

Urothelial tumors of Renal Pelvis and ureter

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Epidemiology

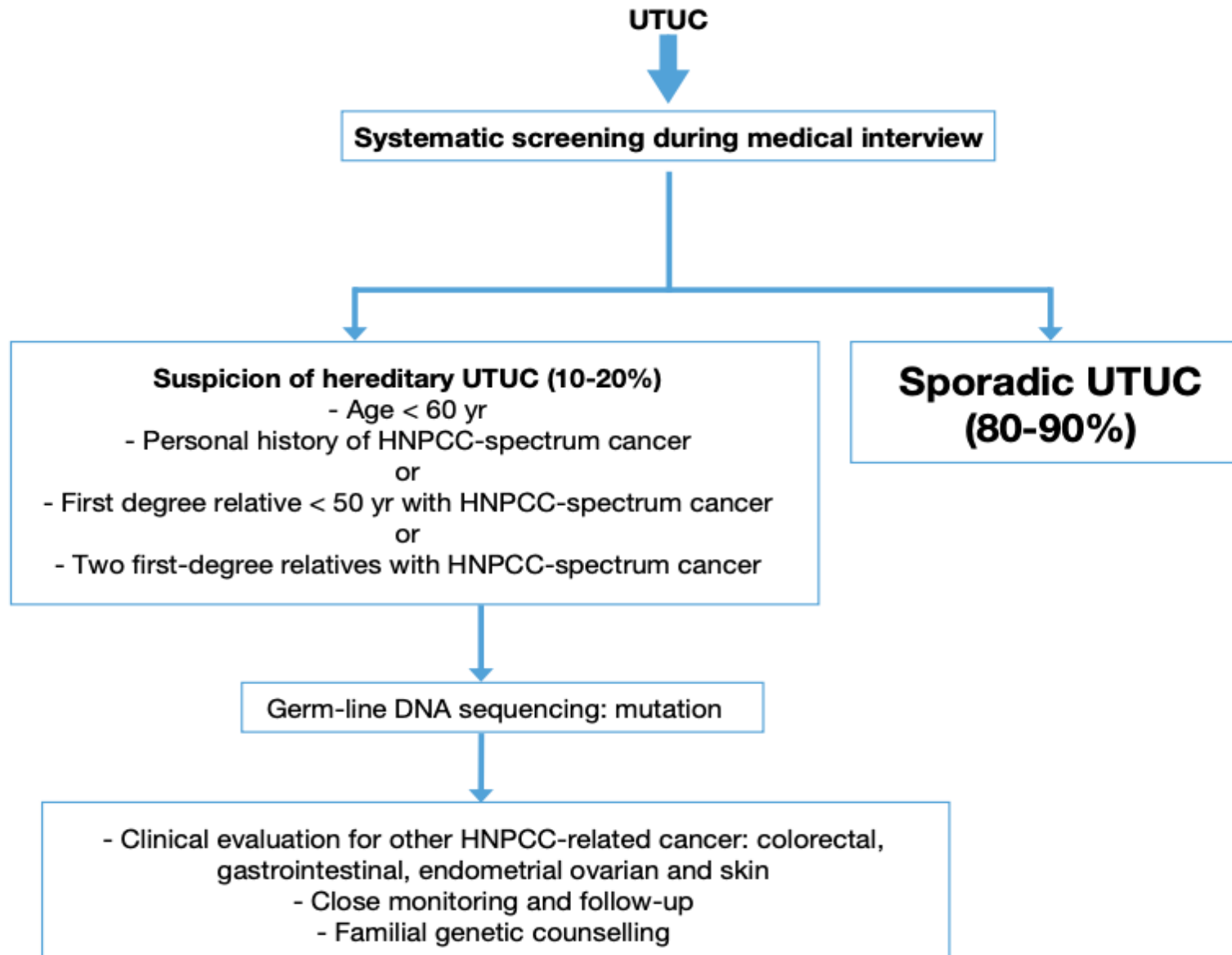
- Tumors of the renal pelvis account for approximately 10% of all renal tumors and only 5% of all urothelial tumors of the urinary tract.
- Ureteral tumors occur about one half as often as tumors located in the renal pelvis.
- Urothelial carcinomas account for more than 95% of urothelial tumors of the upper urinary tract followed by Squamous cell and adenocarcinoma variant.

- The mean age for upper urinary tract urothelial tumors is 65 years. The peak incidence is seen in 7th and 8th decade.
- Male-to-female ratio 3:1.
- Upper tract urothelial tumors are twice as common in white people as in people of African descent.
- Unlike bladder cancer, in which 80% of tumors are noninvasive, only 40% of upper tract tumors are noninvasive.

Etiology

- Tobacco smoking is associated with more than 3-fold increased risk
- Analgesic abuse is also a risk factor for UTUC. It is independent from and synergistic with renal papillary necrosis.
- Occupational exposure to agents used in the petrochemical, plastic, and tar industries has been linked to an increased risk of UTUC.
- UTUC is associated with Balkan nephropathy
- Urothelial carcinoma is associated with Lynch syndrome type II
- Squamous cell variant accounts for 1-7% of total cases is associated with staghorn calculi

- Losses of *P53*, *P19*, and *P16* are associated with low-grade cancers, while a loss of *RB1* has been associated with higher-grade, more aggressive
- high levels of MSI seem to correlate with a more favorable prognosis, particularly in younger patients with T2 or T3/N0 disease.
- E-cadherin, hypoxia-inducible factor-1 α , Ki-67, survivin (a protein apoptosis inhibitor), epidermal growth factor receptor (EGFR), and telomerase RNA component have been identified as independent markers of advanced disease and/or prognosis.
- Survivin has been measured in the urine of patients with urothelial carcinoma of the bladder and was found to be highly sensitive and specific for the presence of this malignancy.



Patterns of Spread

- Urothelial tumors spread conventionally in a cephalad to caudad direction.
- Approximately 30-75% of patients with UTUC develop Bladder Tumors
- The risk of UTUC in patients with a bladder malignancy is 2-4%
- Lymphatic extension
 - The most common locations for spread, depending on the site of the primary tumor, include paraaortic, paracaval, ipsilateral common iliac, and the pelvic lymph nodes (for distal ureteral tumors).
- Hematogenous seeding also occurs, with the liver, lung, and bone being the most common sites for metastases.

Rates of distribution for UTUC

- Renal pelvis: 58%
- Ureter: 35% (73% of which are located in the distal ureter)
- Both renal pelvis and ureter: 7%
- Bilateral: 2-5%

