Non-Muscle-Invasive Bladder Cancer

Last Updated Friday, 14 November 2008

{niftybox width=180px,float=right,textalign=left}

Online article, 2007, discussing the controversies of treating high risk, T1 tumors with BCG:

Long-Term Follow-up of Patients with Stage T1 High-Grade Trafnsitional Cell Carcinoma Managed by Bacille Calmette-Guérin (BCG) Immunotherapy

Urology Volume 69, Issue 1, January 2007

Experts have published a simple risk calculator that can be downloaded free from the EORTC web site; Alternatlely, there is a summary on webcafe, Markers of Recurrence and Progression

The European School of Urology Management of Superficial Bladder Cancer Online course

European Urology Ass.: Management Guidelines on non-invasive TCC as well as muscle-invasive/ metatastic bladder cancer, and more.

External sites from Expert M.A.O'Donnell, U of Iowa-

- Bladder Cancer Research Institute

- BCG+Interferon Alpha for Superficial Bladder Cancer: Physician's protocol

- Projects in Knowledge: New Prospects in the Treatment of Superficial Bladder Cancer.

The value of a second transurethral resection in evaluating patients with bladder tumours Eur Urol. 2003 MaMiladi M, Peyromaure M, Zerbib M, Saighi D, Debre B.Department of Urology, Cochin Hospital Paris, France." RESULTS: Transurethral resection of the bladder has two shortcomings: underestimating clinical stage, and overlooking other lesions. CONCLUSIONS: A second transurethral bladder resection may be warranted for T1 tumours, and for invasive tumours when a bladder preservation is planned."

Medline Abstract

{/niftybox}Stage Ta, T1 and CIS (carcinoma in situ)

First read about staging.

On this page: descriptions, risk graph, treatment options and links to further info on this site. For external resources see

the sidebar.

Three 'substages' of non-muscle-invasive bladder tumors are recognized:

Ta-papillary tumor confined to the urothelium (inner lining of the bladder)

T1-papillary tumor invading the underlying lamina propria

Tcis (also written as TIS, CIS, carcinoman in situ)-flat- reddened lesion with high grade histologic features confined to the urothelium

Benign Papilloma or low-grade papillary tumor-what is the difference? see below

Guidelines on diagnosis and treatment of superficial bladder cancer from the European Urologic Association, 2004- below

---

Non-muscle-invasive bladder cancer, stage Ta, grade 1

80% of bladder tumors present as 'superficial'; the the term should not be mistaken for something totally without risk. Of late, experts in the field of uro-oncology are questioning the common sense of using the term 'superifical' to denote subsets of tumors with very variable risk and prognoses. {Eliminate the term superfical bladder cancer; J Urol. 2006 Feb;175(2):417-8.Nieder AM, Soloway MS.}

There are different degrees of risk according to several known prognostic factors, the most important of which are grade (aggressiveness of the tumor cells) and depth of invasion (stage Ta vs. T1). Low grade, Ta tumors larger than 3 cm, and/or the presence of multiple tumors have been shown to pose risk of recurrence (see graph below).

Upon initial diagnosis of a non-invasive Ta, low grade, well differentiated tumor, surveillence with no further treatment after transurethral resection has long been standard. Follow up cystoscopies are important; if no tumor recurrence is seen after one year, follow ups may be lengthened.

Recurrence, which may be expected in 50% to 75% of cases but is usually of the same grade and stage, can then again be successfully treated by repeat TUR. There is evidence that one instillation of intravesical (instilled in the bladder) chemotherapy can delay the time between recurrences. [See also: intravesical chemo]

Ta, low grade papillary tumors progress in grade or become invasive less than 5% of the time, and are high in grade in only 1% to 3% of cases. In contrast, stage T1 tumors may be high grade in 30% to 50% of cases and are rarely low grade.1 Carcinoma in situ is considered a high risk form of bladder cancer with a widely variable outcome. Although all three kinds of tumors are considered non-invasive (formerly referred to as "superficial"), their outcomes are clearly different.

