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Pathology of Carcinoma *in Situ* of the Urinary Bladder and Related Lesions

George M. Farrow, MD

Department of Pathology, Mayo Clinic, Rochester, Minnesota 55905

Abstract In the United States, nearly all cases of bladder cancer are of the transitional cell type, and epidemiological evidence indicates that among these, approximately 80% present initially as more or less well-differentiated, superficial papillary neoplasms with a tendency for multifocal or diffuse involvement of the urothelial surface and/or recurrent tumor episodes, but with limited potential for invasive growth or a lethal outcome. Bladder tumors with lethal potential generally begin as poorly differentiated, sessile growths that are usually invasive at first diagnosis. Carcinoma *in situ* is a change that must be elicited among intact surface cells before progressive proliferation results in a tumor mass. Evidence for such an association is both temporal and spatial. Since most transitional cell carcinomas begin as well-differentiated tumors, *i.e.*, resembling normal urothelium, recognition of early neoplastic alteration before a papillary structure forms is unlikely and most of the evidence is spatial based upon urothelial changes adjacent to papillary tumors. The morphologic definition of carcinoma *in situ* is arbitrary and generally defined as a total replacement of the urothelial surface by cells which bear morphologic features of carcinoma, but which lack architectural alteration other than an increase in the number of cell layers, *i.e.*, a flat lesion. The Union Internationále Contra Cancer/American Joint Committee on Cancer (UICC/AJCC) staging scheme for bladder cancer distinguishes non-invasive papillary growths as Ta and carcinoma *in situ* as Tis. Because detection of carcinoma *in situ*, either by cytology or biopsy, depends upon recognizable malignant morphologic characteristics, studies of the lesion tend to be limited to the higher grade or more anaplastic examples. Carcinoma *in situ* may exist in the urothelium adjacent to a papillary or invasive bladder cancer in which case the term "concomitant" has been used. If at initial presentation the bladder cancer is detected while still entirely *in situ*, the term "primary" carcinoma *in situ* is used. Primary carcinoma *in situ* tends to be more indolent than the concomitant type. The lesion is usually widespread in the urothelium, and can involve the epithelium of the distal ureters, Brunn nests in the lamina propria, and the periurethral prostatic ducts and glands. Static image cytometry with DNA analysis has indicated that the cells of primary carcinoma *in situ* differ from muscle invasive transitional cell carcinoma by exhibiting a considerably greater nuclear DNA content.

Key words: bladder, carcinoma *in situ*, chemoprevention

In the United States, nearly all cases of bladder cancer are of the transitional cell type. Epidemiological evidence indicates that among these, approximately 80% present initially as more or less well-differentiated superficial papillary tumors with a tendency for multifocal or diffuse involvement of the urothelial surface and for recurrent tumor episodes over time, but with limited potential for invasive growth or a lethal outcome. Thus, in 1991, there were an estimated 50,200 new cases of bladder cancer with 9,500 deaths from the tumor [1]. Bladder tumors with a lethal potential generally begin as sessile or flat growths and are often invasive at first detection [2–4]. Thus, 20% of the cases account for more than 80% of the deaths, although a minority of the superficial papillary tumors may dedifferentiate or become more anaplastic with repeated tumor episodes over time.

In a mechanistic view of epithelial cancer, before progressive proliferation of transformed cells eventuates in an invasive tumor, a neoplastic state must be elicited among intact surface epithelial cells. Carcinoma *in situ* is one stage in the dynamic state of progressive cellular transformation from normal through a variable phase of increased proliferation, disordered growth or maturation, to a frequently irreversible state we recognize as cancer.

Evidence for a pre-existing *in situ* phase preceding the development of an invasive tumor is both spatial, as determined from mapping studies of the urothelium surrounding visible neo-

plasms [5–12], and temporal, from studies of bladder tumor cases initially detected in an *in situ* stage and followed until the development of an invasive tumor [13,14].

Due to the range of configurations and degrees of differentiation among bladder carcinoma, the morphologic definition of carcinoma *in situ* is likely to be arbitrary. Nevertheless, it is critical as a starting point for all future discussions. Like uterine cervical cancer, bladder carcinoma *in situ* is generally defined as a neoplastic transformation of the epithelial surface without architectural alteration other than a possible increase in the number of cell layers [15]. It is implicit in this definition that cellular anaplasia be present. However, unlike cervical carcinoma, the majority of bladder neoplasms are first recognized as papillary growths; only a small proportion are initially flat. Of the papillary tumors, a significant proportion are composed of well-differentiated cells; therefore, structure, not cellular anaplasia, is the criterion of neoplasia (Fig. 1). Some alteration of the epithelial cells must have occurred prior to the development of the papillary structure. These neoplasms are usually non-invasive at the initial diagnosis and are considered *in situ*. A minority dedifferentiate or become more anaplastic. The best studied example of the lesion, flat cervical carcinoma *in situ*, actually represents a step in the evolution of most examples of cervical squamous cell carcinoma—tumors which most often are sessile. Papillary carcinomas of the cervix represent an evolution of neoplasia outside usual bounds. Arbitrarily restricting the term "carcinoma *in situ*" only to those transitional cell neoplasms of the bladder which are flat and meet the criteria of cervical carcinoma excludes from consideration those lesions operative in the evolution of most bladder neoplasms. Nevertheless, there is a consensus that only flat (non-papillary), non-invasive neoplastic lesions of the surface epithelium be identified as carcinoma *in situ* (Fig. 2). Wide support for this opinion is reflected in the current Union Internationále Contra Cancer/American Joint Committee on Cancer (UICC/AJCC) staging schemes where non-invasive papillary tumors are separate from carcinoma *in situ*.

