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# Long-term results of primary adenocarcinoma of the urinary bladder: A report on 192 patients

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**Abstract**

**Objectives:** To evaluate the clinical presentation and treatment end results of primary adenocarcinoma of the urinary bladder, and to determine the significant independent prognostic factors that determine this outcome.

**Patients and Methods:** Of 3659 patients who underwent cystectomy, 192 had adenocarcinoma of the urinary bladder, with a relative frequency of 5.2%. Most of these patients (68.2%) presented in late stages (P3 + P4). The incidence of pelvic lymph nodes involvement was 25.5%. Mucinous adenocarcinoma was reported in 28 patients (14.6%), papillary in 20 (10.4%), signet ring in 14 (7.3%), while not otherwise specified was reported in 130 (67.7%) in the cystectomy specimens.

**Results:** Mucinous and signet-ring histologic subtypes showed increased frequency of high stages and high grades, and more nodal involvement than the papillary and not otherwise specified. All patients were treated with radical cystectomy and pelvic lymphadenectomy with (69 patients) or without (123) postoperative radiotherapy. The 5-year disease-free survival rate was 46 ± 4% for all patients with adenocarcinoma. Postoperative radiotherapy improved the disease-free survival significantly. The 5-year disease-free survival rate for the postoperative radiotherapy group was 61 ± 6% compared to 37 ± 5% for the cystectomy alone group ($P = 0.002$). Local control rate was significantly improved from 53 ± 7% for cystectomy alone to 96 ± 3% for postoperative radiotherapy patients ($P = 0.00001$). Distant metastases were the leading cause of death in the postoperative radiotherapy group.

**Conclusions:** Within the limitations provided by retrospective studies, it could be concluded that postoperative radiotherapy improved the disease-free survival through its effect on local control. The disease-free survival independent prognostic variables were tumor stage, postoperative radiotherapy, nodal involvement, and adenocarcinoma subclassification. These factors, except the adeno-subclassification, were also found to determine the local control rate. On the other hand, the independent prognostic factors for distant metastasis were lymph nodal involvement, stage, and adeno-subclassification. 

*Keywords:* Urinary bladder neoplasm; Adenocarcinoma; Radical cystectomy; Adjuvant radiotherapy; Prognostic factors

## 1. Introduction

Adenocarcinoma of the urinary bladder is classified according to its origin into 3 categories: primary, urachal, and metastatic [1]. The reported incidence of primary adenocarcinoma was 0.5% to 2% of all urinary bladder malignancy [2]. However, it is more frequently encountered in areas where bilharziasis is endemic. This incidence ranged between 5% and 11.4% [3–7]. Metaplastic changes of potentially unstable urothelium were considered as the causative factor for the development of adenocarcinoma of the urinary bladder [8]. It was proposed that the metaplastic potential of the urothelium has 2 distinct patterns [9]. Progressive invagination of hyperplastic epithelial buds into the lamina propria (Von Brunn nests) leads to the formation of cystitis cystica. Subsequently, metaplasia of the urothelial lining of these cysts to columnar mucin-producing cells results in the

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production of cystitis glandular, which is a premalignant lesion [10]. Moreover, cuboidal or columnar metaplasia of the surface epithelium can occur with no downward invagination. Chronic vesical irritation and infection were mentioned as predisposing factors for these changes [8,9]. This effect may explain the higher incidence of these tumors among patients with bilharzial cystitis.

The pathologic characteristics, clinical behaviors, and response to different lines of treatment were not clearly identified, mostly because of the rare incidence and lack of universal standardized treatment. The largest 2 published series reported on 185 patients with primary adenocarcinoma treated with radical cystectomy and pelvic lymphadenectomy [6] and 142 patients treated with radical cystectomy with or without postoperative radiotherapy [7]. The majority (76%) of patients in the first series had early stage disease (i.e., P1 and P2, Union Internationale Contre le Cancer 1997), while the majority (67.6%) of the second had late stage disease (i.e., P3 and P4). The 5-year disease-free survival rate for patients with early stage disease was excellent, while patients with advanced stages (i.e., P3 and P4) had a statistically significant lower survival rate in the 2 series.