Update 2006: New data support 'watchful waiting' instead of automatic removal of low grade, Ta non-invasive bladder tumors, see,

"Observation of Ta,grade 1 bladder tumors, Acceptable? on webcafe

Also: Expectant treatment of small, recurrent, low-grade, noninvasive tumors of the urinary bladder,.."As long as the tumors are low grade, the risk of invasion or metastasis is zero. Every small papillary tumor does not require removal when observed. Some of these tumors grow very slowly and, with proper reassurance, can be safely monitored. "Mark Soloway; Miami; Urologic Oncology: Seminars and Original Investigations Volume 24, Issue 1 , January-February 2006, Pages 58-61 PubMed

Watchful Waiting Policy in Recurrent Ta G1 Bladder Tumors - Conclusions: Small, recurrent papillary bladder tumors after resection of low-grade Ta tumor(s) pose minimal risk for the patient. A watchful waiting policy— without resection of the tumor—may be considered in these patients Ofer N. Gofrit, et al.Israel; European Urology Volume 49, Issue 2 , February 2006, Pages 303-307 PubMed

Evaluation of Risk

The combination of cystoscopy findings and pathology characteristics of the tumor allows for the stratification of patients into a high risk or low risk group for cancer recurrence and progression. This assists decisions on intravesical therapy.

low risk

high risk

Multiple, frequent recurrence
no
yes

Appearance
papillary, fine stalk
papillary, thick stalk or sessile

Size
<3cm
>3

Number of lesions
<3
>3

Transurethral resection

complete
incomplete (residual tumor)

Stage
Ta
T1, Tcis

Grade
I/II
III

click here for more graphs: Predicting recurrence and progression in stage Ta-T1 bladder cancer: the use of the EORTC risk tables

Risk factors for superficial recurrences include multiple tumors, tumors larger than 3 to 4 cm. positive urine cytology, tumors involving the submucosa (stage T1) and dysplasia (abnormal cell appearance) in random mucosal biopsy specimens.

“Recognition that a significant percentage of transitional cell neoplasms are benign is more than an exercise in semantics. Patients presenting with these lesions have a low risk (<10%) of ever developing a life-threatening bladder cancer and probably will not benefit from prophylactic therapy with topical agents. Long-term follow-up is, of course, necessary but it need not be aggressive, especially after the first 2 years. Patients can take comfort in having a benign tumour rather than a bladder cancer.” 8

Other reports have suggested prognostic distinctions among tumors that penetrate the lamina propria only microscopically (stage T1a), those that penetrate more extensively up to the layer of the muscularis mucosae (stage T1b), and those that penetrate through the muscularis mucosae to involve extensively the deeper portions of the lamina propria (stage T1c). These distinctions have not been incorporated into the commonly accepted staging system. 1

Stage T1 - not exactly "non-muscle-invasive" anymore?

Clinical "T" staging means staging with the best tools at the disposal of the physician(s), as opposed to the "P" stage, which refers to the post-cystectomy pathology specimen (the removed bladder). The "P" stages have shown that T1 bladder cancer is often understaged.

Recent data has suggested that stages Ta and T1 are of different biological origins, and in many cases are indeed separate tumor entities with marked genetic differences. Independent of treatment, true bioligical progression of Ta, low grade tumors is very rare, while in a significant amount of cases, pT1 carcinomas are early stages of potentially highly malignant tumors that will consequently need surgical intervention. The distinction is critical because of an increasing tendency of urologists to perform early cystectomy for recurrent pT1 carcinomas, though as of yet there is no proven accepted method of distinguishing which T1 tumors will definitely become invasive.7

T1 disease, irrespective of grade, has already demonstrated the biological ability to invade, and has a reported progression rate of 29%. If a T1 tumor is extensive, multiple, recurrent, high grade, or has shown p53 overexpression, the risk of invasion is higher. Therefore, the diagnosis of high grade T1 tumors and CIS may justify the use of intravesical chemotherapy to prevent progression to muscle invasion. 6

Second TUR? New data is appearing suggesting that a second TUR be performed after a T1 diagnosis as this can catch residual tumor and improve outcome (see sidebar for reference).

Controversy: There is ongoing debate about the best management of Grade III, pT1 tumors, whether early radical therapy (cystectomy) is indicated or if it is safe to delay treatment until definite recurrence has been identified. Molecular biomarkers are being actively investigated as a means of determining treatment strategies, but are not yet in everyday practice. See also; Biomarkers

CIS-carcinoma in situ, is relatively rare, comprising approximately 10% of cases and is also considered a superficial tumor (does not penetrate the bladder lining), and is usually associated with concomitant high grade, invasive TCC in adjacent or distant urothelium (secondary CIS). Carcinoma in situ is a high-grade and aggressive manifestation of TCC that has a highly variable course. The treatment of CIS has undergone dramatic changes since this malignancy was first recognized. While cystectomy was once recommended as the initial treatment of choice, recognition of the highly variable prognosis and the uniformly high response rate to intravesical BCG has prompted a more conservative approach to management. 2

The symptoms of bladder CIS may be mistaken for urinary tract infection, prostate disease, or neurogenic bladder incontinence (leaky bladder due to defects in the nervous system). CIS may involve nearby organs such as the urethra, periurethral glands (glands around the urethra), and prostate. In fact, because CIS can be dangerously silent within the prostate, many doctors recommend routine biopsy of the prostate in male CIS patients.

