

Current clinical practice guidelines on chemotherapy and radiotherapy for the treatment of non-metastatic muscle-invasive urothelial cancer: A systematic review and critical evaluation by the Hellenic Genito-Urinary Cancer Group (HGUCG)

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Contents

1. Introduction	37
2. Methods	37
2.1. Search strategy and data abstraction	37
2.2. Data synthesis and development of a therapeutic algorithm	37
3. Results	38
3.1. Existing guidelines	38
3.1.1. Definition of LoE and GoR	38
3.1.2. Evaluation according to IOM criteria	38
3.2. Data synthesis-proposed algorithm	39
3.2.1. Bladder cancer	39
3.2.2. Upper urinary tract and urethral urothelial carcinomas	45
4. Discussion	45
Conflict of interest statement	46
Reviewers	46
References	46
Biographies	49

Abstract

Radical cystectomy is the treatment of choice in localized muscle-invasive urothelial cancer. Nevertheless, relapses are frequent and systemic chemotherapy has been employed in order to reduce this risk. In addition, bladder preservation strategies are appealing. During the last decade, there has been a difficulty in conducting and completing large-scale trials in urothelial cancer. This has resulted in relatively few changes in the existing guidelines. Recent studies have created renewed interest in certain fields, such as the role of chemo-radiotherapy and management of unfit patients. In addition, application of certain guidelines has been limited in everyday practice. We conducted a systematic review of

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the existing guidelines and recent randomized trials not included in these guidelines, and developed a treatment algorithm, regarding non-surgical therapies for non-metastatic, muscle-invasive urothelial cancer based predominantly on patients' fitness for the available therapeutic modalities.

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1. Introduction

Urothelial cancer (UC) may develop anywhere transitional epithelium is present, from the renal pelvis to the ureter, bladder, and proximal two-thirds of the urethra. The majority of cases (approximately 90%) originate in the bladder and the clinical spectrum is divided into non-muscle invasive, muscle-invasive and metastatic disease with different prognosis and treatment [1].

Several national and international urological, radiation oncology and medical oncology Societies and Associations have published their own guidelines on UC [2–6]. Nevertheless, their utility in everyday practice may be limited due to a variety of reasons [7–10]. Practical issues and a difficulty for clinicians in the community to follow all the new available data and information have been suggested as possible causes [7,9]. In addition, given the historical difficulties in completing trials in MIBC, relevant clinical questions have not been answered with data of high level of evidence (LoE) and information not reflected in guidelines are needed to support or refute current practice. Finally, issues associated with the development of guidelines may limit adherence in everyday practice. For example, variation in the definition of the levels of evidence (LoE) and Grading of Recommendations (GoR) result in differences in the strength of recommendations regarding the various treatment modalities. This variation underlines the considerable heterogeneity in the development and reporting of guidelines. For these reasons, the Institute of Medicine (IOM) report “Clinical Practice Guidelines We Can Trust” established standards for developing trustworthy CPGs [11]. In a recent review of lung, breast, prostate and colorectal cancers guidelines, a significant diversion from these standards has been detected [12]. Such evaluation for CPGs in UC has not been carried out so far.

Non-metastatic muscle-invasive UC (MIUC) is a model for multidisciplinary approach in Oncology. Hence, the development of and adherence to CPGs are essential for the optimal management of these patients. The HGUCG represents a platform aiming to improve the collaboration among all Greek specialists focused in the management of urogenital cancer. One of our main priorities is the establishment of clinical practice guidelines (CPGs) and their implementation to the community. Since an adequate number of guidelines are available, we decided not to develop our own guidelines de novo but to synthesize them through a systematic review of the existing CPGs and their critical evaluation, taking into consideration the most recent developments

and the problems encountered in everyday practice. This review focuses on existing guidelines for non-metastatic MIUC. Since radical cystectomy with bilateral pelvic lymph node dissection remains the undisputed standard for this disease, we did not perform a review on surgical therapy but we focused on guidelines regarding non-surgical therapies used in association with or instead of definitive surgery.

2. Methods

2.1. Search strategy and data abstraction

A systematic review was performed in accordance with the PRISMA guidelines [13]. The protocol of this systematic review has been submitted to the Institutional Review Board of Alexandra Hospital, Medical University of Athens, Greece and is available upon request. Eligible articles were identified by a search of MEDLINE bibliographical database for the period from January 1, 2008 up to September 22, 2013. The search strategy included the following keywords: (recommendation [ti] OR recommendations [ti] OR consensus [ti] OR guideline [ti] OR guidelines [ti] OR consultation [ti]) AND (society OR societies OR college OR association OR associations) AND ((bladder OR urothelial) AND (carcinoma OR carcinomas OR cancer OR cancers OR neoplasm OR neoplasms)).

All studies providing CPGs/Expert recommendations regarding the non-surgical treatment of MIUC were considered eligible for this systematic review. Language restrictions were applied (only articles in English, French, Spanish and Deutsch were considered eligible). Two investigators (FZ and SP), working independently, searched the literature and extracted data from each eligible study. In addition, we checked all the references of retrieved articles, in order to identify additional potentially eligible articles. If a group, association or society produced updated guidelines, only the most recent study was included. Finally, full length recommendations, if available, were also cross checked against the relevant papers in order to retrieve information not included in the papers. Respective guideline manuals were also reviewed if necessary to clarify methodological or ethical issues.

2.2. Data synthesis and development of a therapeutic algorithm

Following the completion of identifying eligible papers, two investigators (AB and VK) independently scored each

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