Bladder cancer histology - rare tumors

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Only 5%-10% of bladder tumors will present as other than transitional cell carcinoma, and because of the rarity of these tumor types there is much less scientific data about treatments. Non-transitional cell bladder tumors are considered to be less responsive to treatments and more aggressive in behavior. Stage and grade at diagnosis is considered the most important prognostic indicator. Although there are exceptions, for rare bladder cancers most experts will choose radical cystectomy (bladder removal) as the primary treatment of choice. Exceptions are for LELC, inverted papillomas and urothelial papillomas, which are less aggressive than other rare variants.

Correct pathology is of paramount importance when considering treatment options and approaches for rare bladder tumors. If possible, it is wise to go to a cancer center of excellence for a second opinion on diagnosis, pathology and/or treatment as major cancer centers are more experienced with non-TCC bladder cancer.

Experts at MD Anderson Cancer Center in Houston, Texas are currently (2006) conducting clinical trials for small cell and urachal bladder cancers (below).

Rare histologic cell types found in bladder cancer:

Squamous cell carcinoma, This type of cancer affects the flat, scale-like cells on the surface of the skin called squamous cells. SCC of the bladder cancer typically forms after many years of chronic infection or irritation (such as by indwelling catheters). By the time squamous cell bladder cancer is detected it is usually at an advanced stage. Although this is the second most common form of bladder cancer, it only accounts for 2-5% of cases in industrialized countries. SCC bladder cancer is more often found in tropical climates and is associated bilharzial parasites. These parasites cause a condition called urinary schistosoma haematobium which can lead to bilharzial bladder cancer. This tumor is the most common form of cancer found in adult males in Egypt, due to the prevalence of bilharzial infestation in the countryside.
The stage and grade of the tumor, as well as lymph node involvement, have the most significant impact on survival. Although metastases in bilharzial associated bladder cancer are uncommon, bone is the most common site of metastasis. 4

Adenocarcinoma of the bladder- 2% of all bladder cancer diagnoses, adenocarcinoma cells have glandular characteristics. Adenocarcinomas may occur as solid tumors, or they may be papillary (wart-like) in nature. Adenocarcinoma can be grouped into one of three categories:

---- primary vesical (involving the bladder proper)
---- urachal - involving the urachus, outside the bladder, can include the navel
---- metastatic - cancer cells that have broken away from the original tumor to grow within the bladder. The most common metastatic adenocarcinomas come from prostate, ovary and colon cancer.

Many adenocarcinomas, urachal or primary, are advanced at the time of diagnosis. According to UK researchers, radiation therapy is not effective against urachal and primary adenocarcinomas, and radical cystectomy is the treatment of choice. The prognosis after radical surgery is often favorable for primary adenocarcinoma of the bladder. 6 Stage and grade are powerful predictors of outcome. 7

Urachal carcinoma of the bladder is a rare tumor that affects the outside of the bladder. Urachal tumours are more commonly found in women as well as younger patients. Tumors may be composed of tissue classified as adenocarcinoma, squamous cell carcinoma (SCC), or even sarcoma. Urachal tumors may cause mucous or bloody discharges in the urine, and they may produce dotted or "stippled" images on X-ray. Urachal tumors often are wider and deeper than expected, difficult to treat and they tend to metastasize and/or recur. 8

Urachal carcinomas are often locally advanced at presentation, which brings with it a risk of distant metastases. However, long-term survival following radical resection occurs in a significant fraction of patients (16 of 35 in the series from MDAnderson), supporting an attempt at margin-negative resection if at all possible. Chemotherapy appropriate for primary - type adeno-carcinomas can induce objective responses but definite increases in survival are as yet unproven. 9

Small-cell carcinoma - SCC is more commonly a malignancy of the bronchus, the cells take on endocrine-like characteristics. Primary small cell carcinomas of the bladder are rare and aggressive. Much of the new understanding about small cell bladder cancer came from reviewing treatment records of 88 patients with the disease treated at M. D. Anderson between 1985 and 2002, when expert researchers reported that patients who responded to neo-adjuvant chemotherapy, and were subsequently downstaged to stage pT2 or less, had a near 100% cure rate. Due to the rapid growth rate and the threat of understaging, there is clear evidence that neoadjuvant chemotherapy is important. Small cell bladder cancer has been shown to be highly responsive to chemotherapy; multi-therapy treatments are beneficial. 10

