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Papillary Tumors of the Bladder

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Abstract The most common neoplasms of the urinary bladder are papillary tumors that vary histologically and cytologically from very well differentiated to highly anaplastic patterns. Biologic behavior of these tumors is closely correlated with morphology, so that cytologically benign tumors (papillomas) are benign in behavior, and increasing anaplasia is associated with increasing clinical aggressiveness. By this definition, 20% or more of bladder tumors should be classified as papillomas. The development of carcinoma occurs in a series of steps, progressing through atypia and carcinoma *in situ* to invasion. Finally, evidence is presented to show that invasive carcinoma often begins from areas of flat carcinoma *in situ* associated with, but not within, co-existing papillary tumors.

Key words: bladder cancer, bladder tumors, carcinoma *in situ*, papillary carcinoma, papilloma, urinary bladder

Papillary tumors as a group are the most common neoplasms of the urinary bladder. Most of the approximately 51,000 new cases of bladder tumor diagnosed annually in the United States are papillary [1]. The male to female ratio is approximately 3 to 1, consistent with the view that many of these tumors result from exogenous exposure to chemical carcinogens in or about the workplace. Interestingly, only about 9500 deaths from bladder cancer are expected in 1992, less than 20% of the cases diagnosed [2]. It is difficult to attribute this low death rate entirely to our ability to treat and cure this disease. Thus, one has to consider that many of the papillary tumors of the bladder are either benign and easily cured by local resection, or indolent in their growth if untreated. Papillary tumors of the bladder which are neglected can grow to fill almost the entire lumen of the bladder with minimal or no invasion of the bladder wall. This benign growth pattern has been recognized for many years. For example, a publication by Dr. Harrison [3] in 1886, describes "villous growths or papillomata" which he says "used to be described under the name villous cancer, but there are no reasons for regarding them as cancerous." He reports that these tumors show no tendency to ulcerate or to invade and involve structures other than the mucous membrane of the bladder, and that they do not implicate glands (lymph nodes) or become generalized. He points out that they may prove fatal by hemorrhage but otherwise can exist for long periods of time without giving any indication of their presence. This was more than 100 years ago.

Using giant sections of the distended bladder of patients with papillary tumors, Dr. Schade (cited in [1]) demonstrated many years ago that papillary tumors may be multiple and may grow to substantial proportions with minimal or no invasion of the bladder wall.

Papillary tumors of the bladder are comprised of a heterogenous family that varies histologically and cytologically from an orderly, structured pattern to disorganized papillary growths of anaplastic tumor cells. These tumors may be single or multiple. Their biologic behavior is closely correlated with their histologic and cytologic morphology, such that increasing anaplasia is associated with increasing clinical aggressiveness. From the most benign to the most malignant, papillary tumors of the bladder are classed as simple papillomas; hyperplastic papillomas with or without atypia; papillomas with areas of carcinoma *in situ*; non-invasive papillary carcinoma having carcinoma *in situ* diffusely present; and, finally, as invasive papillary carcinoma.

An illustration of the simple benign papilloma is papillary tumors in which the fronds are delicate, thin, single, or branching with a cen-

tral fibrovascular core on which the epithelium (urothelium) closely resembles the normal bladder urothelium. The cells of the surface epithelium are orderly, well-oriented, and cytologically benign. In the hyperplastic papilloma, the epithelium clothing the fibrovascular core is many cell layers thick, yet the cells making up that epithelium are still cytologically benign, orderly in their arrangements, and oriented with the long axis of their ovoid nuclei orthogonal to the central vascular core. By contrast, papillary carcinoma is made up of cytologically malignant epithelium on a fibrovascular core. The epithelial cell nuclei are relatively large, hyperchromatic, and granular, with coarsely textured chromatin, and often an irregular, wrinkled nuclear configuration. In addition, the cells have lost their orientation and are loosely disarranged. Simple papillomas are relatively uncommon, accounting for perhaps 1% or 2% of the papillary tumors. Hyperplastic papillomas are much more common, accounting for at least 20% of tumors, or more if one includes hyperplastic papillomas with atypia. Papillary carcinomas are usually hyperplastic but not invariably so.