Whereas superficial bladder cancer has the appearance of a solid or papillary tumor, in carcinoma in situ, the involved mucosa is reddish and velvety to granular. The areas are patchy and ill defined and sometimes bleed easily.

In some instances, bladder CIS may have features of Paget's disease, an inflammatory form of cancer that affects organs such as the breast. Pagetoid CIS may cause the bladder lining to flake off or slough. In other cases, CIS may involve groups of bladder cells known as von Brunn's nests. Association with von Brunn's nests is important, as it may influence the type of treatment chosen by the physician.3 Patients with CIS involving von Brunn's nests -- that is, pockets of cells that extend more deeply below the bladder surface -- will have tumor cells that are unexposed and, consequently, unaffected by intravesical therapy. Thus, intravesical therapy is not suitable for individuals with von Brunn's CIS.

Occasionally (1% of cases or less), CIS is found without associated invasive TCC (primary CIS). Only one third of primary CIS invades the lamina propria or muscle wall, and the mortality rate is only 7% to 20%, as opposed to 45.2% for secondary CIS.4 5

If carcinoma in situ is localized and not accompanied by irritative symptoms, it may not lead to infiltrating disease. Diffuse symptomatic carcinoma in situ is an early and aggressive form of the disease.

For more information about CIS and it's management see Dr. Lamm's BCG treatment recommendations here at WebCafe.

Treatments

For recurrent, superficial high grade tumors, or as a preventative measure in high-risk patients after TUR, various chemotherapeutic agents may be instilled in the bladder, and use of such agents has been shown to increase disease free intervals. see also intravesical chemo

In case of high grade Ta or T1 tumors either primary or recurrent, BCG (bacillus Calmette-Guerin, an immunotherapy) has been shown to be most effective, especially with carcinoma in situ. Compared with TUR alone in patients with Ta and T1 lesions, treatment with BCG delayed progression to muscle-invasive and/or metastatic disease, improved bladder preservation, and decreased the risk of death from bladder cancer. New evidence is showing that maintentance therapy as defined in Dr. Lamm's protocol has reportedly further lowered risk of recurrence. 8

2007: Online article discussing the controversies surrounding treatment of high risk bladder cancer: Long-Term Follow-up of Patients with Stage T1 High-Grade Transitional Cell Carcinoma Managed by Bacille Calmette-Guérin (BCG) Immunotherapy Urology Volume 69, Issue 1, January 2007

Cystectomy is advised in the case of large or high grade T1 lesions, or in the case of muscle invasive disease stage T2 and higher. Segmental (partial) cystectomy is appropriate in only a small subset of patients, such as those with a singular papillary tumor near the dome of the bladder, though due to the high recurrence rate, segmental cystectomy is not often advised.

Interstitial implantation of radioisotopes with or without external-beam irradiation is also used as a first line therapy for Ta-T1 lesions. Used more in the UK and Europe; see also radiation

Intravesical immunotherapies include BCG, and Interferon; Key Hole Limpets; Interleukin and Bropirimine, an oral agent, are being actively investigated. BCG is also used in a percutaneous vaccine form.

Photodynamic therapy and intravesical hyperthermia combined with intravesical chemotherapy (also known as electromotive intravesical chemotherapy) are being investigated for use in superficial bladder cancer. Chemoprevention trials are also being conducted. The combined modalities approach may also be considered in cases of high grade T1 tumors.

Benign Papilloma or low-grade papillary tumor-what is the difference?

Benign urothelial papilloma of the bladder: a review of 34 de novo cases Magi-Galluzzi C, Epstein JI The Cleveland Clinic Foundation, Cleveland, OH, and The Johns Hopkins Hospital, Baltimore, MD, USA Mod Pathol. 2004; 17 (suppl 1): 165A Abstract-PubMed

Urothelial papilloma of the bladder is uncommon, and represents less than 3% of papillary bladder tumors. We retrospectively studied 34 patients who were diagnosed with urothelial papilloma of the bladder. In all cases, the diagnosis of papilloma was the first manifestation of urothelial neoplasia.