Page discussing the clinical trials at MDAnderson for small cell and urachal bladder cancer: Click here
Rhabdomyosarcoma. This tumor type begins in the soft tissues or connective tissue (e.g., tendon or cartilage) and can occur anywhere in the body. Rhabdomyosarcoma is the most common tumor of the lower genitourinary tract in children (mean appearance at five years of age), and rarely, is found in adults. In 2006 the Journal of Urology reported great improvements seen over the last 20 years, with cure rates in children as high as 80% and bladder preservation as high as 60% reported. The treatment of bladder-prostate rhabdomyosarcoma has evolved into multimodal therapy, including chemotherapy, radiotherapy and organ sparing surgery with bladder preservation. 11

Sarcomatoid carcinoma tumors arise mainly from connective tissue, which includes skin, tendons, muscles, bones, and cartilage.

Carcinosarcoma of the urinary bladder is a rare tumour. The majority of such tumours are not diagnosed until tumour growth is already far advanced. Owing to the small number of cases there is no clinically proven form of management. In contrast with non-muscle-invasive transitional cell carcinoma of the bladder, non-muscle-invasive carcinosarcoma of the bladder has always invaded the lamina propria, since in addition to the carcinomatous degeneration of the mucosa, sarcomatous degeneration of the underlying submucosal stroma is also present. Any local surgical treatment, such as TUR or partial cystectomy, involves the risk of incomplete tumor removal. Therefore, radical cystectomy appears to be the treatment of choice for both superficial and invasive carcinosarcoma of the urinary bladder. 12

The clinical usefulness of separating carcinosarcoma (carcinoma with sarcomatous component) from sarcomatoid carcinoma (carcinoma with spindle cell carcinomatous component) is uncertain. A German review from 1998 concluded that carcinosarcoma and sarcomatoid carcinoma of the bladder are highly aggressive malignancies with a similar outcome regardless of histological findings and treatment. Pathological stage is the best predictor of survival. 13

Undifferentiated carcinoma is another rare tumor which accounts for less than 1% of all bladder cancers. Undifferentiated carcinomas show no mature epithelial (bladder lining) cells. Some forms have "small cell" elements that look like the small cell cancers that may occur in the lungs. If small cell carcinoma of the bladder is confirmed, the patient should be evaluated for a primary lung cancer. Primary small cell carcinoma of the lung may have metastasized to the bladder and may look like undifferentiated carcinoma. 14

Leiomyosarcoma is usually a malignancy of smooth muscle origin; an extremely rare (less than 0.5% of cases) and aggressive bladder tumor variant. 15 Historically, patient survival has been poor and management has been based upon information obtained from a relatively small number of cases with diverse treatment regimens. Because the efficacy of chemotherapy and radiotherapy remains unclear, the treatment of choice is by radical cystectomy or partial cystectomy when tumor location and size permit. 16.

Update Sept '07: a report of a chemotherapy regimen for this cancer: "...a near-complete pathologic response to neoadjuvant chemotherapy with a unique regimen: gemcitabine and docetaxel. Further study of this anthracycline-sparing regimen is warranted."30

Micropapillary urothelial carcinoma/bladder cancer, a rare histological variant (0.7%) thought to be related to adenocarcinoma, with high metastatic potential. Usually found with high grade TCC, this variant behaves differently than invasive TCC in that it may present as diffuse cancer underneath benign bladder mucosa, thus making it difficult to detect. 17 Since even the focal presence of micropapillary bladder carcinoma is associated with a poor prognosis, recognition of this entity is important. Due to paucity of data regarding treatment outcomes, patients with nonmuscle invasive micropapillary UC often receive intravesical therapy in an attempt at bladder preservation. However, a recent study from experts at MDAnderson reported that BCG does not work on Ta and T1 micropapillary lesions, and early cystectomy, before progression can occur, is the treatment of choice. 18

Pheochromocytoma of the bladder - Tumors of this type are extremely rare (0.06%) in the bladder. Pheochromocytoma usually occurs as a benign tumor of the adrenal gland, of which only 5% will be found to be malignant. This number is higher when pheochromocytomas occur outside of the adrenal glands. Even a small pheochromocytoma tumor can produce large amounts of hormones such as adrenaline and dopamine, which tend to greatly increase blood pressure and heart rate. 19
Bladder pheochromocytomas may be hormonally active with elevated catecholamin metabolites, which can help in their diagnosis. Symptoms related to hypertension may be present. Treatments such as full or partial cystectomy and transurethral resection have been performed with good results.20

