particularly talking about surgery. In general, we want to preserve renal function when it's feasible, and finally, obviously, minimize morbidity to people, to the people that we take care of.

Really, selection of surgical intervention should be based on the extent of the disease obviously, and grade, and stage. As Dr. Shabsigh mentioned, staging is pretty difficult based off of the tools that we currently have. Obviously, the most important things are patient factor and goals. In somebody who has compromised renal function or a single kidney, this could be a real life-altering decision as we decide what to do.

Surgical Options

Goals:

- Achieve Cancer Control in Patients with localized disease
- Preservation of renal function when feasible
- Minimize morbidity to the patient

Selection of Surgical Intervention Should be Based on:

- Extent of the disease
- Grade
- Stage
- Patient factors and goals (compromised renal function, solitary kidney)

In terms of surgical options, they really break down into two categories. One is kidney sparing approaches, which could be endoscopic treatment, and then kidney or organ sparing approaches such as segmental or distal ureterectomy, and then the role of removing the whole kidney, which we call nephroureterectomy. In that arena, whether you do it through an open, or a robotic, or a laparoscopic approach, I'll talk about that a little bit, and then the role of the lymph node dissection to assess local regional disease.

Surgical Options

Options:

- Kidney Sparing Approaches
 - Endoscopic treatment
 - Segmental/Distal Ureterectomy
- Nephroureterectomy
 - Role of Minimally Invasive Surgery
 - Role of Lymphadenectomy

This is a little bit of a busy slide, and I apologize for that. But to touch base on kidney sparing approaches, this is really an option for low-risk upper tract urothelial cancer, and some of this is based off of the European guidelines. We're talking about unifocal disease, so really just on one side, not in both kidneys; low-grade cytology ... so the urine-based cytology is often a useful test for us because most of the time cytology for low-grade upper tract urothelial cancer will come

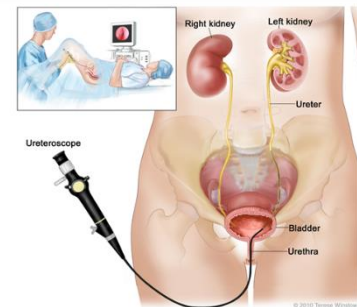
back negative, because cytology is not terribly sensitive for low-grade disease and it's better for high-grade disease ... and then, you really want a ureteroscopic biopsy that does demonstrate low-grade disease, although you have to put this in context of what the imaging looks like, because sometimes there can be regions of the tumor that exhibit low-grade features and other areas that exhibit high-grade features. That's only one component. Clearly, the last point is a CT scan doesn't show concern for invasion. And in people who have compromised renal function, you can get an MRI, that could be helpful as well.

And so, endoscopic ablation of urothelial cancer means that you're going in with the ureteroscope, which Dr. Shabsigh already described, which is a long, thin, flexible or semi-rigid scope placed through the bladder into the ureter. And tissue can be obtained by the use of various instruments, and then tissue can be ablated using various instruments. So different types of laser ... holmium, thulium, or monopolar energy with a Bugbee.

Surgical Options: Kidney Sparing Approaches

Options:

- Kidney Sparing Approaches:
 - Option for Low-risk upper tract urothelial cancer (EAU Guidelines)
 - Unifocal disease
 - Tumor size < 2cm
 - Low grade cytology
 - Ureteroscopic biopsy shows low grade cancer
 - CT scan does not demonstrate concern for invasion
 - Endoscopic Ablation of Urothelial Cancer means:
 - Ureteroscopy: A long thin flexible or semirigid scope is placed into the ureter through the urethra and bladder
 - Tissue can be obtained by the use of various instruments
 - Tissue can be ablated using laser (Holmium) or monopolar energy (bugbee)
 - Percutaneous approaches allow urologists to access kidney directly from the skin through a tract to be able to use larger instruments (larger tumors, solitary kidney)



<https://www.cancer.gov/publications/dictionaries/cancer-terms/def/ureteroscopy>

You can also access a kidney in some circumstances, for low-grade disease, percutaneously, which means basically you're going in through the back, directly into the kidney. And this can be useful for large tumors that are low-grade, in solitary kidneys in the renal pelvis. Although it does carry a little bit more risk, because you are creating a new access to the kidney.