While many texts have taught for a number of years that all papillary tumors should be classified as papillary carcinoma, there is increasing evidence and now a number of recent reports to support the view that low grade, papillary tumors composed of orderly arranged, cytologically benign, epithelial cells are clinically benign even if hyperplastic, and should be classified as papillomas. One of the earliest of these reports by Nichols and Marshall in 1956 [4] demonstrated that the survival of patients with histologically and cytologically benign papilloma was exactly the same as the age-matched survival of the general population for a period of at least 5 years following conservative treatment of their tumors. In a second study by Bergqvist *et al.* in 1965 [5], 300 patients with bladder tumors were followed for a period of 8 years. Of these, 64 (21%) patients had low grade papillary tumors, and none died as a result of their bladder tumors. One patient developed a new carcinoma of the bladder 5 years later and eventually died of that second, cytologically malignant tumor. It is important to point out that 21% of tumors in Bergqvist's series fell into the category of low grade, cytologically benign papillary tumor. This is much greater, of course, than the 1% or 2% of bladder tumors that meet the restrictive definition of papilloma in which the epithelial component is normal appearing urothelium. The probability of death from bladder cancer in Bergqvist's study increased with increasing grade of tumor. His was the first major study to demonstrate the importance of grade as a prognostic feature for bladder tumors. In a study by Limas *et al.* in 1979 [6], 12 of 53 patients had low grade bladder tumors, *i.e.*, Grade I bladder tumors, and none developed invasive cancer. Of the remaining 41 patients, the probability of invasion increased with increasing grade of the tumor from 36% for Grade II tumors, to 75% for Grade III tumors, and 80% for those patients who had lower grade tumors changing to higher grade at the time of recurrence.

Lerman *et al.* [7] reported a study of 125 patients examined at Memorial Sloan Kettering Cancer Center for papillomas of the bladder. Twelve of the 125 patients (10%) later developed carcinoma of the bladder. Forty of the 125 patients had atypical papillomas, either initially or in recurrence, and all of the 12 patients who subsequently developed carcinoma were among the 40 who had atypical papillomas. This is consistent with, and suggests, that carcinoma developing in an originally benign papilloma does so by progressive steps through atypia, to fully developed carcinoma *in situ*, and then to invasion. The atypical papilloma, as defined in the Memorial Sloan Kettering study, is a papillary tumor in which the epithelial cells are atypical and disorderly although cytologically benign. There may be mild variations in nuclear size and shape but no significant hyperchromasia or other nuclear abnormality. The time to development of carcinoma of the bladder in recurrent tumors in Lerman's study ranged from 3 to 12 years in 10 of the 12 cases; in one of the other cases, invasive carcinoma developed at the end of one year, and in the other case, papillary carcinoma *in situ* developed 20 years after the original papilloma, and invasive carcinoma did not develop until 32 years after the original papilloma.

Papilloma with carcinoma *in situ* is defined as a cytologically benign papillary tumor within which there is one, or usually several, areas of cytologically malignant epithelium. This finding is not unusual and is consistent with the thesis

of this presentation—that papillary carcinoma develops in a step-wise fashion presenting first as atypia within a benign papilloma, then as focal areas of carcinoma *in situ* within that papilloma, and finally as diffuse papillary carcinoma *in situ* or non-invasive, papillary carcinoma.

Carcinoma defined by the cytologic and histologic features already described must be present at least focally, although it is usually present diffusely, before there is evidence of invasion. This has very useful practical applications for the pathologist who, when presented with fragments of papillary tumor obtained by transurethral resection, is often called upon to decide whether or not there is invasive carcinoma. Exophytic papillary tumor may be accompanied by inverted papilloma and by extension of papilloma into Brunn's nests. It may sometimes be very difficult to exclude or define the presence of superficial invasion from these biopsy fragments. However, one can be sure that if the papillary tumor is quite low grade, that is, if it is histologically and cytologically benign, that invasion will not occur and that the diagnosis of a non-invasive papillary tumor can be made with confidence.

One might argue that papillary carcinoma could begin from flat carcinoma *in situ*, and certainly that is a theoretical possibility. However, while flat carcinoma *in situ* is relatively common and may be accompanied by minor papillations or folding of the mucosa, it is extremely unusual to find cases that illustrate the transition from flat carcinoma *in situ* to papillary carcinoma. The flat carcinomas *in situ* almost invariably invade directly into the subepithelial stroma as they progress. They do not progress by developing into exophytic papillary carcinomas. On the other hand, areas of atypia and carcinoma *in situ* are found quite frequently in otherwise benign-appearing papillomas so that examples of the transition from papilloma to papillary carcinoma are common.