In case of advanced disease, chemotherapy with vincristine, and dacarbazine may help slow the tumor's growth. Radioisotope "MIBG" is said to be helpful. Side effects of excess hormonal secretion caused by the tumor can treated with phenoxybenzamine(dibenzyline) and/or beta-blockers.19

Lymphoepithelioma-like carcinoma (LELC) resembles lymphoepithelioma of the nasopharinx occurring in other sites. The incidence of LELCB is 0.4%-1.3% of all bladder carcinomas. Awareness of an LELC component in a urinary bladder tumor is important in order to avoid misinterpreting these tumors as malignant lymphoma or severe chronic cystitis because of different therapeutic approach, as well the favorable outcome of this histologic subtype, especially the pure or the predominate pattern. In addition, there is strong suggestive evidence that it responds to chemotherapy and there is the potential of salvaging the bladder. 21

Radical surgery with adjuvant systemic therapy may be indicated for focal muscle invasive LELC. 22

Lymphoepithelioma-like carcinoma, whether in pure or mixed form, has a similar prognosis to ordinary urothelial carcinoma when treated by cystectomy.29

Inverted papilloma IP is an uncommon benign tumor of the urinary tract. The tendency for multiple tumors, recurrence, and association with transitional cell carcinoma (TCC) suggest possible malignant potential, leading to conflicting clinical conclusions regarding the need for surveillance. Even in cases where IP's appear benign, the presence of atypical cytology requires exclusion of TCC with an inverted pattern. However, in histologically proven solitary bladder IP with no associated TCC, cystoscopic surveillance may not be necessary. 23

Urothelial papilloma of the bladder is another rare entity that represents less than 3% bladder tumors. The biologic potential of urothelial papilloma of the bladder is uncertain as there are only limited studies published on this issue. Patients with urothelial papillomas have a low incidence of recurrence and rarely progress to develop urothelial carcinoma. It seems reasonable to avoid labeling these patients as having cancer. It remains to be studied whether and when patients with papillomas who have no evidence of recurrence or progression no longer need to be followed. 24

Plasmacytoid Carcinoma The clinical presentation of this type of bladder cancer is frequently late because there is often no hematuria present. Cases showed coarse and indurated mucosal folds and thickened bladder walls, with no grossly identifiable tumor. Plasmacytoid bladder cancer is considered a very rare and aggressive form of bladder cancer.25

A list of both aggressive and non aggressive bladder tumors (TCC-transitional cell) as described by the World Health Organization (WHO) can be found on WebCafe here: http://blcwebcafe.org/content/view/146/157/#vecchio

Clinical trial using chemotherapy for rare bladder tumors:
OBJECTIVES: Non-transitional cell carcinomas account for 5% to 10% of urothelial tract tumors and are each characterized by unique demographics, risk factors, and patterns of spread. A unifying feature of these malignancies is their aggressive course and poor outcome without standard chemotherapeutic regimens. Given the rarity of these tumors, no prospective data are available to guide management. METHODS: Patients with unresectable/metastatic adenocarcinoma or squamous cell, small cell, sarcomatoid, or poorly differentiated carcinoma of the urothelial tract were eligible for enrollment. Treatment consisted of paclitaxel 200 mg/m² intravenously on day 1, cisplatin 70 mg/m² intravenously on day 1, ifosfamide 1500 mg/m² intravenously on days 1 to 3 plus mesna. Granulocyte colony-stimulating factor was administered with each cycle. The treatment was started again every 3 to 4 weeks for a maximum of six cycles. RESULTS: A total of 20 patients were enrolled. They had the following histologic types: adenocarcinoma in 11, squamous cell carcinoma in 8, and small cell carcinoma in 1. Patients received a median of four cycles (range one to six). The treatment was generally well tolerated, and the toxicity was predominantly hematologic. Overall, 7 (35%) of 20 patients (95% confidence interval 15% to 59%) achieved a major response (3 partial and 4 complete). The median survival for patients with adenocarcinoma was 24.8 months (95% confidence interval 10.2 to 32.3), and for those with squamous cell carcinoma it was 8.9 months (95% confidence interval 5.4 to not yet reached). CONCLUSIONS: The results of our study have shown that this regimen (ifosfamide, paclitaxel, and cisplatin) is active in patients with advanced non-transitional cell carcinoma of the urothelial tract. To our knowledge, this is the first prospective study of a chemotherapeutic regimen in this patient population. PMID: 17320659 [PubMed - in process]

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