

19 Concomitant Radiation and Chemotherapy in Muscle-Invasive Bladder Cancer

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19.1 Introduction

Organ- and function preservation has become a major goal in contemporary oncological treatment concepts. In some tumor sites, e.g., breast, larynx, anal cancer or soft tissue sarcomas, organ preservation is considered as standard approach for most patients with radical surgery restricted to salvage treatment for failures after conservative therapy. Urothelial bladder cancer is a radiosensitive disease and radiation therapy offers an effective method for organ preservation, especially if combined with simultaneous chemotherapy.

19.2 Organ Preservation in Urinary Bladder Cancer: Theoretical Aspects

Radical cystectomy is considered as standard of care for muscle-invasive bladder cancer by most urologists; however, the concept of organ preservation by limited surgery and radiochemotherapy which is currently used in larynx, other head and neck, or anal-canal cancers may also be effective in urothelial bladder cancer. Despite evidence from several series, this approach is so far not widely accepted (GOSPODAROWICZ 2002). In a

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survey, MOORE and coworkers (1988) asked expert physicians about their attitude on treatment of locally advanced bladder cancer. Nearly all U.S. urologists and medical oncologists favored radical cystectomy as standard approach. In contrast, one-third of the British urologists recommended radiotherapy (Table 19.1). The best explanation for these discrepancies is the fact that radiotherapy has been widely used as primary treatment for locally advanced bladder cancer in the UK. Large series from single institutions in Great Britain and the largest randomized trial, also from the UK, have over years proven the general efficacy of radiotherapy.

Additional theoretical support for an organ-preserving approach comes from the biology of muscle-invasive bladder cancer. In general, muscle-invasive cancers ($T \geq 2$) behave more aggressively as compared with the more frequent superficial tumors. They are characterized by a higher risk of local recurrence after transurethral surgery as well as a high frequency of occult systemic spread. Even in case of radical cystectomy, about 50% of all patients will eventually die from metastatic disease. This situation is comparable to lymph-node-positive breast cancer. Organ-preserving treatment in breast cancer has been clearly demonstrated to be as effective as radical mastectomy in terms of overall survival. The same holds probably true for muscle-invasive bladder cancer.

Moreover, urothelial cancers are relatively radio-sensitive. The TCD50 (calculated from selected series or estimated from series with preoperative radiotherapy and planned cystectomy) is comparable or even lower than the TCD50 of squamous cell carcinomas of the head and neck (MACIEJEWSKI and MAJEWSKI 1991). The efficacy of radiotherapy or combined radiochemotherapy in head and neck cancers, however, has been proven.

19.3

Limitations of Historical Series

Most historical series of radiotherapy for bladder cancer have yielded survival figures inferior to those obtained in surgical series of the same time period. These differences in outcome (absolute difference in 5-year overall survival about 20% for T2 category and 10% for T3 category) do not necessarily reflect a superiority of radical surgery but are due mainly to other reasons. In most series, radical cystectomy was used as primary treatment for muscle-invasive bladder cancer with radiation restricted for patients unsuitable for major surgery; thus, radiotherapy patients reflect a negative selection with regard to age distribution and performance status despite comparable clinical stages. Age and performance status, however, are major independent prognostic factors in locally advanced bladder cancer, together with pretreatment anemia and elevated erythrocyte sedimentation rate. These patient-related prognostic factors have a stronger impact on long-term survival than T-category and can be used for the prediction of treatment outcome especially in irradiated patients. The selection bias in historical series becomes evident if one compares series from the same institution or region and if one further analyzes the results of subgroups. For example, two reports from the Norwegian Radium Hospital summarize the results of surgery and radiotherapy for bladder cancer over the same time period in a distinct region of Norway (FOSSA et al. 1993; WAEHRE et al. 1993). Surgery was the treatment of first choice; therefore, surgical patients were significantly younger and had a better stage distribution and less comorbidity than irradiated patients. The highly significant difference in survival between surgically treated and irradiated patients (5-year survival 58 vs 24%) decreases if one compares subgroups of comparable age and T-categories (DUNST et al. 2001). Taking into account the lacking

Table 19.1. Expert physicians' attitude toward radiotherapy in bladder cancer (probably depends more on geographical and educational factors than scientific data). (Adapted from MOORE et al. 1988)

Recommended therapy	U.S. urologists (%)	British urologists	Medical oncologists	Radiation oncologists
Cystectomy	60	11	29	4
Preop. XRT + cystectomy	8	15	18	39
Chemotherapy + cystectomy	20	4	25	8
Definitive radiotherapy (XRT)	0	44	0	31
Others	12	26	20	18