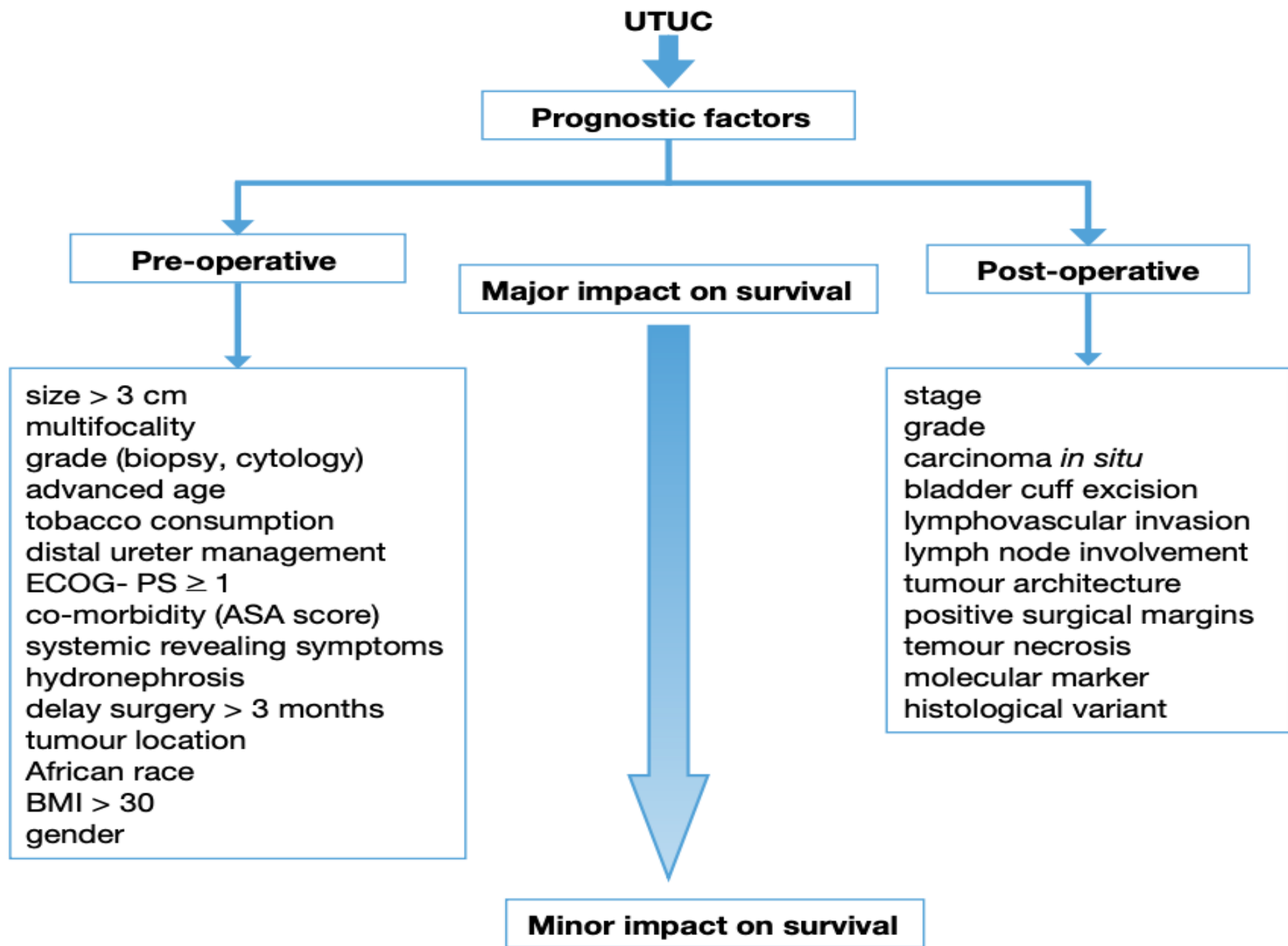
Presentation

- Gross or microscopic hematuria - 75% of patients; the most common clinical finding
- Flank pain - 20% of patients; results from gradual obstruction/distention of the collecting system or, in cases of acute colic, from obstruction by a blood clot
- Dysuria or irritative voiding symptoms - 6% of patients
- Weight loss, anorexia, flank mass, or bone pain - manifestations of advanced disease that manifest in a minority of patients

Diagnostic Recommendations

Recommendations	GR
Urinary cytology should be performed as part of a standard diagnostic work-up.	A
A cystoscopy should be done to rule out concomitant bladder tumour.	A
CTU must be part of the diagnostic work-up.	A
Diagnostic ureteroscopy and biopsy should be performed, certainly in cases where additional information will impact treatment decisions.	C
Retrograde ureteropyelography is an optional tool for the detection of UTUC.	C

CTU = computed tomography urography; GR = grade of recommendation.



Staging (AJCC / TNM 2009)

- **Primary tumor categories are as follows:**

- TX - Primary tumor cannot be assessed
- T0 - No evidence of primary tumor
- Ta - Papillary noninvasive carcinoma
- Tis - Carcinoma in situ
- T1 - Subepithelial connective tissue invasion (lamina propria invasion)
- T2 - Muscularis invasion
- T3 – For renal pelvis only: Tumor invades beyond muscularis into peripelvic fat or the renal parenchyma
- T3 - For ureter only - Tumor invades beyond muscularis into periureteric fat
- T4 - Tumor invades adjacent organs, or through the kidney into the perinephric fat

- **Regional lymph node categories are as follows:**

- NX - Regional lymph nodes cannot be assessed
- N0 - Negative nodes
- N1 - Metastasis ≤ 2 cm in greatest dimension in a single lymph node
- N2 - Metastasis > 2 cm in a single lymph node, or multiple lymph nodes

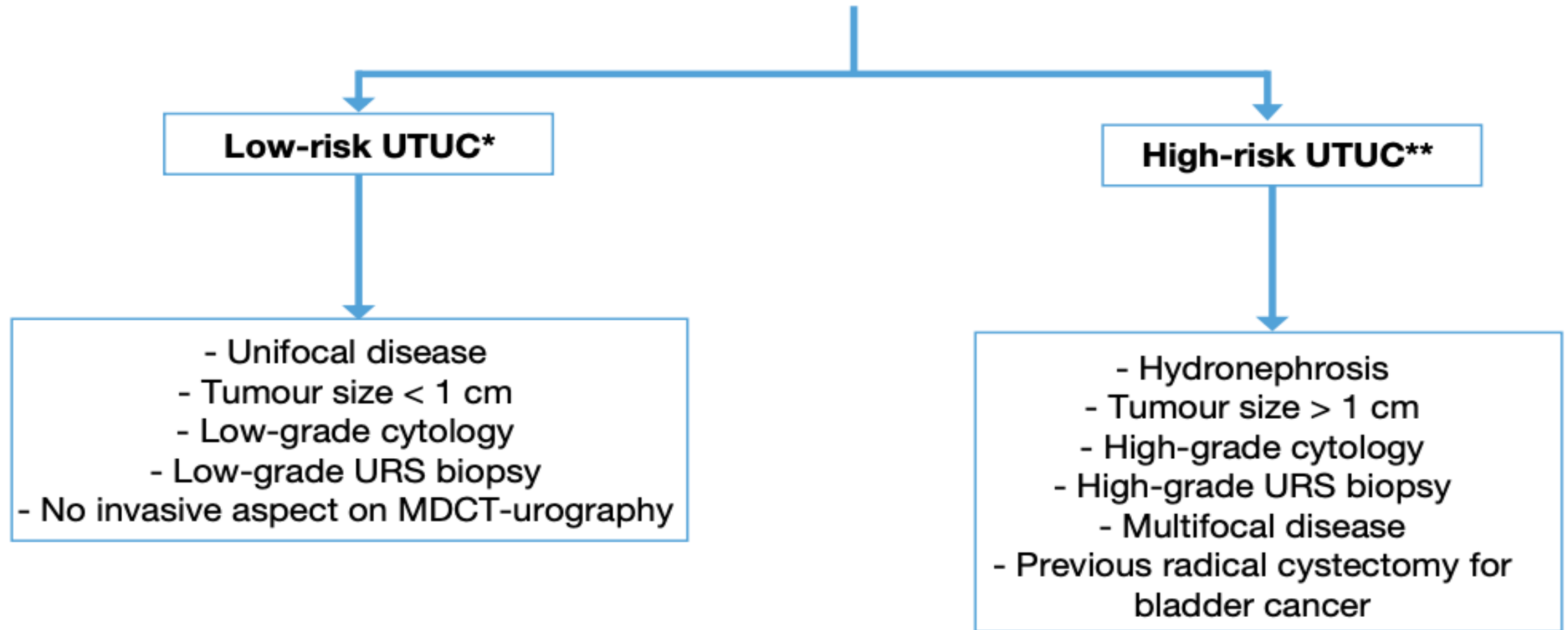
- **Distant metastasis categories are as follows:**

- M0 - No distant metastasis
- M1 - Distant metastasis

American Joint Committee on Cancer Prognostic Group

Stage	Tumor	Node	Metastasis
0a	Ta	N0	M0
0is	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
IV	T4	NX, N0	M0
	Any T	N1	M0
	Any T	N2	M0
	Any T	Any N	M1

UTUC



** All of these factors need to be present*

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MDCT = multidetector-row computed tomography; URS = ureterorenoscopy.

Surgical management

- European Association of Urology (EAU) indications of low risk are all of the following:
- Unifocal tumor
- Tumor size < 2 cm
- Low-grade cytology
- Low-grade ureteroscopic biopsy
- No evidence of an invasive lesion on CT urography
- The EAU recommends offering kidney-sparing surgery as the primary treatment option for these low-risk tumors.

- Flexible ureteroscopy can be considered if complete tumor resection, laser ablation, or destruction can be achieved, but a risk of understaging and undergrading remains and closer, more stringent surveillance is needed.
- Segmental ureteral resection with wide margins provides adequate pathological specimens for staging and grading while preserving the ipsilateral kidney and permitting lymphadenectomy.
- Complete distal ureterectomy and neocystostomy is indicated for noninvasive, low-grade tumors in the distal ureter that cannot be removed completely via endoscopy.

High grade tumors management

- Radical nephroureterectomy is the only potentially curative treatment for most patients with urothelial carcinoma of the renal pelvis or ureter.
- Radical nephroureterectomy includes removal of the contents of Gerota fascia, including the ipsilateral ureter with a cuff of bladder at its distal extent.
- For both renal pelvis and ureter tumors, once the pathologic staging is obtained, patients with pathologic stage pT2, pT3, pT4, or N+ should be considered for adjuvant chemotherapy with or without radiotherapy.
- Neoadjuvant chemotherapy may be considered in selected patients.

Lymph node dissection

- In a retrospective analysis of 169 patients who underwent nephroureterectomy for non-metastatic upper tract urothelial carcinoma, Kondo et al reported a definite survival advantage in lymph node–positive patients with higher T stages, namely pT3 and above, who underwent a complete lymphadenectomy. Multivariable analysis showed that complete lymphadenectomy was a significant prognostic factor for cancer-specific survival ($P = 0.009$) as well as T stage (pT3 or less, $P = 0.0004$) and tumor grade (G3, $P = 0.0001$).