Postoperative radiotherapy as an adjuvant therapy proved to increase the disease-free survival through improvement of the local control of patients with relatively advanced stages P2b, P3, and P4a with transitional, squamous and adenocarcinoma [4,7,11]. Irradiation has shown efficacy in a series [12] reporting on small numbers of bladder adenocarcinoma, and it is clearly effective in adenocarcinomas that occur at other sites (e.g., breast, cervix, uterus, prostate, parotid, rectum). The aim of this study was to report on a large series of primary adenocarcinoma of the bladder, its clinicopathologic characteristics, and treatment end results. All patients were treated with radical cystectomy and bilateral pelvic lymphadenectomy with or without adjuvant postoperative radiotherapy.

## 2. Patients and methods

A total of 3659 patients with bladder cancer were subjected to radical cystectomy and pelvic lymphadenectomy from January 1994 to December 2003, at National Cancer Institute Cairo University and Minia Oncology Center (October 1998 to December 2003). The files of the patients were reviewed, and those who had the pathology of primary adenocarcinoma of the bladder were thoroughly examined. Of the 3659 patients who underwent cystectomy, 192 (5.2%) had adenocarcinoma. The pathologic specimens were reviewed by the same pathologist (A.N.) and subclassified according to Grignon et al. [13]. Specimens with extension to the prostate had to prove negative prostate-specific antigen immunohistochemical stain to be included in this study. They divided vesical adenocarcinoma into 5 histologic subtypes: (1) enteric (papillary), when the architectural and cytologic features resembled those of the typical colonic adenocarcinoma; (2) mucinous, when the tumor was characterized by single cells or nests of cells floating in lakes of extracellular mucin; (3) signet ring, when the tumor was composed of single signet-ring cells diffusely permeating the tissues; (4) adenocarcinoma not otherwise specified, when the pattern did not fit into any of these previously mentioned categories; and (5) mixed, when the tumor showed 2 or more patterns with no single pattern accounting for more than 75% of the materials. Detailed characteristics, treatment, and follow-up of these 192 patients were thoroughly examined because they were the main concern of this report.

Radical cystectomy and pelvic lymphadenectomy were performed in 133 males, and anterior pelvic exenteration with pelvic lymphadenectomy was the treatment in 59 females according to El-Sebai [14]. Of the 192 patients, only 69 (35.9%) received postoperative radiotherapy using 6 or 15 MV photon, according to the patient's separation, giving 50 Gy/5 weeks/25 fractions using 3 fields (1 anterior and 2 posterolateral) technique. The target volume included the entire true pelvis and extending upward from the first sacral vertebra to the lower border of both obturator foramina. The lateral borders of the radiotherapy fields were 1 cm lateral to the pelvic brim. The anterior border included half the symphysis pubis, and the posterior border included the anterior 1/3 of the rectal wall [4,11]. Postoperative radiotherapy was indicated in pathologic stages P2b, P3, and P4a. The choice of adjuvant postoperative radiotherapy depends entirely on surgeon belief. In the absence of definite evidence, some surgeons believe that adenocarcinoma is radioresistant and not expected to benefit from adding postoperative radiotherapy, while others believe the opposite. Patients were regularly followed up and examined to detect signs and sites of treatment failure, depending on clinical findings, radiologic or histopathologic evidence, whenever possible. Follow-up ranged between 0.1 and 108 months, with a median of 49 months.

### 2.1. Statistical analysis

Comparison between different percentages and frequencies were performed using the standard Student *t*-test, *F*-test, and chi-square test. The 5-year disease-free survival rates, local control rates, and distant metastasis-free rates were measured using the Kaplan-Meier product limit method [15]. The disease-free survival period was defined as the period from the date of radical cystectomy to the date of occurrence of any relapse, either local or distant. Patients who died of any other cause were considered failures at death. The local control period was defined as the period from radical cystectomy to the date of detection of local recurrence. Any other event, either distant metastasis, uremia, or death caused by accidental disease was considered as censored. The period of freedom from distant metastasis was defined as that from the date of surgery to the detection