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Original Research

Pathological downstaging and survival after induction chemotherapy and radical cystectomy for clinically node-positive bladder cancer—Results of a nationwide population-based study

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KEYWORDS
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Abstract ***Background:*** Induction chemotherapy (IC) for clinically node-positive bladder cancer is applied without clinical evidence of improved outcome. Our objective was to compare complete pathological downstaging (pCD) and overall survival (OS) for IC versus upfront radical cystectomy (RC) in cT1-4aN1-3M0 urothelial carcinoma (UC).

Study initiated by The Netherlands Comprehensive Cancer Organization (IKNL), The Netherlands Cancer Institute (NCI) and Dutch Uro-Oncology Studygroup (DUOS).

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Induction;
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Methods: This population-based study included 659 cN+ patients treated with RC between 1995 and 2013. IC was applied in 212 (32%) patients. We defined pCD as ≤(y)pT1N0 at RC. Multivariable analyses were preformed to identify independent predictors of pCD and OS.
Results: In cN1 and cN2–3 patients, 31% and 19% of patients proved to be pN0 at upfront RC. In cN1, pCD was achieved in 39% following IC versus 5% for upfront RC ($P < 0.001$). In cN2–3 UC, rates were 27% versus 3% ($P < 0.001$). Three-year OS for pCD and ypCD were 81% and 84%, respectively. Three-year OS rates were 66% versus 37% (cN1) and 43% versus 22% (cN2-3), again in favour of IC ($P < 0.001$). In multivariable analyses, IC was associated with pCD (Odds ratio, 14; 95% confidence interval [CI], 7.4–25) and a 53% decreased risk of death (Hazard ratio [HR], 0.47; 95% CI, 0.36–0.61). Indication bias and unequal distributions of factors associated with OS (e.g. patients proceeding to RC) limit interpretation of our results.
Conclusions: Patients with clinical nodal involvement should not be neglected. Up to 1/4 of patients with cN+ disease had pN0 at upfront RC. Moreover, IC followed by RC for clinically node-positive UC was associated with improved pathological downstaging compared with RC alone. A potential OS benefit for IC needs to be validated in a randomised trial.
Take home message: IC followed by RC for clinically node-positive UC is associated with improved pathological downstaging compared with RC alone. A potential OS benefit for IC needs to be validated in a randomised trial.

1. Introduction

In recent years, neoadjuvant cisplatin-based combination chemotherapy (NAC-CBCC) has gained acceptance and is considered state of the art in the treatment of cT2-4aN0M0 bladder cancer (BC) [1–5]. A meta-analysis of 11 randomised controlled trials (RCTs) reported an absolute 5-year overall survival (OS) benefit of 5% for patients who received NAC [1]. Clinical evidence for the use of induction chemotherapy (IC) in patients with clinically node-positive disease (cN+) is lacking. However, given a higher risk of disease recurrence and death, administration of IC appears persuasive if one assumes a hazard ratio (HR) of benefit that is at least equal to the N0 setting. Few relatively small retrospective studies on IC have suggested that complete pathological downstaging (pCD) is associated with beneficial long-term survival, whereas the prognosis of non-responders remained poor [6–8]. These studies are limited by low patient numbers and lack comparison to upfront radical cystectomy (RC) in cN+ patients. The primary aim of this population-based Netherlands Cancer Registry (NCR) study was to compare pCD in patients who underwent either upfront RC or IC followed by RC for cT1-4aN1-3M0 urothelial carcinoma (UC) of the bladder. The secondary aim was to perform an exploratory analysis on OS in the two cohorts.

2. Methods

2.1. Patients and study concepts

The Netherlands currently has a population of approximately 17 million people. According to the NCR, 10.388 patients underwent RC with curative intent as primary treatment for BC in the Netherlands between 1995 and 2013 [4]. Of these, 659 patients included in the present report underwent either upfront RC or RC following IC for cT1-4aN1-3M0 UC (Fig. 1). Patients who received neoadjuvant radiotherapy underwent partial cystectomy or salvage procedures were excluded. Cytological fine needle aspiration or histopathological confirmation of nodal invasion before RC or IC could not be retrieved from the NCR. Patients with cN3 disease ($N = 15$) were grouped together with those staged cN2. Specifications on particular chemotherapeutic agents and number of treatment cycles were not registered in the NCR.

2.2. The Netherlands Cancer Registry

The NCR is an independent government-funded organisation. Its purpose is to monitor, evaluate and improve current oncological care on a nation-wide basis. The NCR registers all newly diagnosed malignancies in the Netherlands. Notification is obtained from the national network and registry of histopathology and cytopathology (PALGA) and the national registry of hospital discharge diagnosis. Independent and trained data managers of the NCR collected data on patient, tumour and treatment characteristics from individual patient files. In the NRC, IC was defined as chemotherapy administered within a maximum of 6 months before RC in clinically-node positive disease. If the interval was longer, RC was not registered as primary treatment. Topography and morphology were coded according to the International Classification of Diseases for Oncology [9], and tumour stage was coded according to the tumour, node and metastasis (TNM)