Matin et al

- A multi-institutional retrospective study by Matin et al identified characteristic patterns of lymph node metastasis in UTUC, depending on the side and anatomical location
- For tumors in the right pelvis and upper ureter,
 - a dissection template encompassing the right hilar, paracaval, and retrocaval regions will remove 82.9% of the involved lymph nodes. Adding the inter-aortocaval region to the template will improve coverage to 95.8%.
- For left-sided pelvic tumors,
 - removal of hilar and para-aortic lymph nodes will ensure removal of 86.9% of the involved nodes. Adding inter-aortocaval lymph nodes will increase the coverage to 90.2% of involved nodes.
- The lower limit is the inferior mesenteric artery. For upper ureteric tumors, dissection should extend up to the aortic bifurcation.
- For distal ureteric tumors,
 - pelvic template dissection involving the common iliac, external iliac, obturator, and internal iliac nodes will remove 75% of involved nodes on the right side and 83.3% of involved nodes on the left side.
 - However, adding paracaval groups for tumors on the left side and para-aortic groups for those on the right side will improve coverage to almost 100%.

Systemic Agents

MitoGel™

- MitoGel™ (Mitomycin C Sustained release solution) received FDA Approval for treatment in adults with low grade UTUC following *OLYMPUS Study*.
- *OLYMPUS* a single arm , multicenter phase three clinical trial of patients with treatment naïve or recurrent low grade non invasive UTUC.
- Of 71 Patients 59% showed complete response at primary response evaluation visit (95% CI 41 -71%; p <0.0001).
- CR at 6 and 12 months were estimated at 89% and 84%.
- NCCN Recommends use of MitoGel™ in low grade non invasive UTUC following endoscopic ablation/resection.

Reference	Study design	Outcome	Number of patients enrolled
Leow JJ, Martin-Doyle W, Fay AP, et al. 2014	Systematic review and meta-analysis	Pooled hazard ratio (HR) for overall survival (OS) was 0.43 (95% confidence interval [CI], 0.21–0.89; P = 0.023) for adjuvant therapy group compared with controls without adjuvant therapy	Prospective study (n = 36) investigating adjuvant carboplatin–paclitaxel and nine retrospective studies, with a total of 482 patients receiving cisplatin-based or non-cisplatin–based AC after nephroureterectomy
Porten S, Siefker-Radtke AO, Xiao L, et al. 2014	Retrospective review between neoadjuvant chemotherapy group and initial surgery group	Neoadjuvant chemotherapy had improved OS and disease-specific survival (DSS) with a 5-year DSS rate of 90.1% and a 5-year OS rate of 80.2% versus DSS and OS rates of 57.6% for those who underwent initial surgery (P = 0.0204 and P = 0.0015, respectively)	Neoadjuvant chemotherapy

<p>uang YC, Chen MF, Shi CS, et al. 2015</p>	<p>Retrospective review of patient records with pT3N0M0 upper tract urothelial carcinoma (UTUC) treated with radical nephroureterectomy and adjuvant therapy versus control group</p>	<p>Statistically significant differences were found between the adjuvant and control groups in 5-year cancer-specific survival rates (80.5% vs 57.6%, P = 0.010) and recurrence-free survival rates (74.4% vs 52.9%, P = 0.026), but no statistically significant difference in overall survival (71.9% vs 49.0%, P = 0.072)</p>	<p>Postoperative adjuvant chemotherapy (n= 60) vs surgery only (n=111)</p>
<p>Urakami S, Yuasa T, Yamamoto S, et al.2015</p>	<p>Retrospective analysis of clinicopathological response to induction chemotherapy and identification of prognostic factors for OS</p>	<p>Clinically objective response to the induction chemotherapy occurred in 75% of patients. Histopathological analysis indicated pT0 status in 20% and pN0 in 33%. Clinical tumor response correlated significantly with achievement of pathological complete response</p>	<p>60 urothelial cancer patients; primary cancer site was the urinary bladder (n= 31; 52%) and upper urinary tract (n=29; 48%)</p>

<p>Lucca I, Kassouf W, Kapoor A, et al. 2015</p>	<p>Retrospective analysis of data of patients with lymph node (LN)-positive UTUC, who underwent full surgical resection followed by adjuvant chemotherapy (AC)</p>	<p>In all patients (T(all) N+), administration of AC had no significant impact on UTUC-related mortality on univariable ($P = 0.49$) and multivariable ($P = 0.11$) analysis. Further stratified analyses showed that only N+ patients with pT3-4 disease benefited from AC. In this subgroup, AC reduced UTUC-related mortality by 34% ($P = 0.019$).</p>	<p>263 patients with LN-positive UTUC underwent full surgical resection. Study group ($n=107$, 41%) received three to six cycles of AC, while controls ($n=156$; 59.3%) were treated with RNU alone</p>
<p>Kim DK, Kim JW, Jung HD, et al. 2019</p>	<p>Systematic review and meta-analysis of adjuvant therapy after radical nephroureterectomy (RNU) in patients with locally advanced UTUC</p>	<p>Compared with patients who underwent RNU only, those who received adjuvant chemotherapy after RNU had HRs for disease-free survival of 0.59 ($P = 0.001$), cancer-specific survival of 0.73 ($P = 0.02$), and OS of 0.84 ($P = 0.02$)</p>	<p>11 studies, comprising 1496 patients who underwent RNU alone and 798 patients who received ACH after RNU</p>

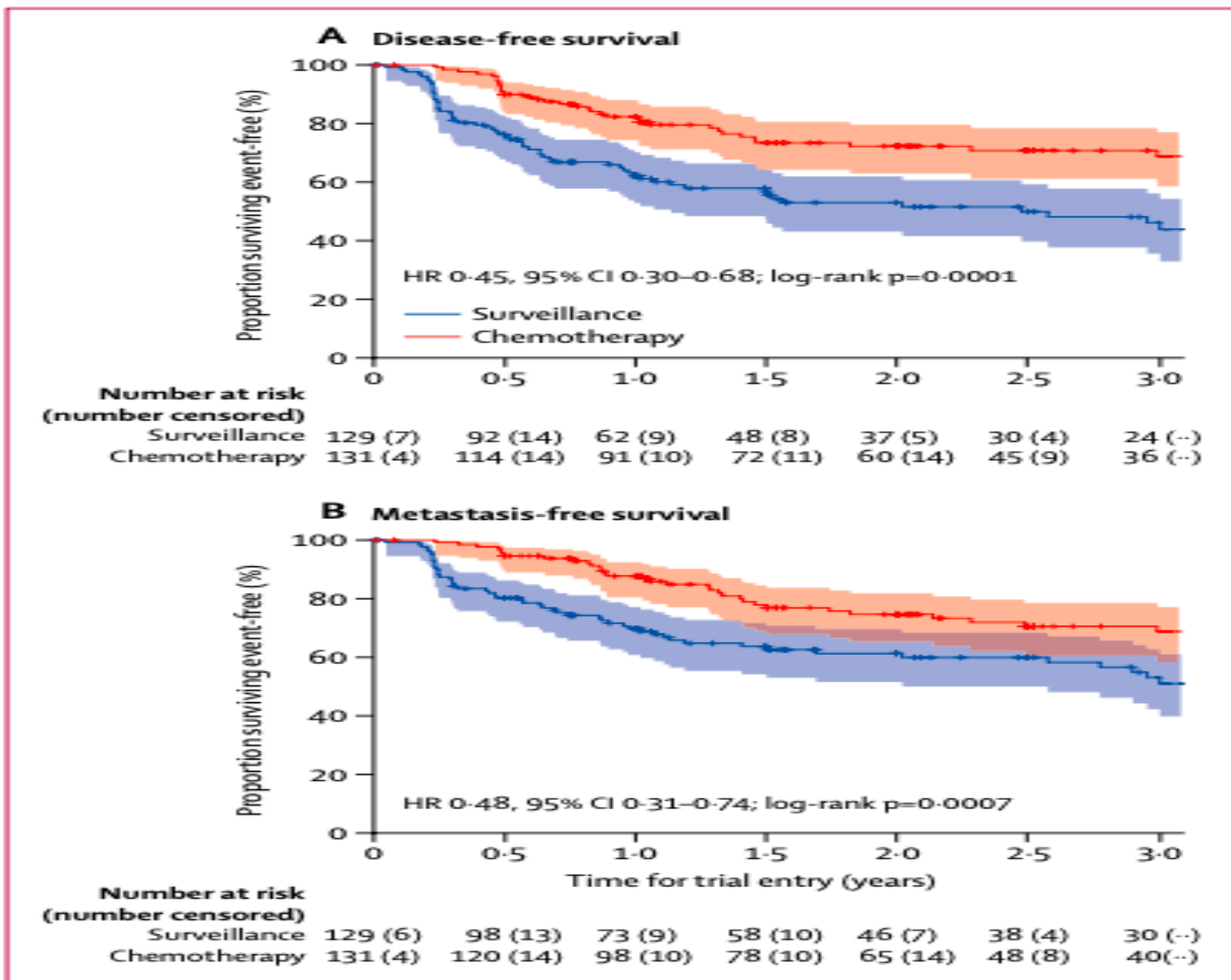
Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial

[Alison Birtle, MD](#)   • [Mark Johnson, MD](#) • [Prof John Chester, PhD](#) • [Prof Robert Jones, PhD](#) • [David Dolling, PhD](#) • [Richard T Bryan, PhD](#) • et al. [Show all authors](#) • [Show footnotes](#)

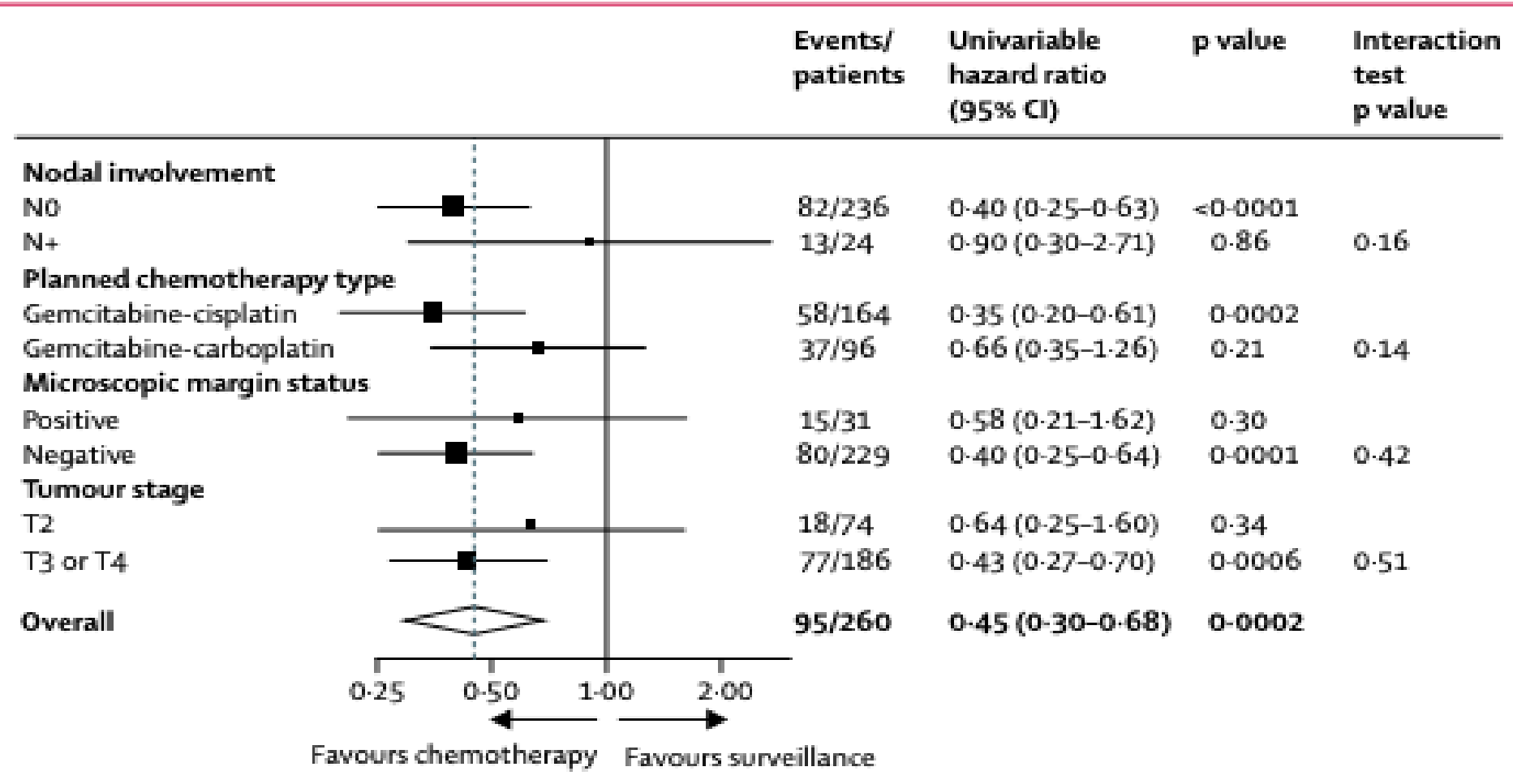
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- Between June 19, 2012, and Nov 8, 2017, 261 participants from 57 of 71 open study sites were enrolled.
- 132 patients were assigned chemotherapy and 129 surveillance.
- Adjuvant chemotherapy significantly improved disease-free survival (hazard ratio 0.45, 95% CI 0.30–0.68; $p=0.0001$) at a median follow-up of 30.3 months (IQR 18.0–47.5). 3-year event-free estimates were 71% (95% CI 61–78) and 46% (36–56) for chemotherapy and surveillance, respectively. 55 (44%) of 126 participants
- Who started chemotherapy had acute grade 3 or worse treatment-emergent adverse events, which accorded with frequently reported events for the chemotherapy regimen. Five (4%) of 129 patients managed by surveillance had acute grade 3 or worse emergent adverse events. No treatment-related deaths were reported.



Disease-free survival and metastasis-free survival



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

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- **Conclusion**
- Gemcitabine–platinum combination chemotherapy initiated within 90 days after nephroureterectomy significantly improved disease-free survival in patients with locally advanced UTUC. Adjuvant platinum-based chemotherapy should be considered a new standard of care after nephroureterectomy for this patient population.

Adjuvant RT

- ????????

- There are no randomized trials on the role of postoperative RT in patients who have had a complete resection of an upper urinary tract cancer
- Cozad et al. reported a retrospective study of 94 patients with urothelial carcinoma of the renal pelvis, of which 77 had resections without residual. On multivariate analysis, adjuvant RT had a significant effect on local control ($P = .02$). In terms of survival, the use of adjuvant radiation therapy was of borderline significance ($P = .07$). Of the 27 patients that were excluded from local failure and survival analysis, 19 had unresectable local disease and of these 11 received radiation therapy. Two long-term disease-free survivors in this group received 45 and 50.4 Gy
- The authors recommended consideration of adjuvant radiotherapy in patients with high grade or stage, close surgical margins, or positive lymph nodes to improve local control.

Cozad et al

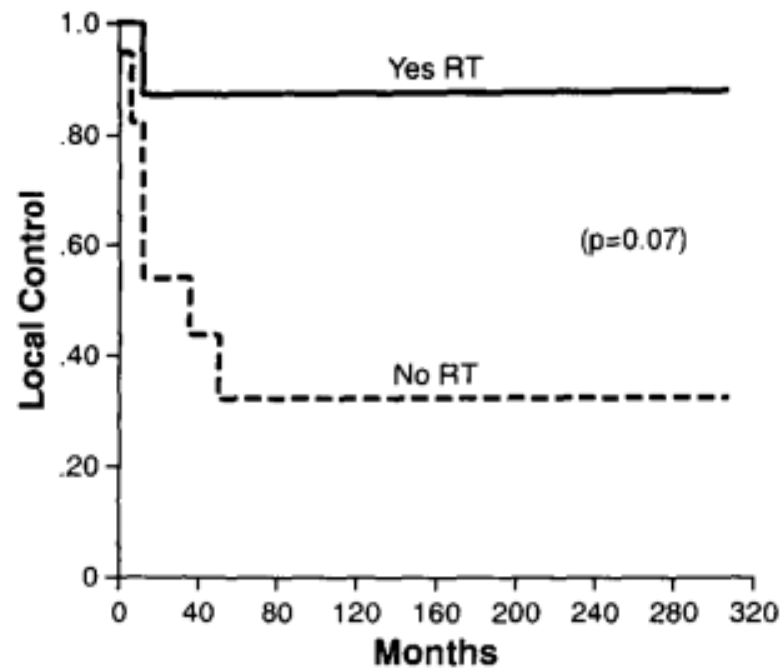


Fig. 1. Kaplan-Meier curves for local control comparing radiation therapy (n = 9) to no radiation (n = 17).

