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Original Research

# Perioperative treatment and radical cystectomy for bladder cancer – a population based trend analysis of 10,338 patients in the Netherlands

Tom J.N. Hermans [a], Elisabeth E. Fransen van de Putte [a], Simon Horenblas [a], Valery Lemmens [b,c], Katja Aben [b,d], Michiel S. van der Heijden [e], Laurens V. Beerepoot [f,1], Rob H. Verhoeven [b,1], Bas W.G. van Rhijn [a,*,1]

[a] *Department of Surgical Oncology, Division of Urology, Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands*
[b] *Department of Research, Netherlands Comprehensive Cancer Organisation, Utrecht, The Netherlands*
[c] *Department of Public Health, Erasmus University Medical Centre, Rotterdam, The Netherlands*
[d] *Department for Health Evidence, Radboud University Medical Center, Nijmegen, The Netherlands*
[e] *Department of Medical Oncology, Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands*
[f] *Department of Medical Oncology, Elisabeth-TweeSteden Hospital, Tilburg, The Netherlands*

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**Abstract** ***Background:*** In Europe, population-based data concerning perioperative treatment (PT) and radical cystectomy (RC) are lacking. We assessed temporal trends in PT (neoadjuvant chemotherapy [NAC], neoadjuvant radiotherapy [NAR], adjuvant chemotherapy [AC], adjuvant radiotherapy [AR]) and RC in the Netherlands and identified patients' and hospital characteristics associated with PT.

***Methods:*** This nationwide, retrospective, population-based study included cTa/is, T1-4, N0-3, M0-1 bladder cancer patients from the Netherlands Cancer Registry who underwent RC with curative intent between 1995 and 2013. PT-administration over time was compared with chi-square tests. Multivariable logistic regression analyses were performed to identify characteristics associated with PT usage. The sub-groups cT2-4N0M0 and cT2-4, N0 or NX, M0 or MX were separately analysed.

* *Corresponding author*: Dept of Surgical Oncology (Urology), Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands. Tel.: +31 205122553; fax: +31 205122459.
*E-mail address:* basvanrhijn@hotmail.com (B.W.G. van Rhijn).
[1] Shared senior authorship.

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***Results:*** In total, 10,338 patients met inclusion criteria. Eighty-six percent did not receive PT, 7.0% received NAC (or induction chemotherapy [IC]), 3.2% NAR, 1.8% AC, and 2.1% AR. NAC usage increased from 0.6% in 1995 to 21% in 2013 ($p < 0.001$), application of NAR decreased from 15% to 0.4% ($p < 0.001$). Usage of AC and AR in 2013 was <1.5%. Comparable temporal trends were found in 6032 patients staged cT2-4N0M0. Multivariable logistic regression analysis revealed that younger age, ≥cT3, ≥cN1 and treatment in academic/teaching hospitals were associated with NAC or IC (all $p < 0.05$).

***Conclusions:*** The increase in NAC administration in the Netherlands reflects a slow but steady adoption of evidence-based guidelines over the last two decades. Considerable variability in patients' and hospital characteristics in the likelihood of receiving NAC exists. Conversely, NAR, AR and AC are hardly administered anymore.

***Take home message***: The increase in neoadjuvant chemotherapy use in the Netherlands reflects a slow but steady adoption of evidence-based guidelines over the last two decades. Perioperative radiotherapy and adjuvant chemotherapy are hardly administered anymore.



## 1. Introduction

Over the last 30 years, no groundbreaking improvements in bladder cancer (BC) stage-specific survival have been made, which might reflect the limitations of local therapy alone, i.e. radical cystectomy (RC) or external-beam radiation [1]. Potential resources to improve survival in muscle invasive bladder cancer (MIBC) include the addition of perioperative radiotherapy or cisplatin-based combination chemotherapy (CBCC) to RC [2–4].

In MIBC, neoadjuvant radiotherapy (NAR) and adjuvant radiotherapy (AR) decrease risk of local recurrence by downsizing the primary tumour and sterilisation of microscopic residues. However, no high quality data exist to support an additive value in terms of survival [2–5]. Survival data regarding neoadjuvant chemotherapy (NAC) are more robust [4,6]. Two large randomised controlled trials (RCT) assessed CBCC prior to RC or radiotherapy versus local therapy alone for cT2-T4a, N0 or NX, M0 or MX BC. They reported an overall 16–33% risk-of-death reduction, corresponding to an increase in 10-year survival from 30% to 36%. Cancer-specific death risk was also significantly reduced by 17–66% [7,8]. A third NAC trial found that the combination of complete downstaging (CD) (ypT0N0) and NAC was associated with a 31.1% absolute risk-of-death reduction at 5-year compared with CD controls (pT0N0)[9]. Evidence for adjuvant chemotherapy (AC) in MIBC is conflicting. A recent meta-analysis of limited quality trials showed a disease-free survival improvement of 34%. The benefit was most apparent in patients treated with CBCC and with nodal involvement [3]. Recent analyses of the National Cancer Data Base registry in the United States showed an increase of NAC use for localised and locally advanced node negative BC from 10% in 2006 to 21% in 2010. The use of AC remained stable at 21% [10]. Currently, population-based data in Europe are not available. A feasibility questionnaire study among major European centres in 2012 reported that 9–22% of patients scheduled for RC were considered for NAC [11]. Multimodal therapy, predominantly with neoadjuvant CBCC, can be considered state of the art and is recommended in contemporary guidelines. It is possible to administer CBCC in 50–70% of patients and approximately 90% complete ≥3 cycles [6,12–14]. Nevertheless, its utilisation has only slowly gained acceptance among clinicians.

We assessed the use of perioperative treatment (PT) with nationwide population-based, Netherlands Cancer Registry data of 10,338 patients who underwent RC with curative intent between 1995 and 2013. Furthermore, patients' characteristics and hospital characteristics associated with the administration of PT were evaluated.

## 2. Patients and methods

### 2.1. Netherlands Cancer Registry

The nationwide population-based Netherlands Cancer Registry (NCR) includes all newly diagnosed malignancies. Notification is obtained from the national network and registry of histopathology and cytopathology in the Netherlands (PALGA) and the National Registry of Hospital Discharge Diagnosis [15]. Independent and trained registration assistants from the NCR collect data on patient, tumour and treatment characteristics from patient files. Topography and morphology are coded according to the International Classification of Diseases for Oncology (ICD-O) and