Three patients (8.8%) developed recurrent papilloma 4, 15 and 18 months after the initial diagnosis of papilloma; one of these patients also showed progression to noninvasive low grade urothelial carcinoma at the time of recurrence (15 months). Three patients (8.8%) progressed to higher grade disease: 2 to non-invasive, low grade urothelial carcinoma (11 and 15 months after the original diagnosis) and 1 to a papillary urothelial neoplasm of low malignant potential at 104 months and a non-invasive low grade ,urothelial carcinoma at 141 months from the initial diagnosis of papilloma. None of the patients demonstrated progression to either lamina propria (T1) or muscularis propria (T2) invasion. Two patients died for unrelated causes. None of the patients died of bladder cancer.

CONCLUSIONS: 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.

Editorial Comment- Dr. Athanase Billis Full-Professor of Pathology

State University of Campinas, Unicamp Campinas, São Paulo, Brazil

....Classification of urothelial (transitional cell) neoplasms of the urinary bladder (Am J Surg Pathol. 1998; 22:1435-48), papilloma is a distinct neoplasm from papillary neoplasm of low malignant potential. The former neoplasm is defined as discrete papillary growth with central fibrovascular core lined by urothelium of normal thickness and cytology, frequent vacuolization of umbrella cells and edema of the stroma. There is no need to count the number of cell layers. It is a rare benign condition comprising less than 3% of papillary urothelial neoplasms. Papillary urothelial neoplasm of low malignant potential is a papillary lesion with minimal architectural abnormalities and minimal nuclear atypia irrespective of cell thickness. In general, the major distinction from papilloma is that in papillary urothelial neoplasm of low malignant potential the urothelium is much thicker and/or nuclei are significantly enlarged. The urothelial papilloma, in contrast, has no architectural or cytological atypia.

Both papilloma and papillary urothelial neoplasm of low malignant potential may develop recurrent or new papillary lesions but only the latter may be associated with invasion or metastases in rare cases. The study by Magi-Galluzzi and Epstein disclosed the clinical behavior of 34 de novo papillomas. The follow-up showed that 6 patients had recurrent disease but none progression to either lamina propria (T1) or muscularis propria (T2) invasion. This paper confirms that papilloma and papillary neoplasm of low malignant potential should be considered separately. The urologist should follow-up patients with papilloma but because they have a low incidence of recurrence and rarely progress to develop noninvasive urothelial carcinoma, it seems reasonable to avoid labeling these patients as having cancer.

For a review of the WHO's classification of the many different types of bladder tumors, see WebCafe's report here

New diagnostic tool: photodynamic diagnosis (PDD), fluourescent cystoscopy

The application of fluorescence cystoscopy and resection clearly improves the detection of the number of CIS lesions per patient and also the number of patients with CIS.' Bladder carcinoma in situ in 2003: state of the art. Witjes JA. Department of Urology, University Medical Center St Radboud, Nijmegen, The Netherlands.

Guidelines on diagnosis and treatment of superficial bladder cancer Oosterlinck W. Department of Urology, University Hospital, Gent, Belgium. March 2004, Minerva Urol Nefrol. PMID: 15195031 [PubMed abstract)

Review of the guidelines of the European Association of Urology (EAU) on superficial bladder tumors, new data which has come available since 2001. It emphasises the data which are evidenced based and clearly explained where still insufficient research is available to make clear recommendations

*Intravenous urethrography (IVU) is only necessary in grade 3 tumors.

*A good transurethral resection (TUR), with muscle in the specimen is essential.

*Random biopsies are only necessary when there is positive urinary cytology or when tumor in situ (TIS) is suspected.

*The variability in pathology interpretation remains a problem which seems not to have been solved by the new WHO 1998 classification. A review of pathology seems indicated when aggressive therapy is planned or there is a discrepancy between the visual findings and pathology.

*The visual judgement of urologists in superficial bladder tumors is very good.

*Second resection is indicated whenever insufficient material is delivered and in any T1 G3 tumor. In the last infiltrative tumors are regularly found. The treatment largely depends on prognostic parameters.

* For recurrence rate multiplicity of the tumor is most important, followed by recurrence rate, volume of the tumor, grade and T category.

* For progression the most important tumor is the anaplasia grade and the T category.

* Up to 50% of T1 G3 tumors and TIS progress to invasive tumors.

* Even low risk tumors still have an important recurrence rate of at least 20%/year in the first years after diagnosis.

*One chemo instillation immediately after TUR is indicated in low and intermediate risk superficial bladder tumors. Intravesical chemotherapy prevents recurrence but not progression. Ideal dosage and schedule of instillation is not clearly defined. Longterm therapy is not worthwhile.