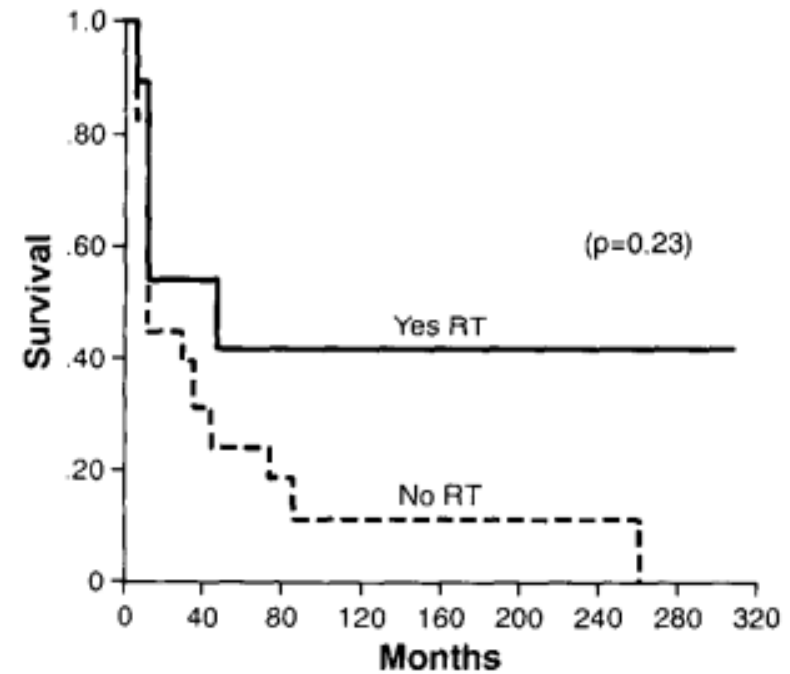


Fig. 2. Kaplan-Meier survival curves comparing adjuvant radiation (n = 9) to no adjuvant radiation (n = 17).

Adjuvant radiotherapy with and without concurrent chemotherapy for locally advanced transitional cell carcinoma of the renal pelvis and ureter

Brian Czito ¹, Anthony Zietman, Donald Kaufman, Uri Skowronski, William Shipley

Affiliations + expand

PMID: 15371822 DOI: 10.1097/01.ju.0000137910.38441.8a

TABLE 2. Treatment outcomes in patients with resection and postoperative RT with or without concurrent chemotherapy

	No. Pts	% 5-Yr Survival	% 5-Yr Local Failure	% 5-Yr Disease Specific Survival	% 5-Yr Metastases-Free Survival
Overall	31	39	33	52	48
RT	22	27	45	41	38
RT + chemotherapy	9	67	22	76	67
p Value		0.01	Not significant	0.06	Not significant

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Adjuvant Treatments for Advanced Stage, Non-metastatic Upper Tract Urothelial Carcinoma: A Multicenter Study

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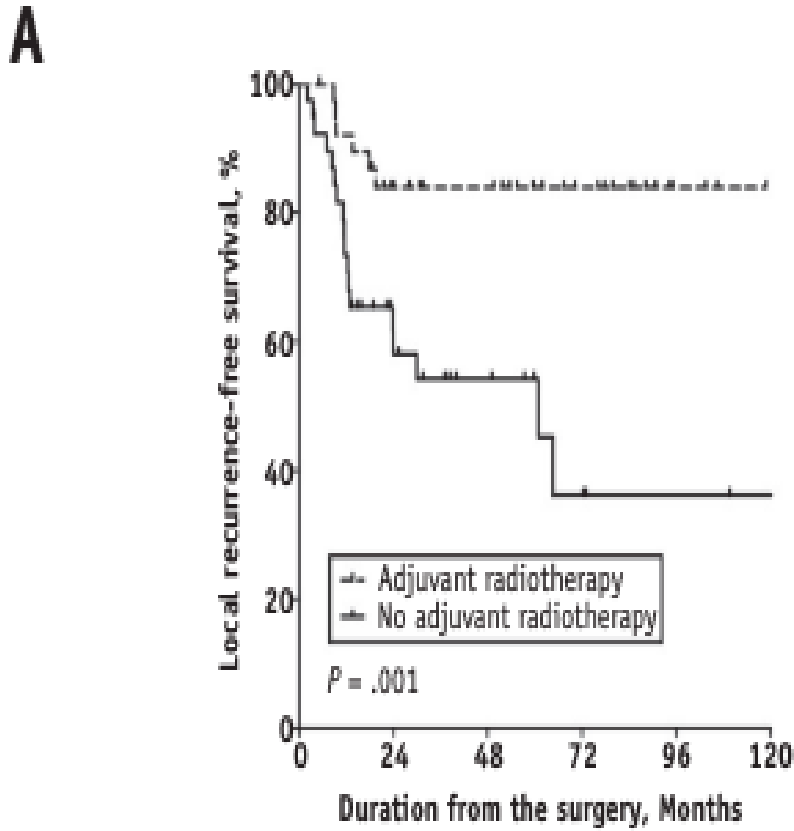
Published: March 25, 2019 • DOI: <https://doi.org/10.1016/j.ijrobp.2019.03.027> •



Purpose: We assessed the efficacy of adjuvant treatments in patients with peripelvic/periureteral fat-infiltrating (pT3b), nonmetastatic upper tract urothelial carcinoma (UTUC) treated with radical nephroureterectomy.

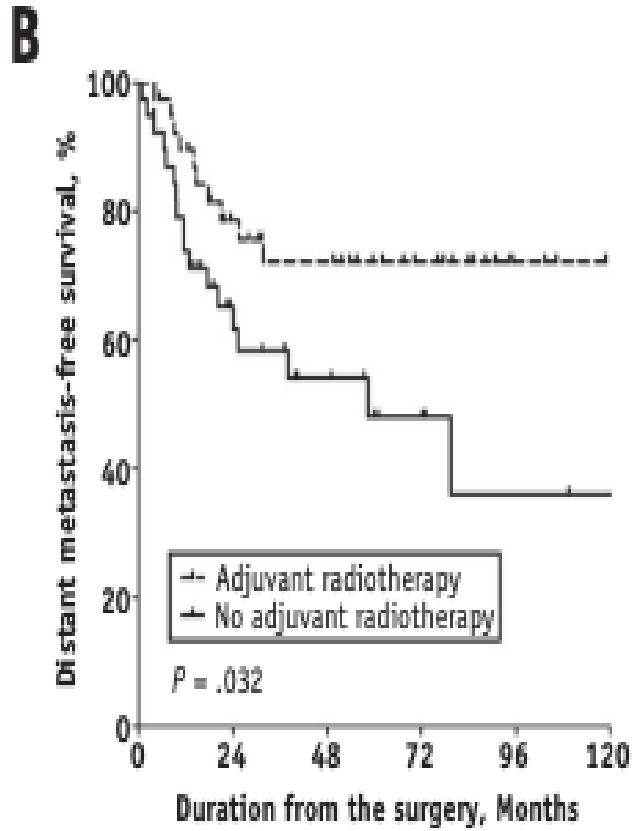
Methods and Materials: The multicenter data of 222 patients with pT3bN0-x disease treated with radical nephroureterectomy were analyzed. The effects of adjuvant radiation therapy and chemotherapy on local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and cancer-specific survival (CSS) were evaluated.

Results: Adjuvant radiation therapy and chemotherapy were given to 39 (17.6%) and 74 patients (33.3%), respectively. Seventeen patients (7.7%) received concomitant adjuvant radiation therapy and chemotherapy. The median follow-up duration was 34.4 months. After adjusting for age, sex, tumor location, multifocality, tumor grade,