The advantages of endoscopic approaches are that you're preserving kidney function, which in some people is really critical. If you look at some of the data, in terms of appropriately selected people, you do wind up having similar outcomes compared to nephroureterectomy. Outcomes may be improved, and I believe Dr. Lerner's going to touch base about this more, with the utilization of other options and other therapies.

The disadvantage is that it does really require a commitment from both the surgeon and the patient to do surveillance, which often requires going back to the OR periodically, doing imaging, and potentially retreating. And certainly, every time you access the urinary tract, you can create problems and scarring, which create risks, including multiple anesthesia events. Occasionally, when we have to leave a stent, that can create discomfort. A theoretical risk is that you can, if you're going in there repeatedly, because we're using pressurized fluid in the urinary tract, you can potentially push cells deeper into the kidney or elsewhere. So those are things just to be concerned about. What's really key here is the appropriate selection of patients.

In terms of other kidney-sparing approaches, they kind of break down into several categories, and one is what we call a segmental ureterectomy. That's really a fancy way of saying that you're cutting out part of the ureter and you're putting two ends back together. It's best for tumors that seem to be kind of in the middle to the upper third of the ureter, and that has to do with blood supply and how blood flows along the ureter, because in certain areas if you try to put the two ends back together, you'll get scarred because it's kind of a watershed area where the blood supply isn't very good.

Surgical Options: Kidney Sparing Approaches

Advantages of Endoscopic Approaches

- Kidney/renal function preservation
- Similar survival outcomes compared to nephroureterectomy (Seisen, 2016; Yakoubi, 2014)
- Outcomes may be improved with the utilization of intracavitary therapy

Disadvantages

- May require intensive surveillance strategies
- Risk of recurrence is high
- Repeated endoscopic interventions may create scarring
- Risk of multiple anesthetics
- Risk of stent discomfort
- Theoretical risk of seeding from use of pressurized irrigation

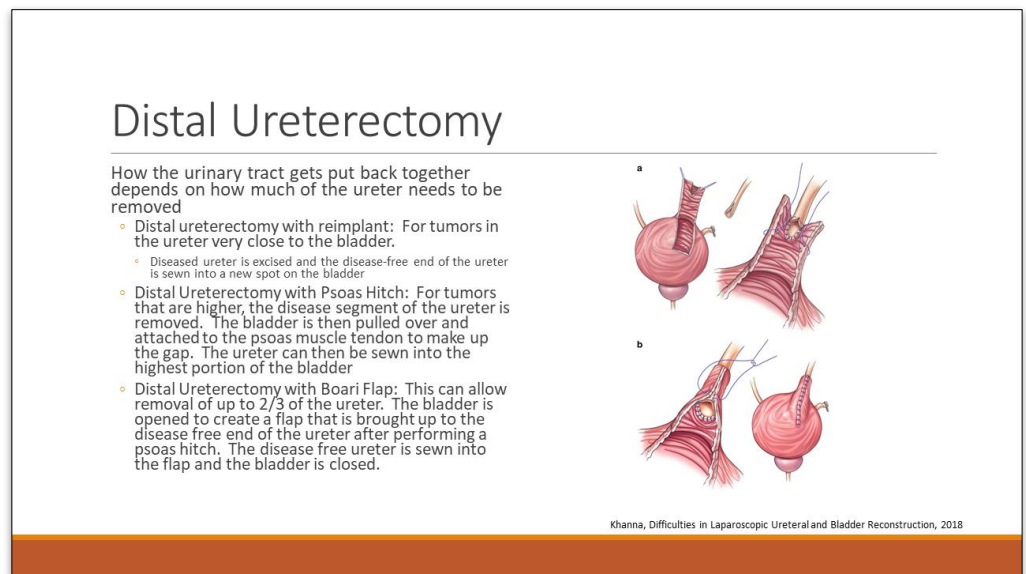
Surgical Options: Kidney Sparing Approaches

Segmental Ureterectomy: surgical excision of the diseased portion of the ureter with re-establishment of continuity of the urinary tract

