

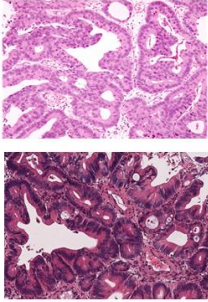


Rare Forms of Bladder Cancer: Adenocarcinoma

Dr. Apolo: The next tumor I want to talk about is adenocarcinoma of the bladder. Adenocarcinoma of the bladder occurs in about .5 to 2% of all bladder cancers. And these may be glandular, colloid, papillary, signet-ring, and clear-cell. Signet-ring tends to be the most aggressive. We subdivide adenocarcinoma into two, either urachal or non-urachal. Urachals account for about 1/3 of the adenocarcinomas. And these occur in younger patients, such as ranging in age 45 to 55. About 2/3 of these are low grade, and they're found in the bladder dome or or midline. The non-urachal adenocarcinomas account for about 2/3 of adenocarcinomas. These often have enteric differentiation, and often have intestinal-type metaplasia.

Bladder Adenocarcinoma

- 0.5-2% of bladder cancers
- May be glandular, colloid, papillary, signet-ring, and clear-cell
- Subdivided into 2 categories:
 - Urachal
 - 1/3 of primary adenocarcinomas
 - Younger age 45-55 years
 - 2/3 are low grade
 - Found in bladder dome or midline
 - Non-urachal
 - 2/3 of primary adenocarcinomas
 - Often enteric differentiation
 - Intestinal-type metaplasia is a predisposing factor
 - Often high-grade and advanced stage at presentation



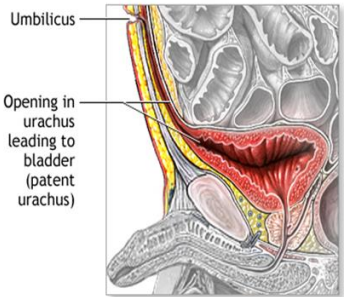
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The predisposing factor in these are high-grade and advanced stage of presentation. It is really important then if a patient is diagnosed with an adenocarcinoma of the bladder that's not urachal, that the patient undergo a workup to make sure that this is not a gastrointestinal tumor, such as a colon cancer or a stomach cancer that has metastasized to the bladder and it looks like it's a primary bladder cancer, but in reality it's a gastrointestinal tumor. So as part of the workup, the patient should've had an endoscopy and a colonoscopy to rule out other adenocarcinomas because this is such a rare histology.

So urachal adenocarcinomas, these arise from the urachal remnant. So that's the embryological connection between the belly button and the bladder that basically is not present in most of us, but can remain present in some patients. And just because it's present, doesn't mean that it's going to become cancerous. So this is really rare. It's a tumor, not technically of the bladder, it's of the urachal, which fits right on top of the bladder, but often presents within the bladder. 90% of these are mucinous producing, and the risk factors are unclear. Chronic infections, as we see with other tumor types haven't really been associated with urachal adenocarcinoma predisposition. And in addition to presenting with blood in the urine, it can also present in an abdominal palpable mass. In terms of the genes, genetically this tumor has mutations in the KRAS, NRAS, and BRAF, which are very similar to colon adenocarcinoma.

Urachal Adenocarcinoma

- Arises from the urachal remnant
- 90% mucin producing
- Risk factors unclear
- In addition to hematuria, may present with a palpable abdominal mass
- Genes frequently mutated
 - KRAS
 - NRAS
 - BRAF




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Surgical Treatment of Urachal Adenocarcinoma

- No standard of care treatment
- No prospective clinical trials
- Consensus: *en bloc* resection of the urachal ligament and umbilicus with complete or partial cystectomy and bilateral lymphadenectomy¹
- Local recurrence 15-18% in first 2 yrs²
 - Risk factors for recurrence:
 - Positive margins
 - Lymph node metastases at time of surgery
 - Failure to resect umbilicus *en bloc* w/ urachal ligament and bladder