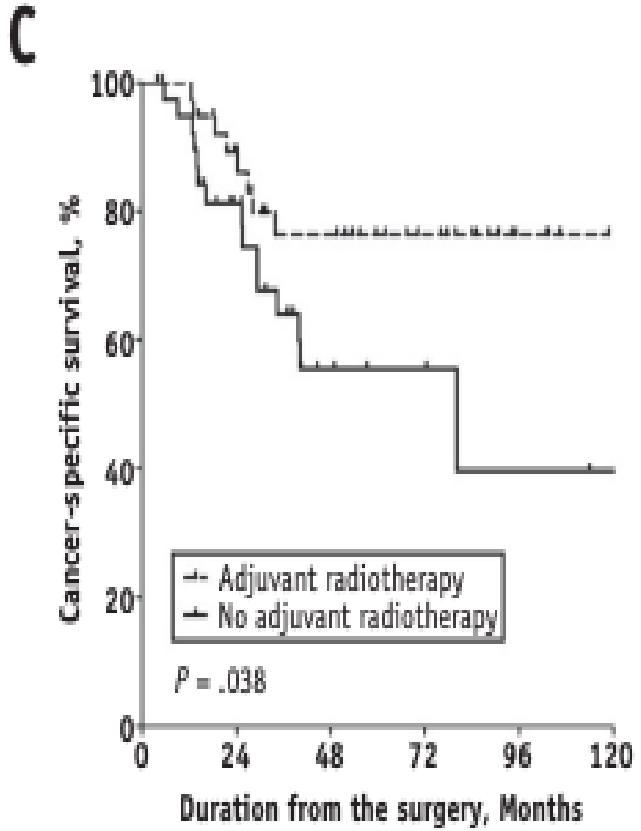
Numbers at risk

No adjuvant radiotherapy	39	17	10	5	3	2
Adjuvant radiotherapy	39	27	22	14	4	1



Numbers at risk

No adjuvant radiotherapy	39	20	12	7	4	3
Adjuvant radiotherapy	39	27	22	14	4	1



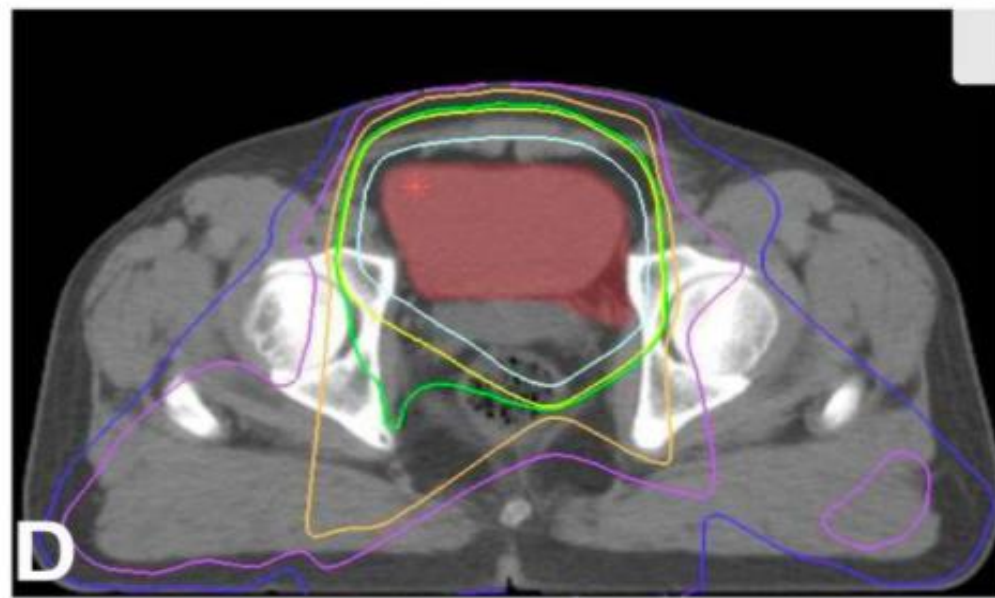
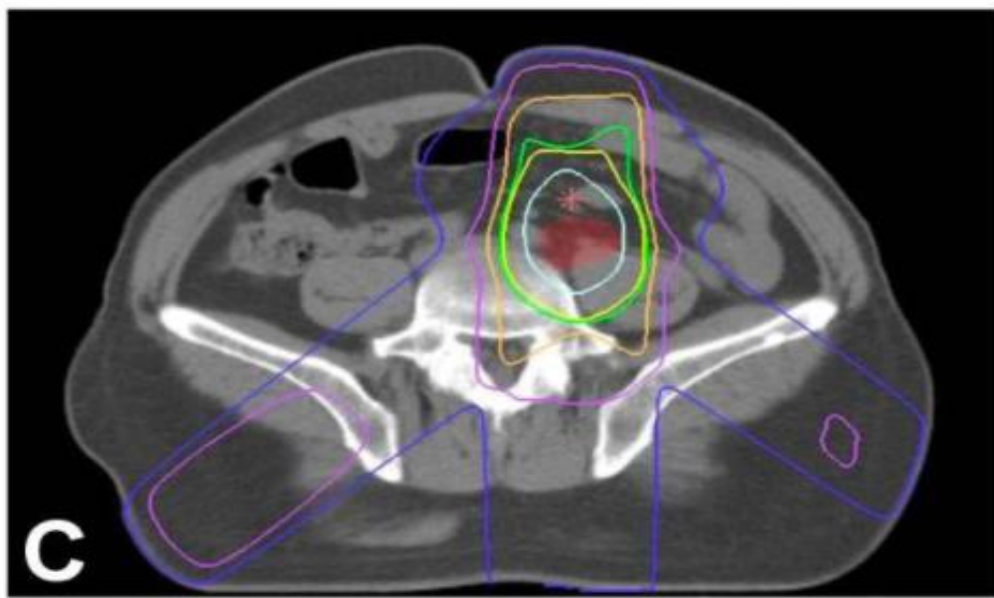
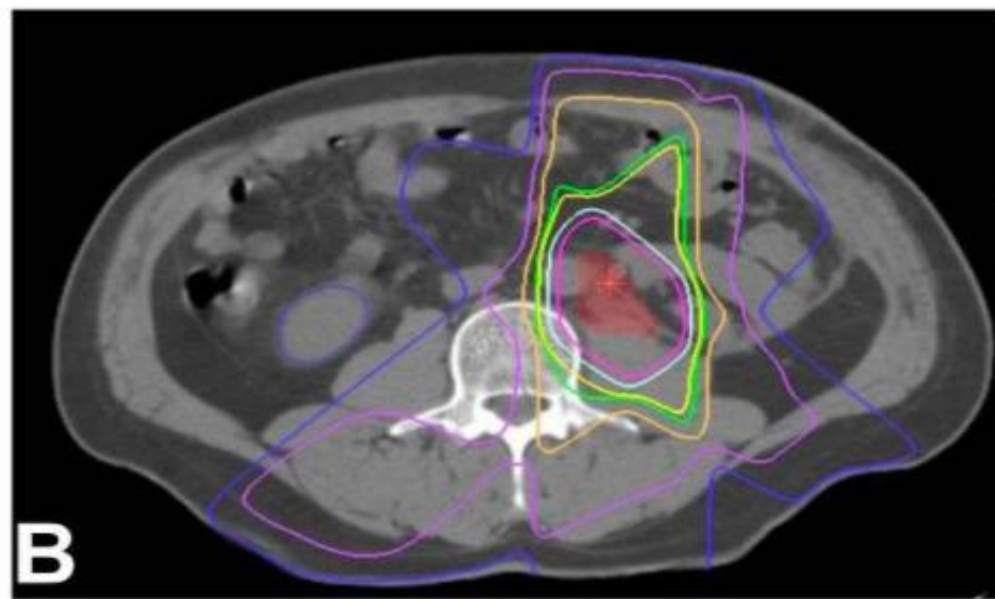
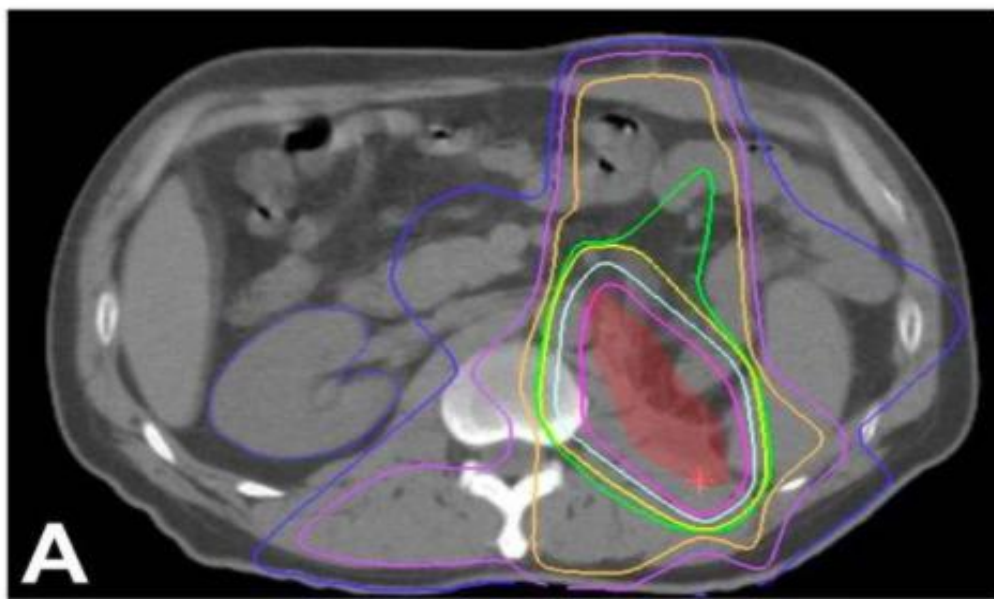
Numbers at risk