- Segmental resection with re-anastomosis of the ureter
 - Best for tumors in the middle to upper third of the ureter
- Distal ureterectomy with or without reconstruction
 - Best for tumors in the bottom 1/3 of the ureter although can be used for longer segments of ureter
- Indications:
 - Similar indications to endoscopic therapy (best for low risk disease)
 - May be considered in patients with high risk disease with compromised kidney function or a solitary kidney
 - Size of the tumor, overall function of the kidney, and ability to perform a tension free reconstruction are critical considerations.
 - Used when endoscopic approaches are not feasible or fail

The other option for tumors that are in the bottom third of the ureter is to do a distal ureterectomy. This may or may not require reconstruction, depending on how much of the ureter you have to take out. I would say the indications are very similar to endoscopic therapy. It's best for low-risk disease, but you can consider it in patients with high-risk disease with compromised kidney function or a solitary kidney. The size of the tumor, the overall function of the kidney, and the ability to kind of put together things without tension for a reconstruction are really critical considerations. And it's used sometimes when endoscopic approaches are not feasible or they fail.

This is just some imaging kind of showing what we can do, in terms of the distal ureterectomy. It's not entirely accurate, because I couldn't find the best image for it, but the take-home message is that sometimes if the tumor is in the very bottom of the ureter, it's simple enough to just cut out that segment, including a small portion of the bladder, free up the bladder a little bit, and sew the ureter into another spot.



To get more length, sometimes what you wind up having to do is free up the bladder more, and you can actually tack it over onto the tendon of the psoas muscle, and that's called the psoas hitch. That allows you to bridge more of a gap, in case you have to take more ureter.

And then finally you can even take more ureter and bridge the gap by doing what's called a Boari flap, and essentially what that is, is raising a tongue of the bladder, flipping it up towards the kidney, and sewing the ureter to the end of that, and then closing up the bladder. And that sometimes can get you almost two-thirds of the way up to the kidney.

There are other options, in terms of reconstruction. You can replace the full ureter, if you have to take it out, with a segment of small intestine. That's called an ileal ureter. Certainly when you get to that point, it can be a lot more complicated.

The advantages of doing this are really the same as endoscopic approaches: you preserve kidney, and again, in appropriately selected people it can result in similar survival outcomes. But the risk is obviously when you're leaving part of the urinary tract on that side, there's a risk of recurrence. And obviously, the more complicated the reconstruction is, the more chance there is for scarring or complications related to that.

So briefly, to talk about nephroureterectomy, it's essentially the removal of the kidney and the entire ureter, including a cuff of bladder around the opening of the ureter into the bladder. That may be performed open, laparoscopically, or robotically. What I tell patients is that if you trust the surgeon, you go with the approach that that surgeon feels most comfortable with. Many people are doing these through minimally invasive approaches, and again, in appropriately selected patients. There's really not a lot of data that suggests that one performs better than the other, but if you trust your surgeon, you go with the approach that they're recommending.

Level 1 evidence does support putting a single dose of chemotherapy into the bladder at the time that you're doing a nephroureterectomy. The reason for that is to reduce the risk of bladder recurrence, which can be as high as 25 to 30%. What the chemotherapy does is essentially block some of those cells, that might be manipulated and go down the ureter as you're doing the kidney surgery, from implanting anywhere else in the bladder.

Surgical Options: Kidney Sparing Approaches

Advantages of Segmental Ureterectomy

- Kidney/renal function preservation
- Similar survival outcomes compared to nephroureterectomy

Disadvantages

- Risk of recurrence is 5-15%
- Complications: strictures, post-operative urine leak

Nephro-ureterectomy

Nephro-ureterectomy is the removal of the kidney and the entire ureter including a cuff of bladder around the opening of the ureter into the bladder.

May be performed open, laparoscopically, or robotically

Level 1 evidence supports the use of a single dose of intravesical chemotherapy to reduce the risk of bladder recurrence which can be as high as 25-30%.

Indications:

- High risk upper tract urothelial cancer (EAU Guidelines)
 - Hydronephrosis (blockage of the kidney)
 - High grade cytology or biopsy
 - Multifocal disease
 - Variant histology
 - Uncontrolled Bleeding from the tumor that cannot be managed endoscopically
- Consideration for neoadjuvant chemotherapy for high risk patients (or adjuvant chemotherapy)
- Lymph node dissection should be performed with nephroureterectomy (should also be considered for segmental resection)

Indications are obviously, this is more for high-risk upper tract disease, a hydronephrosis ... a blockage of the kidney ... a high-grade cytology or biopsy, multifocal disease, and variant histology. I would also say uncontrolled bleeding from the tumor that can't be managed endoscopically.