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¹Steiber-Radtke A, et al. Multimodality management of urachal carcinoma: the M. D. Anderson Cancer Center experience. J Urol, 2003; 169: 1295-8
²Herr, H.W, et al. Urachal carcinoma: contemporary surgical outcomes. J Urol, 2007; 178: 74-9; discussion 78; Ashley, R.A, Inman BA, Sebott J, Leibovich BC, Blute ML, Kwon ED, Zincke H. Urachal carcinoma: clinicopathologic features and long-term outcomes of an aggressive malignancy. Cancer, 2006; 107: 713-20

And there is no standard treatment and no perspective clinical trial, but in terms of the surgical treatment for a urachal adenocarcinoma, the treatment is an en bloc resection of the urachal ligament and umbilicus. So basically, take out the belly button, take out that whole section, and it can be a partial or a complete cystectomy. This is probably one of the only tumors that when invasive, it's okay to do a partial cystectomy. Generally we do a radical complete cystectomy, which is complete removal of the bladder. For urachals, it's actually

okay to do a partial cystectomy as long as an en bloc resection is done of the urachal ligament and umbilicus, and also, a bilateral lymphadenectomy. So there is a risk of local recurrence after the surgery in about 15 to 18% of patients. The highest risk is in the first three years. And the risk factors for recurrence includes positive margins, lymph node metastases at the time of surgery, or failure to resect the umbilicus en bloc with the urachal ligament at the time of surgery. Next slide.

Bladder Adenocarcinoma Chemotherapy Treatment and Outcomes

Author (et al.)	n	Regimen	Result
Logothetis ¹	3	5-FU, Doxorubicin, Mitomycin	2 PR; not durable
Siefker-Radtke ²	9	5-FU + Cisplatin	33% RR
(MD Anderson)	1	Paclitaxel, Methotrexate, Cispl	1 response
	5	M-VAC	No responses
Galsky ³ (MSKCC)	6	Ifos, Paclitaxel, Cisplatin (ITP)	1 response
Tran ⁴	1	FOLFOX	1 PR
Siefker-Radtke ⁵	26	Gemcitabine, 5-FU, Leucovorin, Cisplatin (Gem-FLP)	1 CR; 3 PR; OS 20 months; 35-40% RR

1 Chemotherapy for adenocarcinomas of bladder and urachal origin. Urology. 26(3):252-5, 1985.
 2 Phase III trial of fluorouracil, interferon alpha-2b, and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in metastatic or unresectable urothelial cancer. J Clin Oncol. 20:1361,2002.
 3 Prospective trial of ifosfamide, paclitaxel, and cisplatin in patients with advanced non-transitional cell carcinoma of the urothelial tract. Urology. 69(2):255-9, 2007.
 4 Metastatic urachal cancer responding to FOLFOX chemotherapy. Can J Urol. 2010 Apr;17(2):5120-3 (abstract)
 5 Multimodality management of urachal carcinoma: the M.D. Anderson Cancer Center Experience. J Urol. 168:1285, 2003.

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So, in terms of the treatment for adenocarcinoma of the bladder, like I said earlier, these tumors genetically look like a mixture between a urothelial and an adenocarcinoma of the colon. So we do borrow from the colon cancer treatment options, which include the chemotherapy 5-FU. And the backbone for chemotherapy for bladder urothelial carcinoma, for just regular bladder cancer, is cisplatin. So a combination of the 5-FU

and the cisplatin have been tried, and these have shown activity. Also, at MD Anderson, a regimen that combined gemcitabine and cisplatin, which is used for urothelial carcinoma, plus 5-FU, which is used for colon cancer, called Gem-FLP, has shown activity. FOLFOX, which is a regimen of oxaliplatin, 5-FU, and leucovorin, which is used for colon cancer in the front-line setting, has also shown activity in adenocarcinoma.

So, the N is the number of patients that have been studied and have been reported. So it's really low. So it's important to note that when we're treating these patients, we have very little evidence as to kind of what works in terms of systemic chemotherapy. Just because these tumors are so rare, and it's so difficult to conduct a clinical trial.

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