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Overview

Concomitant Chemoradiotherapy for Muscle-invasive Bladder Cancer: The Way Forward for Bladder Preservation?

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ABSTRACT:
Muscle-invasive bladder cancer is a common malignancy with a high mortality rate. Despite ongoing debates about the optimal primary intervention, radical cystectomy remains the cornerstone of first-line therapy in many institutions. Over the past decade, bladder-preserving strategies involving transurethral resection (TUR), chemotherapy and radiotherapy have evolved. However, the advantage of these approaches over radiation treatment as monotherapy has yet to be fully evaluated. In other tumour models, most notably cervical and anal cancer, radiation and chemotherapy delivered concomitantly have resulted in significant survival advantages. Here, we consider the potential value of this approach in the treatment of invasive bladder cancer. Concomitant chemoradiotherapy is currently the mainstay of several bladder-preserving programmes reported in the medical literature. Overall, local control and survival rates compare favourably with contemporary cystectomy series; however, difficulties in drawing valid conclusions are highlighted. Concomitant chemoradiotherapy may have a role in the management of certain patient subgroups, and the debate should remain open. Further large-scale randomised trials are needed, and information regarding bladder function and quality of life after treatment is lacking at present. The importance of close follow-up and prompt salvage cystectomy is emphasised. Sherwood, B. T. *et al*. (2005). *Clinical Oncology* **17,** 160–166

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Introduction

Muscle-invasive transitional cell carcinoma of the bladder is a common urological malignancy with a relatively poor prognosis. In many institutions, particularly in the USA, radical cystectomy remains the preferred primary treatment modality for organ-confined (T2–4/N0/M0) disease. Chemoradiotherapy, as an alternative strategy aimed at bladder preservation, is a controversial topic in the field of urological oncology for several reasons. Practitioners may regard the extent and duration of treatment needed as excessive, or feel concerned that the opportunity for a curative cystectomy may be missed after a failed course of treatment. This is compounded by the belief that recurrence in a preserved bladder increases the risk of death from cancer [1]. Cystectomy and continent diversions may certainly be more difficult after chemoradiation [2].

About 25% of bladder tumours are muscle invasive at presentation, a feature that is associated with significant risk of metastasis (30–60%). In contemporary radical cystectomy series, 5-year survival rates vary with tumour stage, being 75–83% for T1 tumours, 63–89% for T2 tumours, 31–62% for T3 tumours and 21–50% for T4 tumours [3,4]. Where external beam radiation is used as monotherapy, survival rates are 61% for T1 tumours, 40–45% for T2 tumours, 26–45% for T3 tumours and 9–12% for T4 tumours [5,6].

Arguments in favour of bladder preservation, based upon the complications of cystectomy and the impact on quality of life, are countered by ongoing improvements in urinary diversion techniques and improved rehabilitation after neobladder construction or nerve-sparing cystectomies. Furthermore, radiation therapy is associated with its own significant morbidity (about 5% [7]), arising from bowel and bladder being included in the radiation field. Unsurprisingly, introducing chemotherapy as a second modality potentially increases normal tissue toxicity, and successful concomitant chemoradiotherapy must therefore strive to improve disease control without compromising normal tissue tolerance.

We have conducted a comprehensive literature review to determine the current status of concomitant chemoradiotherapy in the management of muscle-invasive bladder

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cancer. Relevant clinical studies over a 10-year period (1993–2003) were identified from searches of Medline, ISI Web of Science and Cochrane databases, using the terms 'bladder cancer', 'chemotherapy', 'radiotherapy' and 'bladder-preservation'. Studies were included that involved at least 14 patients, and in which local response rates or bladder preservation rates were available in addition to survival data. References from papers obtained from the search were also reviewed. The literature review was carried out by BTS.

Mechanisms in Combined Radiotherapy and Chemotherapy

The concept of combined modality therapy in cancer treatment, using chemotherapy and radiotherapy, is designed to reduce the need for surgery by maximising the interaction between the radiation and the chemotherapeutic agent. Combining chemotherapy and radiotherapy is, of course, not a new concept, but despite its widespread application, the mechanisms underlying chemotherapy and radiotherapy interactions are incompletely understood.