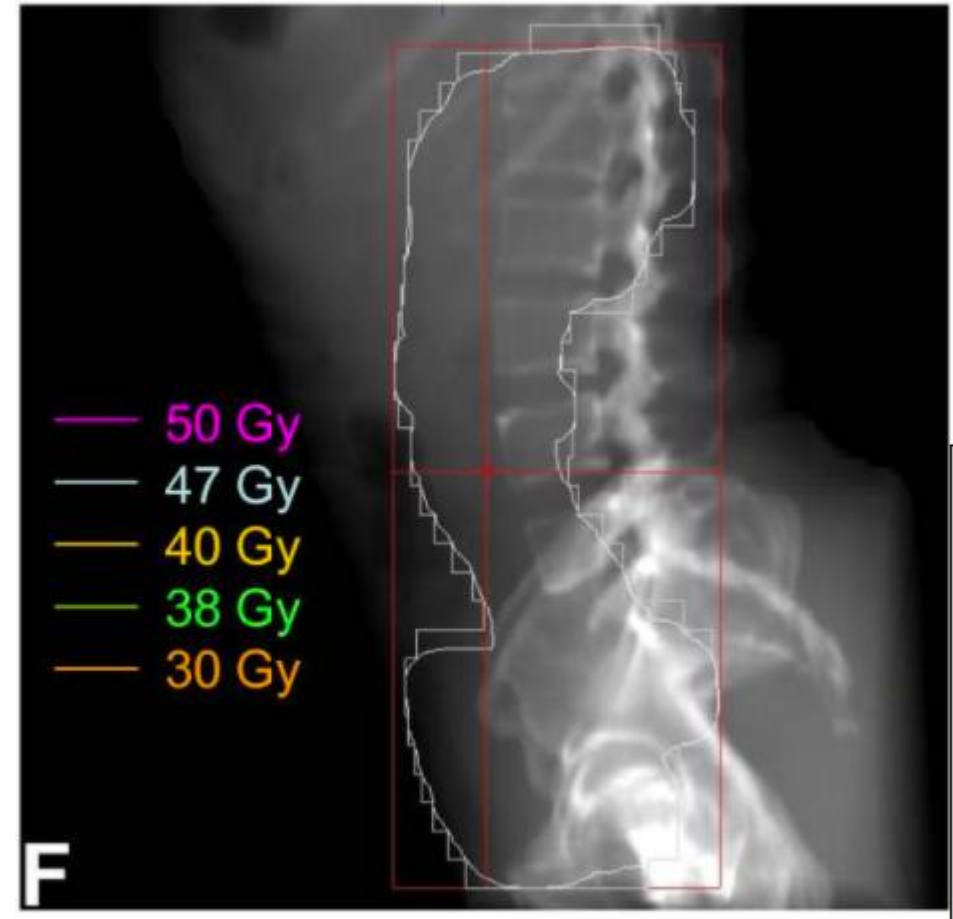
No adjuvant radiotherapy	39	26	11	9	7	5
Adjuvant radiotherapy	39	31	23	15	5	1

(A) Local recurrence-free survival (LRFS). (B) Distant metastasis-free survival (DMFS). (C) Cancer-specific survival (CSS). Adjuvant radiation therapy significantly reduced the local recurrence (A; 5-year LRFS, 83.9% vs 54.2%; $P = .001$), distant metastasis (B; 5-year DMFS, 72.1% vs 48.1%; $P = .032$), and cancer-specific death (C; 5-year CSS, 76.4 vs 55.5%; $P = .038$) in pT3b upper urinary tract carcinoma.

RT Planning

- Dose 45 – 50 Gy using 1.8 - 2 Gy per fraction 5 days a week
- Boost 10 – 14 Gy in case of R1 and R2 Resection
- Using appropriate beam technique and portals
- Clinical Target Volume
 - Ipsilateral renal fossa and the course of the ureter, the whole bladder, and the paracaval and para-aortic lymph nodes,





Digitally reconstructed radiograph for views of (E) 0° gantry and (F) 90° gantry. Internal pink and White lines represent the CTV50 and CTV40 respectively.

- In another retrospective study (Chen et al) of 133 patients with urothelial carcinoma of the renal pelvis, 67 patients received external beam RT following surgery (RT group) and 66 patients received intravesical chemotherapy (non-RT group). The clinical target volume included the renal fossa, the course of the ureter to the entire bladder, and the paracaval and para-aortic lymph nodes. The tumor bed or residual tumor was targeted in 14 patients. The median radiation dose administered was 50 Gy. There was a significant difference between the survival rates for these groups based on patients with T3/T4 stage cancer. A significant difference was observed in the bladder tumor relapse rate between the irradiated and nonirradiated bladder groups ($P = .004$).
- The authors concluded that radiation therapy may improve the overall survival for patients with T3/T4 cancer of the renal pelvis or ureter and delay bladder tumor recurrences.

Proton Beam Therapy



[Mol Clin Oncol](#). 2019 Jul; 11(1): 24–30.

PMCID: PMC6547882

Published online 2019 May 20. doi: [10.3892/mco.2019.1861](https://doi.org/10.3892/mco.2019.1861)

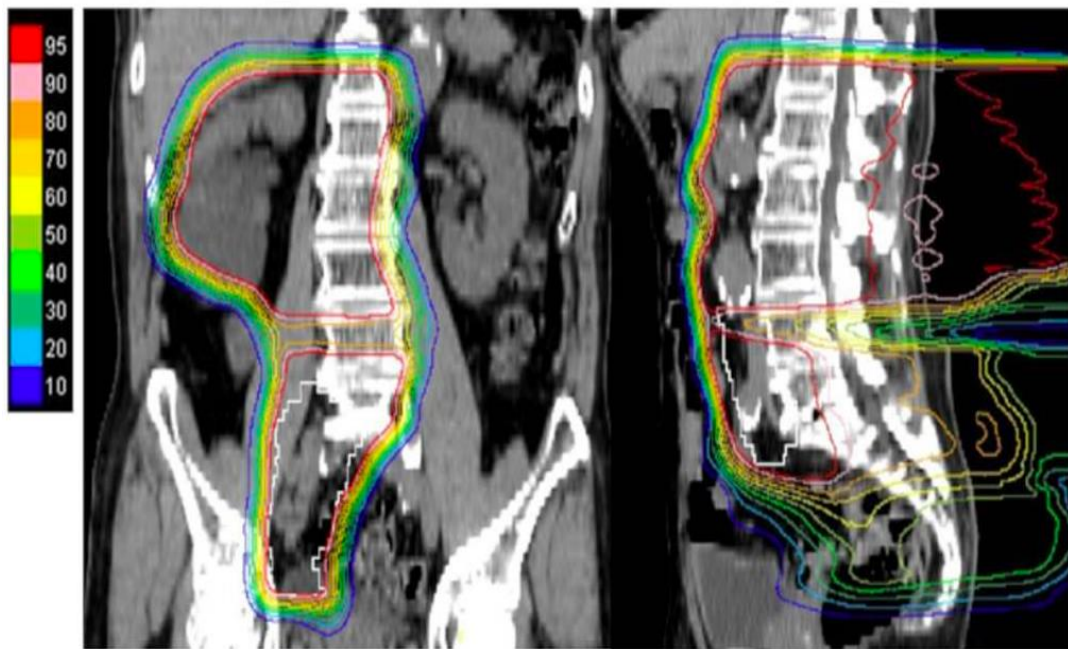
PMID: [31289673](https://pubmed.ncbi.nlm.nih.gov/31289673/)

Proton beam therapy for renal pelvis and ureter cancer: A report of 5 cases and a literature review

[Takashi Iizumi](#), [Hitoshi Ishikawa](#), [Yuta Sekino](#), [Kayoko Ohnishi](#), [Masashi Mizumoto](#), [Tetsuo Nonaka](#), and [Hideyuki Sakurai](#)