* Bacille Calmette-Guerin (BCG) therapy is indicated in all tumors at high risk for progression. In tumors at high risk for recurrence it is also superior to intravesical chemotherapy, but its side-effects are more pronounced.

* Local or systemic side-effects are not related to efficacy and side-effects do not increase over time. The ideal schedule for BCG has not yet been found. It is however clear that some kind of maintenance therapy is necessary to obtain good results.

* BCG failure is probably any tumor which recurs at 3 and 6 months under BCG therapy.

* One third dose seems as sufficient as a full dose BCG.

* That BCG can spare the bladder in T1g3 tumors is largely documented but the chance to save the bladder when the tumor is still present after 2 cycles of BCG is very low. Cystectomy is indicated in these BCG failures.

* Vitamin E, A, and Lactobacillus Casei are probably effective in the prevention of the disease.

* Stopping smoking is advocated.

* Cystoscopy is still the gold standard in follow-up. It is advocated at 3 months and thereafter according to the prognostic parameters.

* High grade tumors are at risk life long.

* Follow-up of 5 years for low risk tumors seems reasonable.

References

Risk graph taken from: Contemporary Management of Superficial Bladder Cancer Julio M. Pow-Sang, MD, and John D. Seigne, MB, BCh http://www.moffitt.usf.edu/pubs/ccj/ Cancer Control, Journal of The Moffitt Cancer Center, July/Aug, 2000 Used with permission

1. References as reviewed in Bladder Cancer: State of the Art Care by Michael J. Droller, M.D; CA Cancer J Clin 1998;48:269-284

Bladder carcinoma as a systemic disease. Cancer 1979;43:2532-2539. Prout GR Jr, Griffin PP, Shipley WU:

Treated history of noninvasive grade 1 transitional cell carcinoma:Prout GR Jr, Barton BA, Griffin PP, et al: The National Bladder Cancer Group. J Urol 1992;148:1413-1419.

The pT1 G3 bladder tumour Birch BR, Harland SJ:. Br J Urol 1986;64:109-116.

Professor G. Steineck, Karolinska Hospital, Stockholm, Sweden, unpublished data.

2. Carcinoma in situ DL Lamm Department of Urology, West Virginia University Health Sciences Center, Morgantown. Urol Clin North Am 1992 Aug;19(3):499-508 PMID: 1636234 UI: 92343122

3. http://www.urologychannel.com/bladdercancer/staging.shtml

4. Pathobiology of Preinvasive Urothelial Neoplasia Author: Jose I. Diaz, MD, Pathology Service, H. Lee Moffitt Cancer Center & Research Institute

[Cancer Control: JMCC 3(6):552-556, 1996. © 1996 Moffitt Cancer Center & Research Institute] full article can be found at http://www.medscape.com/

5. Carcinoma in situ of the urinary bladder: clues to host involvement in human carcinogenesis. Orozco RE, Martin AA, Murphy WM. Department of Pathology, University of Tennessee, Memphis. Cancer. 1994;74:115-122. PMID: 8004567 UI: 94273074

6. http://www.duj.com/Article/Schenkman.html Superficial Bladder Cancer Therapy References as reviewed by Drs. Emmanuel Schenkman, M.D. and Donald L. Lamm, M.D.

Superficial bladder cancer: Progression and recurrence. Heney, N.M., Ahmed, S., Flanagan, M.J., et al J Urol 1983; 130:1083-1086.

Natural history of bladder cancer. Bostwick, D.G.: J Cell Biochem., 1992;161:31-38. (29%)

Carcinoma in situ (review) D.L.Lamm Urol Clin North Amer. 1992; 19:499-508

7. Pussycats and baby tigers: non-invasive (pTa) and minimally invasive (pT1) bladder carcinomas are not the same!

G.Sauter; MJ Mihatsch J Pathol 1998 Aug;185(4):339-41 PMID: 9828830 UI: 99046270

8. Transitional Cell Papilloma: Revisiting An Old Concept

William M. Murphy Department of pathology, Immunology and Laboratory Medicine,

University of Florida College of Medicine, Gainesville, Fla. USA

Volume 3, Number 4 Oct. 1996

9. Maintenance BCG immunotherapy of superficial bladder cancer: A randomized prospective Southwest Oncology Group Study (meeting abstract).

Lamm DL, Crawford ED, Blumenstein B, et al: Proc Annu Meet Am Soc Clin Oncol 1992;11:A627. Abstract.