When discussing the ways in which multimodality therapy might be more effective than chemotherapy or radiotherapy alone, it is important to appreciate the distinction between additive processes, whereby each treatment exerts its own independent effect and synergy, whereby one modality effectively modifies the response of the other. Initially, it was assumed that concomitant chemotherapy and radiotherapy interacted via simple spatial co-operation, whereby ionising radiation was responsible for local control and chemotherapy targeted sub-clinical metastases at more distant sites. In fact, radiotherapy and chemotherapy can interact much more closely. Adding a chemotherapeutic agent may cause radiosensitisation, giving rise to an alteration in the shape of the cell-survival curve after irradiation. This may be due to direct tumour cell cytotoxicity, or inhibition of sub-lethal or potentially lethal radiation-induced damage repair [8], leading to an enhanced response. Chemotherapy may also act synergistically with radiotherapy by targeting cells in radioresistant phases of the growth cycle, leaving a population of synchronised, more radiosensitive (G_2 and M phase) cells. Unfortunately, although attractive in theory, this effect is not readily exploitable for therapeutic gain. The biological basis of chemotherapy and radiotherapy interactions is outlined in Table 1.

In concomitant chemoradiotherapy, radiotherapy and chemotherapy agents are given, as the term implies, simultaneously. Neo-adjuvant chemoradiotherapy involves a course of chemotherapy followed by radiotherapy, with the two treatments being separated by a variable time interval.

Neo-adjuvant Chemoradiotherapy

In neo-adjuvant chemoradiotherapy, initial cycles of chemotherapy are aimed at debulking the primary tumour, thereby rendering the reduced number of cells more susceptible to cell death by ionising radiation. Such a process may also enhance the radiosensitivity of the residual tumour by making it less hypoxic. It is also suggested that sequential treatment may be less toxic than than concurrent treatment. Although this approach makes intuitive sense, the results of such strategies are variable in clinical practice. Indeed, in some solid tumours, it has been suggested that initial chemotherapy causes accelerated repopulation of resistant clones, compromising the ability of radiation therapy to achieve control [9]: the so-called 'leaner, meaner' tumours.

Table 1 – The biological basis of chemoradiotherapy interactions

Spatial co-operation
Prevention of emergence of resistant clones
Cell-cycle synchronisation
Hypoxic cell sensitisation
Hypoxic cell killing by chemotherapy
Inhibition of potentially lethal and sub-lethal radiation-induced damage repair
Inhibition of cellular repopulation during fractionated radiotherapy

In bladder cancer, the Advanced Bladder Cancer meta-analysis collaboration provided the most comprehensive assessment of neo-adjuvant chemotherapy in this disease to date [10]. The analysis included data from 2688 patients from 10 randomised trials of neo-adjuvant regimens, in which patients received definitive local treatment with or without neo-adjuvant systemic chemotherapy. Platinum-based combination chemotherapy showed a significant beneficial effect on overall survival, with a 5% improvement in survival at 5 years (from 45% to 50%). This effect was observed when definitive local therapy involved either radiotherapy or radical cystectomy. The meta-analysis was insufficiently powered to allow valid evaluation of individual regimens, or to reliably determine the effect of single-agent cisplatin on survival. Unfortunately, the implications of this meta-analysis for clinical practice are further limited by the fact that few of the included trials allowed meaningful conclusions to be drawn about toxicity and quality of life, both of which are of paramount importance when discussing primary treatment options.

Concomitant Chemoradiotherapy

By delivering radiotherapy and chemotherapy simultaneously, the opportunity for cross-resistant tumour cells to become established is minimised. In addition, the delivery of potentially curative radiation therapy is not delayed.

Cisplatin is one of the agents most closely investigated for its interactions with ionising radiation. Like several other drugs, it has been shown to inhibit the repair of radiation damage. Specifically, cisplatin exerts its cytotoxic effects by chelating guanine residues, yielding monofunctional adducts and intra-strand or inter-strand cross-links. If a cisplatin adduct and a radiation-induced single strand break arise simultaneously within close proximity, the result is mutual inhibition of effective repair [11,12].