A

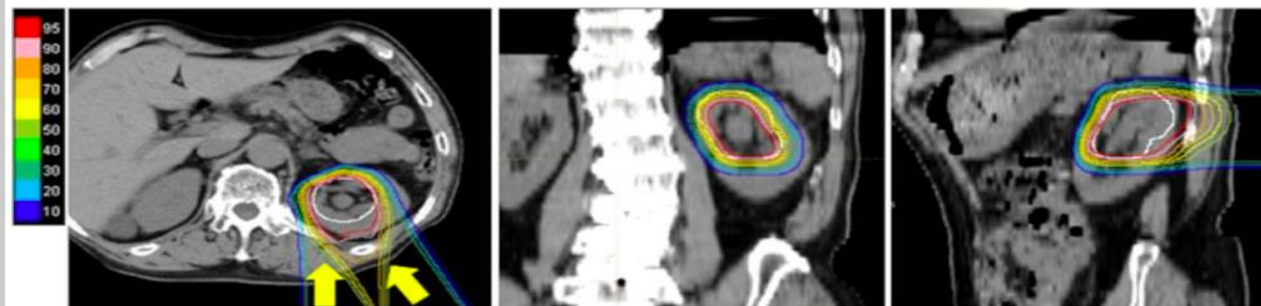
B



A

B

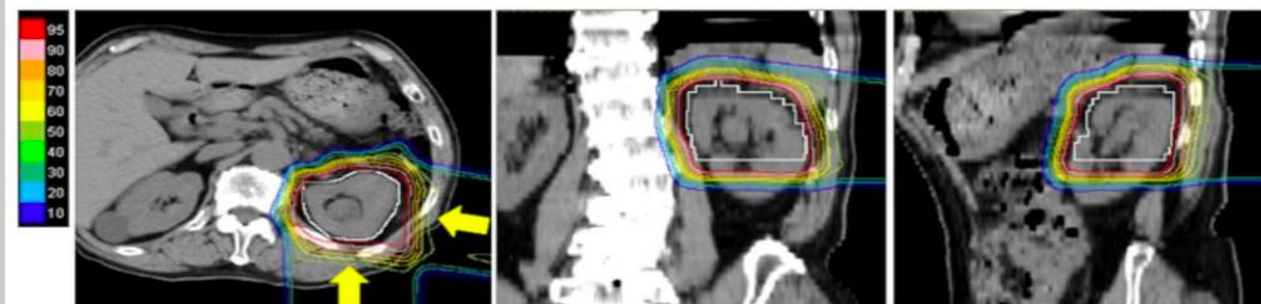
C



D

E

F



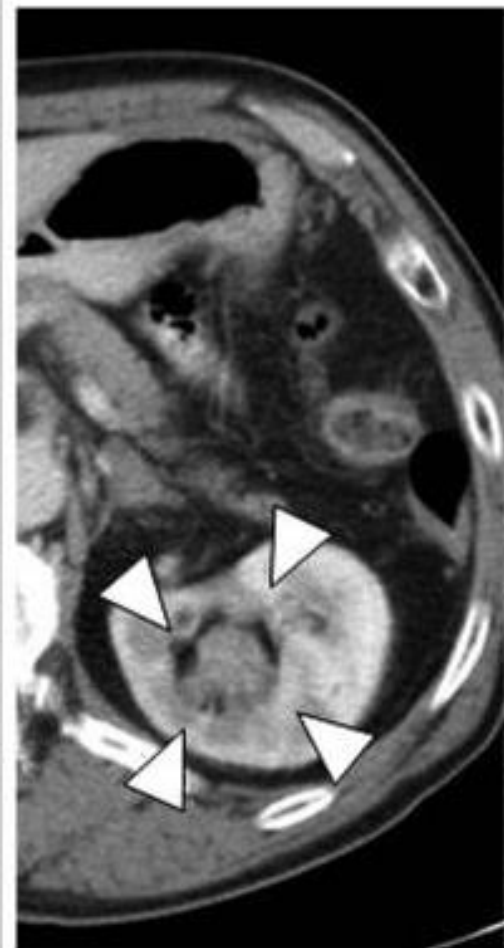
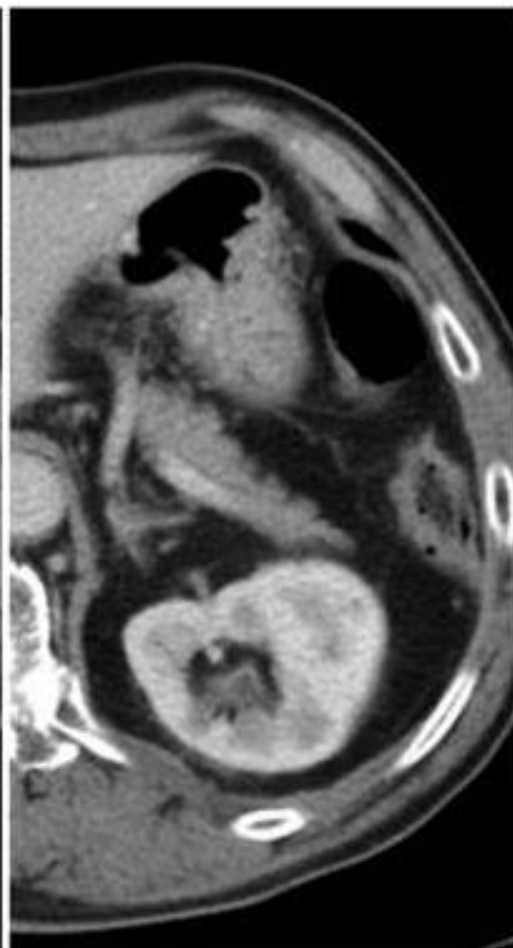
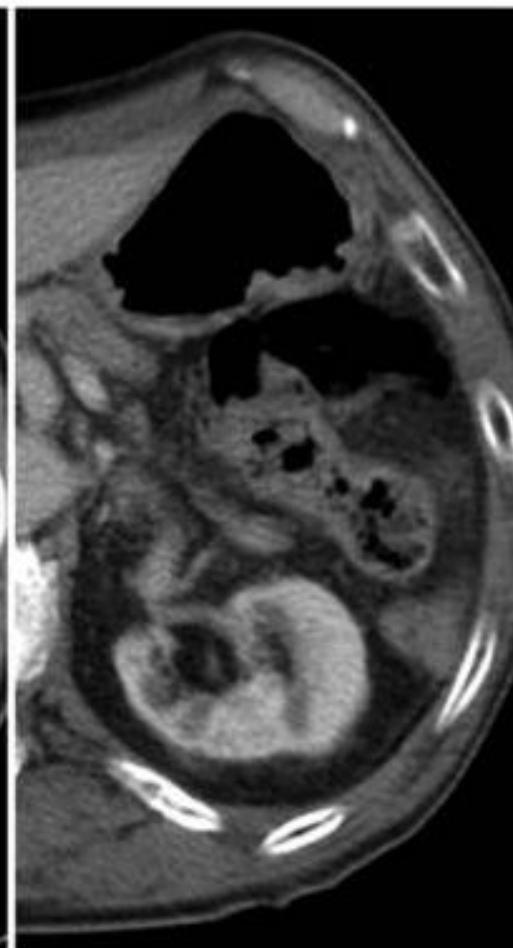
A**Pre****B****3 months****C****9 months****D****36 months****E****48 months**

Table 1.

Patient and treatment characteristics.

No.	Age (years)	PS	Site	Size (cm)	Cytology/Biopsy	TNM	Risk	Fractionation		
								[Gy (RBE)/fr]	RT field	Chemother
1	72	0	Renal pelvis	3	—	T1/2N0M0	High	72.6/22	Limited	No
2	85	1	Renal pelvis	2	Class V	T1/2N0M0	High	72.6/22	Limited	No
3	59	1	Ureter	25	Class V	T3N2M0 (ycT4N0M0)	High	66/33	Extended	Yes (prior to PI)
4	80	0	Ureter	3	Urothelial carcinoma	T1/2N0M0	High	66/33	Extended	No
5	64	0	Renal pelvis	4	Class V	T4N2M1 (ycT3N2M0)	High	66/33	Extended	Yes (prior to PI)

Table II.

Summary of treatment outcomes.

No.	Recurrence	Recurrence site	Time to recurrence (months)	Status	Survival (months)
1	No			Alive without disease	97.5
2	Yes	Local (within RT field: Primary site)	36	Dead with recurrence	66.3
3	Yes	Liver	1	Dead with recurrence	4.6
4	Yes	Local (out of RT field: Bladder)	48	Alive with disease	62.2
5	Yes	Lung	28	Alive with disease	40.3

Table III.

Summary of treatment morbidities.

Acute			
No.	Hematological (grade)	Non-hematological (grade)	Late (grade)
1	None (0)	Dermatitis (<u>2</u>)	None
2	None (0)	Dermatitis (<u>1</u>)	Hematuria (<u>2</u>)
3	Anemia (<u>1</u>)	Dermatitis (<u>1</u>), urinary frequency (<u>1</u>)	None
4	Thrombocytopenia (<u>1</u>)	None (0)	GI bleeding (<u>1</u>)
5	Anemia (<u>1</u>), thrombocytopenia (<u>1</u>)	Dermatitis (<u>1</u>), diarrhea (<u>1</u>)	None

Follow Up

- **Cystoscopy** and selective urine cytology at 3-month intervals postoperatively for the first year
- every 6 months during the second year.
- CT urography, excretory urography, or retrograde ureteropyelography can be performed at 3- to 6-month intervals to evaluate the upper tract.
- **Ureteroscopy** is the most sensitive tool for detecting recurrence
- 3-month intervals initially,
- 6 months after the first year.
- At 2-5 years, cystoscopy and ureteroscopy are continued at 6-month intervals.

After RNU, \geq 5 years	GR
<i>Non-invasive tumour</i>	
• Cystoscopy/urinary cytology at 3 months and then yearly.	C
• CT every year	C
<i>Invasive tumour</i>	
• Cystoscopy/urinary cytology at 3 months and then yearly.	C
• CT urography every 6 months over 2 years and then yearly.	C
After conservative management, \geq 5 years	
• Urinary cytology and CTU at 3 and 6 months, and then yearly.	C
• Cystoscopy, ureteroscopy and cytology <i>in situ</i> at 3 and 6 months, and then every 6 months over 2 years, and then yearly.	C

CTU = computed tomography urography; GR = grade of recommendation; RNU = radical nephroureterectomy.

Recent Advances in Follow up

- Several novel markers in addition to urine cytology and fluorescence in situ hybridization (FISH) may be helpful in detecting recurrent urothelial carcinoma.
- A prospective study by Siemens et al determined that the accuracy of diagnostic markers was as follows :
- Urinary fibrinogen/fibrin degradation products (FDPs) – Sensitivity 100%, specificity 83%
- Bladder tumor antigen (BTA) – Sensitivity 50%, specificity 62%
- Urine cytology – Sensitivity 29%, specificity 59%

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Thank you