I believe Seth is going to talk about this a little bit more: consideration for new adjuvant chemotherapy for high-risk patients, or adjuvant chemotherapy. And then, I'm not going to drill down into it too much, but a lymph node dissection should be performed with nephroureterectomy, and it also should be considered for segmental resection.

So again, this is just some imaging. I would say most series demonstrate no difference in cancer control. Key driver of outcome is the surgeon, in following appropriate cancer surgical principles: clipping the ureter early during dissection, avoiding spillage of tumor, performing a lymph node dissection, and removing an appropriate bladder cuff.

Nephro-ureterectomy

Most series demonstrate no difference in cancer control between open, laparoscopic or robotic-assisted approaches

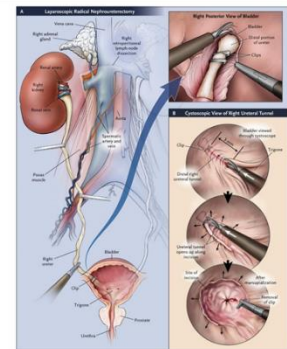
The key driver of outcomes is if the surgeon follows cancer surgery principles

- Clip ureter early during dissection
- Avoid spillage of tumor
- Perform a lymph node dissection
- Remove an appropriate bladder cuff

Advantage: ipsilateral cancer control

Disadvantage

- Loss of renal function
- Surgical risks
- Risk of recurrence in contralateral kidney and bladder



Dahl, NEJM, 2004

Advantage is obviously it's going to give you good ipsilateral cancer control. The disadvantage is loss of renal function, normal typical surgical risks, and the risk of recurrence in the contralateral kidney and the bladder, which is low.

And I think at that point, I'm done, and I'm going to hand it over to Dr. Lerner. Thanks.

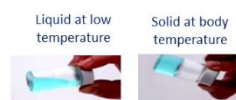
Dr. Lerner: Probably one of the more common scenarios we deal with is low-grade upper tract urothelial carcinoma, so these have a tendency to be multiple throughout the kidney pelvis or ureter. They're non-invasive, they're low-grade, so they're not a real threat to spread, but they oftentimes result in a requirement for removal of the kidney and ureter to control the disease.

Recently we completed a clinical trial with a company, UroGen. I do have a conflict as both a consultant, and I was scientific principal investigator of the trial that led to the FDA approval of a product called Jelmyto. This is a combination of a reverse thermal gel, which you can see in the figure there. At cold temperature, say at an icebox, it's a liquid that's injectable through a

Low Grade UTUC

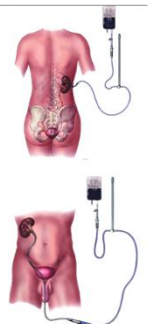
JelMyto – FDA approved April 2020

- Can be administered through a retrograde catheter or nephrostomy tube
- MitomycinC (MMC) admixed with thermoreversible gel
- MMC released over 4-6 hours



Other chemotherapy options

- Gemcitabine, Mitomycin C (without gel)



ureteral catheter or a nephrostomy tube. And then at body temperature, it forms a semisolid material that is combined with mitomycin C.

And so what that does is it provides a very long exposure to a chemotherapy drug that we know is quite effective in low-grade disease of the lower urinary tract, and solves a problem of drug retention in the kidney. In the bladder we don't have a problem because you can hold a volume in the bladder for two hours. You can't do that in the kidney because of gravity. This solves that problem, and it led to a 59% complete response rate of a measurable tumor in the kidney, somewhere between five and 15 millimeters. The approval is for low-grade disease.

Now, if this is not available or not possible to administer, other chemotherapy drugs ... mitomycin by itself, gemcitabine ... are also effective, and can be administered, as you see in this graphic here, through a nephrostomy tube, so that's a tube that goes through the side, directly into the kidney, or through a catheter that we put in from the bladder back into the kidney. And so we now have a new standard of care and a treatment option that, for many patients, may help them spare the kidney.