Because detection of carcinoma *in situ*, either by cytology or biopsy, depends upon recognizable malignant morphologic characteristics,

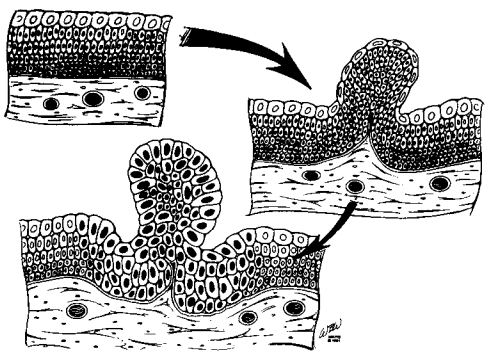

Fig. 1. Schematic representation of the evolution of superficial papillary bladder tumor.

studies of the lesion tend to be limited to the higher grade or more anaplastic examples [5,16]. Criteria for anaplasia are: increased cellularity, nuclear crowding, disturbances of cellular polarity, failure of differentiation from the base to the surface, polymorphism, irregularity in size of cells, variations in chromatin pattern of the nuclei, displaced or abnormal mitotic figures and giant cells [17]. Carcinoma *in situ* is defined as a lesion in which there is definite anaplasia of the surface epithelium without formation of papillary structures and without infiltration (Fig. 3).

Based upon clinical presentation, carcinoma *in situ* has been subdivided into primary, secondary, and subsequent categories (Table I). When carcinoma *in situ* exists in the urothelium adjacent to a papillary or invasive bladder tumor, it is termed "concomitant." If at initial presentation, the bladder tumor is detected

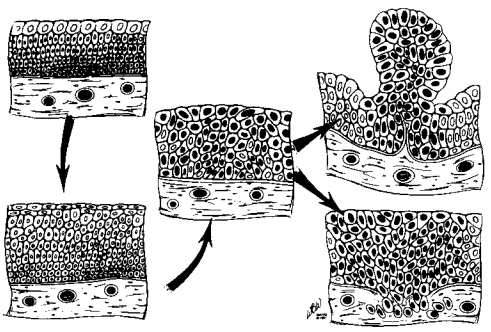

Fig. 2. Schematic representation of the evolution of most lethal bladder tumors through stages of dysplasia, carcinoma *in situ*, and papillary and invasive carcinoma.

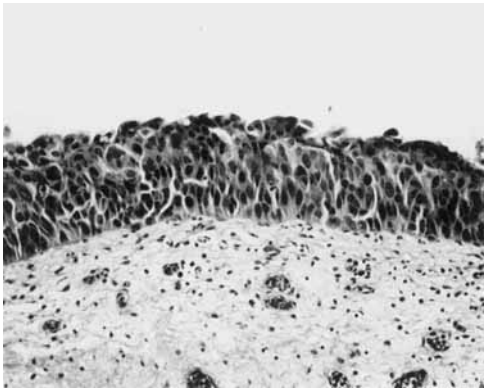

Fig. 3. H & E 250×. Carcinoma *in situ*.

while still entirely *in situ*, the term "primary" carcinoma *in situ* is used. At the present time, the vast majority of cases of carcinoma *in situ* worldwide are represented by the "secondary" and "subsequent" types. Cases of "primary" carcinoma *in situ* are detected much less frequently, and most patients complain of symptoms of cystitis. Organized studies of primary carcinoma *in situ* are possible only when screening programs exist which utilize tests such as urine cytology.

Division of carcinoma *in situ* cases into clinical categories does have limited usefulness in predicting outcomes. In secondary concomitant cases, prognosis and therapeutic intervention strategy are likely to depend upon the status of the gross neoplasm. Associated widespread carcinoma *in situ* may necessitate a more radical approach in cases where the associated gross neoplasm would otherwise be managed by more conservative therapy. A secondary "concomitant" carcinoma *in situ* which persists after treatment for an already invasive neoplasm would seem more likely to pursue a rapid course to invasion than a case of primary carcinoma *in situ*. Secondary "subsequent" carcinoma *in situ* might, on the average, be intermediate, but the status of the relative natural history of the various subcategories is not clear.