A very interesting and instructive paper was published in 1976 by Althausen, Prout and Daly [8], emphasizing the importance of flat carcinoma *in situ* in the mucosa adjacent to papillary tumors. They studied 78 cases of low grade, non-invasive papillary tumors, (which by the definition described here would be classified as papillomas); 41 had normal appearing adjacent mucosa, 25 had atypia in the adjacent mucosa, and 12 had carcinoma *in situ* in the adjacent mucosa. Only three of the 41 with normal appearing adjacent mucosa (7%) subsequently developed invasive carcinoma. Nine of the 25 (36%) having atypia in the adjacent mucosa subsequently developed invasive carcinoma, and 10 of the 12 (83%) with carcinoma *in situ* in adjacent mucosa developed invasive carcinoma at a later time. Thus, it appears that flat carcinoma *in situ* accompanying or adjacent to a low grade papillary tumor is the determining factor with respect to whether or not invasive carcinoma will occur, and the papillary tumor itself becomes almost irrelevant.

Another study of interest was reported by the National Bladder Cancer Collaborative Group in 1977 [9]. In that report of the exfoliative cytology of bladder tumors, it was surprising to find that 43% of the low grade or Grade I tumors had positive cytology. Assuming that the cytologic examinations were done by qualified cytotechnologists and cytopathologists, the only possible explanations are that the malignant cells came from undetected foci of carcinoma *in situ* within the low grade tumors, or that they came from mucosa elsewhere in the bladder. The latter explanation seems the most likely. Accepting the fact that approximately 43% of the patients with low grade papillary tumors had unsuspected areas of carcinoma *in situ* elsewhere in the bladder, one would expect recurrences of carcinoma at other sites in these patients. In fact, in an accompanying publication from the same group, they reported recurrences of superficial bladder tumors in 80% of the patients treated after transurethral resection [10]. Half of these recurrences (41%) were at other sites in the bladder, consistent with our speculation that the positive cytology derived from unsuspected foci of carcinoma elsewhere in the bladder, separate from the original papillary tumor.

We note that 70 to 80% of non-invasive bladder tumors will recur after resection, with increasing likelihood of recurrence in patients who have multiple bladder tumors either simultaneously or over a period of time, and in patients who have large tumors. Ten to fifteen percent of the patients with papillary tumors will eventually have muscle invading carcinomas. The evidence in a number of reports sug-

gests that in many cases the invasive carcinomas do not develop from the papillary tumors but from flat carcinoma *in situ* in adjacent or distant areas of the bladder. There are three publications worthy of reference that support this view. The first by Kaye and Lange [11] in 1982 involved a study of 166 patients who presented with bladder cancers invading into muscle; 139 had no prior history of bladder tumors. Thus, these carcinomas began *ab initio* from flat areas of carcinoma *in situ*; they did not arise from prior papillary tumors. A second, similar report by Brawn in 1982 [12] described 104 consecutive patients with invasive carcinoma of the bladder. Eighty-four (81%) had no prior papillary tumor. Finally, in a paper in 1983, Hopkins, Ford, and Soloway [13] reported on 90 patients with muscle invading bladder cancers, of whom 82 (91%) had no prior superficial bladder cancer. Of the eight patients who did have prior superficial bladder cancer, one was known to have had flat carcinoma *in situ*. Thus, the evidence strongly suggests that most of the low grade, papillary tumors behave as benign tumors, and that those that do become invasive do so by steps that include the development of carcinoma *in situ* within the papillary tumor prior to appearance of invasive carcinoma. While the great majority of papillary tumors can be treated by local ablation before developing into invasive carcinoma, most of the invasive bladder cancers (about 80%) appear *ab initio* and do not develop from papillary tumors.

In summary, papillary tumors of the bladder composed of uniform, cytologically benign epithelium are clinically benign and not capable of invasion, and should therefore be classified as papillomas. Carcinomas of the bladder develop by transformation of the epithelium in a papilloma or in flat mucosa and do so by progression through atypia and carcinoma *in situ*. The multifocal origin of carcinoma in space and time is typical and is evident within papillomas as well as in flat mucosa. Papillary tumors, whether benign or malignant, signal a "neoplastic diathesis" of the entire urothelium in that patient. Thus, the patient at highest risk of papillary tumor or flat carcinoma is the patient who has already had papillary tumors, particularly if the patient has had multiple papillary tumors or large papillary tumors. Finally, papillary carcinoma *in situ* is more easily controlled by conservative resection than is flat carcinoma *in situ*. This may be in part because the papillary tumor is more easily visualized, or it may be because it is more indolent than flat carcinoma *in situ*. In any case, invasive carcinoma usually develops from the flat mucosa with carcinoma *in situ*, even in patients who have had papillary tumors.

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