This is a slide that I borrowed from Phillip Pierorazio from Hopkins for another program that we did, and I'm addressing high-grade disease now, again, non-invasive. So again, we have an option here, particularly in patients who have carcinoma in situ, so this is a flat, high-grade lesion, very similar to what we see in the bladder, and you can access the kidney much like Dr. Weizer described. We can biopsy it, we can see, we can get cytologies, and if we have a diagnosis of CIS, we can treat using these same techniques through a nephrostomy tube or a ureteral catheter by giving BCG up into the kidney pelvis, using the same schedule that we do in the bladder.

High Grade Non-Invasive UTUC

- Intracavitary BCG
 - Similar schedule as for bladder cancer
 - 6 weekly treatments; consider maintenance
- Many challenges
 - BCG supply
 - Poor quality and inconsistent efficacy data¹
 - BCG: response rates 64–100% in CIS³
- Mode of delivery⁴
 - Lack of dwell time
 - Need reliable access to the upper tract
- Complications^{1,3}

1. Carmignani L, et al. Rev Urol. 2013;15:145-53.
2. Mostafid AH, et al. BJU Int. 2020 Jun;125:817-826.
3. Park BH, Jeon SS. Korean J Urol. 2013;54:426-32.
4. Mandalapu RS et al. World J Urol. 2017;35:355-65.

Courtesy Phil Pierorazio, MD

The problems are multiple, as you can imagine. BCG supply; we've got to have BCG in order to do it. We have the issue of retention. There's no high-level evidence really supporting this, but we do know that you can get initial complete response rates that are quite high for patients with CIS. You have to be very, very careful in administering this in the upper urinary tract because if BCG gets into the lymphatic or blood circulation, there have been really catastrophic complications associated with this, although not so much in more contemporary treatment, so contemporary times. It's effective if it's available, and it's another option for our patients.

Dr. Lerner: For a high-grade invasive disease, we're presented with a similar issue that we have in muscle invasive bladder cancer, where there's an increased risk of spread to the lymph nodes that drain the kidney, and then lung, liver, and bone, so microscopic or micrometastatic disease. And we have high-level evidence supporting the combination of chemotherapy plus surgery, removal of the bladder, for bladder cancer. We don't have the similar high-level evidence in the upper urinary tract, but we've

extrapolated to begin incorporating this and doing clinical trials to address the utility of giving chemotherapy, either before or after, say, removal of the kidney and/or ureter.

There's a number of things that we can do to identify patients that are at high-risk, so certainly a high-grade biopsy; a sessile, meaning a nodular tumor rather than a papillary tumor; and then we can use some of the findings on CT or MRI to give us a sense that this may be a more invasive cancer that we might perceive endoscopically. Or with ureteroscopy.

The idea of giving chemotherapy first is that's when there's optimal kidney function. We've got two kidneys in place, and that's the time to give the chemotherapy upfront. Complete response rates are not the same as what they are in the bladder, so we have in the bladder somewhere between 35 and 40% complete response rates. Most retrospective series have reported between 12 and 15, and depending upon the chemotherapy regimen, as high as maybe one-third. But you don't see

any complete response rate without chemotherapy. Where you see this, about 10 to 15% of the time in the bladder, because the surgeon's been able to remove the tumor with the transurethral resection.

Integration of Systemic Therapy – Neoadjuvant Cisplatin-Based Chemotherapy

Based in part on Level I evidence for patients with muscle invasive bladder cancer

Can identify patients at increased risk for locally advanced and/or micrometastatic disease

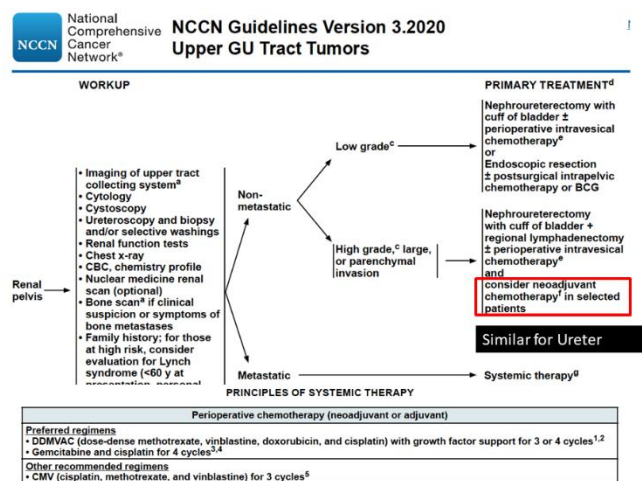
- High grade, sessile, CT/MRI appearance