TABLE I. Clinical Classification of Transitional Cell Carcinoma *in Situ*

Secondary
Concomitant
In association with gross neoplasm
Persistence after removal of neoplasm
Subsequent
Development after treatment of a gross neoplasm
Primary
Initial diagnosis—*in situ* stage

The most valuable test for the detection of carcinoma *in situ* is a properly conducted and accurately interpreted urine cytologic examination. Depending on the cytopreparatory technique employed, the appearance of the neoplastic cells will vary slightly. In my own experience using unfixed fresh urine and a membrane-filter technique, the cytologic presentation of carcinoma *in situ* is typified by large neoplastic cells that most often occur singly. These cells may be numerous or rare, depending on the extent of mucosa affected. The cytologic features are not specific for the *in situ* state, but the cells are more regular in outline and more cytoplasm is present than that observed in the usual invasive cancer. Bladder washing or irrigation specimens yield many well-preserved cells, and some cytologists favor this technique over study of voided urine. However, because of its invasive nature, this procedure is not suitable for routine diagnostic use.

Mapping studies performed by systemic biopsy of the bladder and by step-sectioning of cystectomy specimens provide useful information on the distribution and extent of the mucosal abnormalities among different categories of bladder tumors. Among those cases of "primary" carcinoma *in situ*, particularly in patients with symptoms of cystitis, the neoplastic transformation is usually widespread, involving more than one-third of the urothelial surface in most cases and as much as 80% in some cases. The trigone region and contiguous posterior wall are most frequently affected. In "secondary" cases, the *in situ* alteration is often limited to the epithelium near the periphery of the gross tumor. An *in situ* component may not be detected in many cases of invasive bladder cancer, perhaps due to overgrowth of the invasive component.

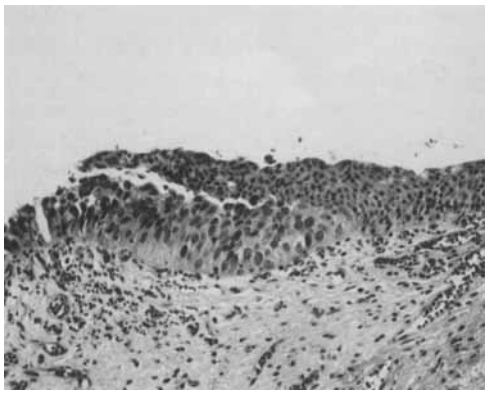

Fig. 4. H & E 200×. Extension of carcinoma *in situ* beneath the intact urothelium.

The urothelium overlying the ureteral orifices is often affected; it is common to find extension of the *in situ* process into the urothelial lining of one or both distal ureters. Similarly, where carcinoma *in situ* involves the lower vesicle neck and prostatic urethra, the neoplastic change may extend into the epithelium lining the periurethral prostatic ducts and even into prostatic glands.

Bladder mucosal atypia (dysplasia) may be evident in a narrow zone around the borders of carcinoma *in situ* implying progression from a premalignant atypia. In cases of "primary" carcinoma *in situ*, a histologic phenomenon may be observed at the junction of normal and neoplastic mucosa, representing accrual of additional mucosa into the neoplastic process by the direct intramucosal spread of malignant epithelial cells. This is much less prominent in "secondary" cases. Two related morphologic forms have been identified. For distances of 1 to 2 mm adjacent to an *in situ* carcinomatous zone, neoplastic cells of the interior or basal layer of epithelium extended along the basement membrane beneath the adjacent intact normal mucosa, lifting the mucosa off its basilar footings (Fig. 4); on further proliferation, the malignant cells form multiple layers and the normal epithelium appears to slough, replaced by layers of malignant cells. A second process, a striking pagetoid-type spread into adjacent epithelium with single cells or clusters of two or three neoplastic cells, may be found as far as 4 mm from an adjacent carcinoma *in situ*. This phenomenon of intramucosal spread is especially prominent at the advancing margin of carcinoma *in situ* in the prostatic ducts and in the mucosa of the distal ureters.

It is likely that a continuous spectrum of biological aggressiveness exists for cases of carcinoma *in situ*. Some tumors which are invasive at first presentation must have passed through the *in situ* phase rapidly. Because of the statistical aberration of "time-lag bias," intervention in populations with a one-time screening event, such as a urine cytology examination, will selectively discover cases of carcinoma *in situ* with the longest time phase, giving a perception of chronicity to primary carcinoma *in situ*. Primary transitional cell carcinoma *in situ* with a prolonged period of non-invasiveness partially results from studying prevalence cases. Application of various techniques to detect molecular markers, antigen deletions, or chromosomal abnormalities, thought to be useful in separating aggressive from non-aggressive low-stage papillary tumors, has not found predictive value in carcinoma *in situ*. Recently, comparisons of nuclear DNA content of invasive transitional cell carcinoma and primary carcinoma *in situ* have shown significant differences [18]. This supports the concept that differences exist in the potential of the cells to evolve into an invasive neoplasm among cases with a long primary *in situ* phase, in contrast to neoplasms which become invasive early.

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