Treat at time of maximal renal function prior to removal of kidney and ureter

Complete response rates 12-38% vs. 0% without chemotherapy

So the guidelines actually do support the use of neoadjuvant chemotherapy for both renal pelvis and for ureteral cancer. So again, the level of evidence isn't as high as it is in the bladder, but it's a recognition that we have a similar situation where the risk of occult, or undetectable metastatic disease, that ultimately will result in progression and potentially a mortality from that.

These are the regimens, the same regimens that we use in the bladder, dose-dense MVAC, which is a four drug combination, or the two drug combination of gemcitabine cisplatin.



What about giving treatment after surgery? Let's say we did not give chemotherapy beforehand, but now we have evidence of a higher risk cancer, so high-grade, invasive, potentially even positive lymph nodes. As Dr. Weizer indicated, we always do a lymph node dissection when we do a nephroureterectomy or a distal ureterectomy. And again, based upon the perceived benefit in muscle invasive bladder cancer, preferred now because we've got pathologic staging: we know exactly what the patient has, and can risk stratify on that basis. And again, the level of evidence.

Adjuvant Therapy - Rationale

Also based in part on perceived benefit in muscle invasive bladder cancer

Lack of accuracy of clinical staging

Pathologic staging identifies patients most likely to benefit

Lack of high-level evidence supporting peri-operative systemic therapy

EAU Guidelines: nephroureterectomy followed by surveillance

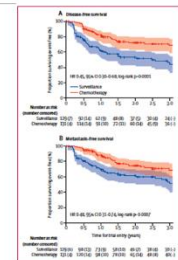
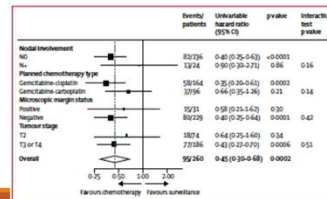
Now the EAU guidelines generally recommend nephroureterectomy followed by surveillance, but you can see from the NCCN guidelines, which are followed typically in the United States, the AUA, the American Urological Association, does not have guidelines for upper tract disease.

The POUT trial was conducted in the UK, and this was a randomized phase three trial of giving chemotherapy after nephroureterectomy. You can see by the figures on the right that there was a clear benefit to the chemotherapy. That's in the red, versus the blue that did not have chemotherapy. They did subgroup analysis, which is this box on the bottom left, and they saw a benefit both in cisplatin combination therapy ... but not so much with carboplatin-based chemotherapy, but the study was not powered to address that question.

POUT Trial

Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial

Alison Biale, Mark Johnson, John Christie, Robert Jones, David Dalling, Richard T Bryan, Christopher Harris*, Andrew Winterbottom*, Anthony Blaker, James W F Catto, Pradeep Chaudhary, Jenny L. Donawick, Paul Anthony Elliott, Ann French, Satinder Jagpal, Benjamin Jenkins, Francis Xavier Keeley, Roger Kockelbergh, Thomas Poules, John Wagstaff, Caroline Wilson, Rachel Todd, Rebecca Lewis, Emma Hall



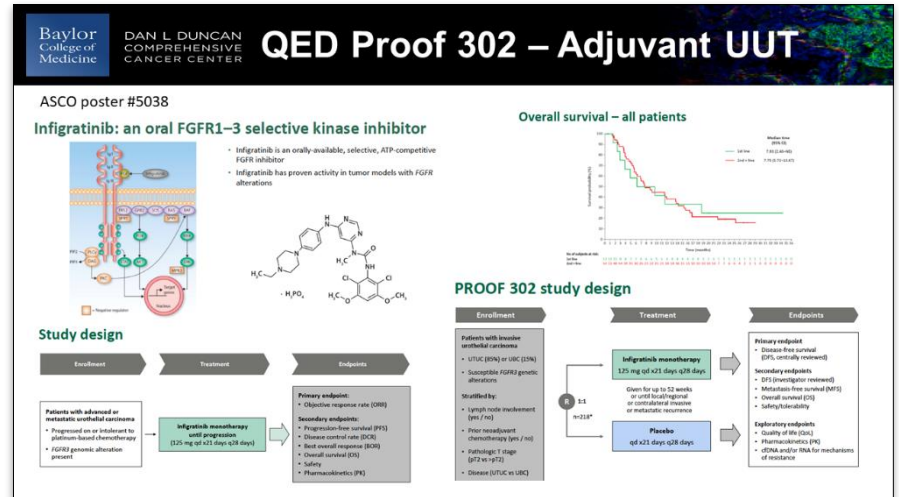
Level I evidence clear benefit

So now we have high-level evidence supporting the use of chemotherapy after surgery for both patients who are platinum-eligible and platinum-ineligible. Okay, so that's a standard of care conducted by this trial in the UK. We're still very interested in conducting clinical trials, and I'll get to the next one, and Dr. Pal might speak to this during his talk.

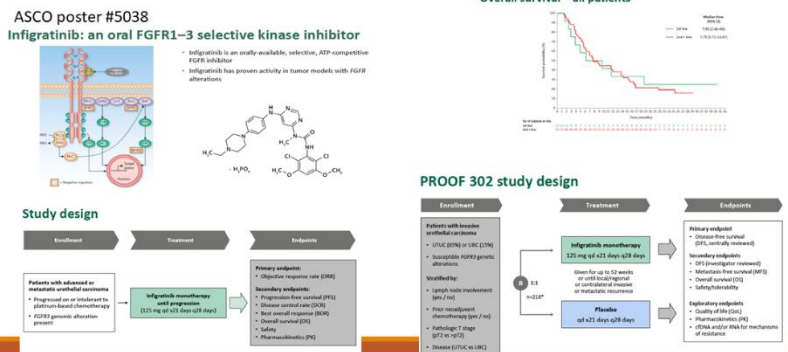
I'm an advisor to QED, who has a drug called infigratinib, and it targets FGFR 1 through 3, and we know that FGFR alterations in upper tract disease can occur as often as, say, 40, 50, and even 60% of patients, whereas in the bladder, it's less frequent, maybe around 20 to 25%.

So they did an early trial in advanced disease, metastatic disease, and showed in both first-line and second-line therapy, that's the Kaplan-Meier curve in the top right, that there is evidence of activity. And so they've now designed a trial that's being led by Monty Pal and Sia Daneshmand, called Proof 302; the Society of Urologic Oncology Clinical Trials Consortium's playing a major role in this. And it's taking high-risk patients after nephroureterectomy that have an FGFR3 alteration, and treating those patients with infigratinib, the targeted agent, or placebo. So this may give us the potential for a new therapy for patients after this surgery.

I just want to speak to this. This is a patient of mine that I've taken care of recently, who had no Lynch Syndrome, and actually Dr. Matin had done a nephroureterectomy on the other side 10 years ago. She presented to our hospital in renal failure, gross hematuria, obstructed left kidney. Put a nephrostomy tube in. Ultimately we were able to make the diagnosis of very large volume, high-grade disease. She had a positive node by PET/CT, and



QED Proof 302 – Adjuvant UUT



Lynch Syndrome

- Pembrolizumab approved for patients with unresectable or metastatic Microsatellite instability high or Mismatch repair deficient solid tumors
- Consider when solitary kidney
- 59yo F – known Lynch
- 10yrs ago right NXU renal pelvis ca
- New gross hematuria
- Left kidney obstructed; ARF; PCN placed
- URS – multiple (3) HG sessile tumors; Bx T1HG; cN1 by PET/CT
- Renal function nl
- Refuses NX
- Pembrolizumab n=18 15+ months
- URS x 2 no visible tumor; bx neg

declined having a nephrectomy, which obviously would have put her on dialysis.

So on the left, we see that one of the immunotherapy drugs that's approved in advanced bladder cancer, pembrolizumab, is approved for patients with unresectable or metastatic microsatellite instability, high or mismatch repair deficient solid tumors, essentially the hallmark of Lynch Syndrome. And so, we've had her on pembro now for about a year and a half. I biopsied her twice, and she's got negative disease, so this is a unique situation for those patients.

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