EUROPEAN UROLOGY XXX (2018) XXX–XXX

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Review – Testis Cancer

Non–risk-adapted Surveillance for Stage I Testicular Cancer: Critical Review and Summary

Phillip Martin Pierorazio [a,b,*], *Peter Albers* [c], *Peter C. Black* [d], *Torgrim Tandstad* [e], *Axel Heidenreich* [f], *Nicola Nicolai* [g], *Craig Nichols* [h]

[a] *Brady Urological Institute, Johns Hopkins Medicine, Baltimore, MD, USA;* [b] *Department of Urology, Johns Hopkins Medicine, Baltimore, MD, USA;* [c] *Department of Urology, University Hospital Düsseldorf, Heinrich-Heine-University, Düsseldorf, Germany;* [d] *Department of Urologic Sciences, The University of British Columbia, Vancouver, BC, Canada;* [e] *St Olavs University Hospital, Trondheim, Norway;* [f] *Department of Urology and Uro-Oncology, Universitätsklinikum Köln, Köln, Germany;* [g] *Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy;* [h] *Section of Urology, Virginia Mason Medical Center, Seattle, WA, USA*

Article info

Article history:
Accepted December 27, 2017

Associate Editor:
Stephen Boorjian

Statistical Editor:
Andrew Vickers

Keywords:
Testicular cancer
Germ cell tumor
Active surveillance

Abstract

Context: Cancer-specific survival for men with clinical stage I testicular cancer (CSITC) is uniformly excellent. Non–risk-adapted active surveillance (NRAS) is a management strategy for CSITC to minimize overtreatment and avoid possible long-term side effects of adjuvant therapy.
Objective: To review the evidence regarding oncologic outcomes for men with CSITC undergoing NRAS and discuss ongoing controversies in the management of CSITC.
Evidence acquisition: MEDLINE/PubMed, Embase, and the Cochrane Central Register of Controlled Trials were searched from January 1, 1987 through January 1, 2017.
Evidence synthesis: A total of 68 studies were included in the critical review. The rationale for NRAS, oncologic outcomes, surveillance protocols, and comparative efficacy of risk-adjusted active surveillance (AS) were reported with strength of evidence and risk of bias evaluated. Cancer-specific survival approaches 100% for men with CSITC undergoing NRAS. Active treatment is limited to 20–30% of patients who will recur; these patients will require salvage chemotherapy and possible retroperitoneal lymph node dissection. Existing AS protocols include imaging and laboratory evaluations that are initially intensive but less frequent with increasing follow-up.
Conclusions: NRAS is an attractive management option for men with CSITC, which maintains outstanding long-term cancer cure while sparing most patients treatment by avoiding prophylactic chemotherapy, radiation, or surgery.
Patient summary: Men with clinically localized (stage I) testicular cancer have an excellent prognosis, regardless of management. Non–risk-adapted active surveillance is an attractive management option where only patients destined to relapse will receive any treatment following orchiectomy. However, individual patient preferences should be discussed in selecting a management strategy.

* Corresponding author. James Buchanan Brady Urological Institute, Johns Hopkins University, 600 N. Wolfe Street, Park 217, Baltimore, MD 21287, USA. Tel. +1 4105025984; Fax: +1 4105027711.
E-mail address: philpierorazio@jhmi.edu (P.M. Pierorazio).

https://doi.org/10.1016/j.eururo.2017.12.030
0302-2838/

1. Introduction

Testicular cancer (TC) is a relatively rare malignancy, accounting for 50 000 new diagnoses worldwide per year and approximately 10 000 deaths [1]. However, TC remains the most common malignancy of men aged 15–44 yr [1,2]. The incidence of TC is highest in the developed countries of North America and Europe, with the greatest number of incident cases in men with clinically localized, stage I disease [3]. The cure rate for men with stage I disease approaches 100% and mortality rates have been decreasing, leaving a significant population of TC survivors—>200 000 men in the USA alone [2]. Given the high proportion of survivors and long life expectancy of these men, management strategies have shifted focus to minimize morbidity and promote long-term well-being of TC survivors, which includes not only oncologic follow-up, but also reduction of treatment-associated long-term toxicities such as early-onset cardiovascular disease, infertility, hypogonadism, and psychosocial coping problems. Non–risk-adapted active surveillance (NRAS) has emerged as a management strategy for patients with stage I TC, and this review will focus on the most contemporary data regarding NRAS.

2. Evidence acquisition

2.1. Objectives

The primary objective was to report oncologic outcomes, including cancer-specific survival and recurrence rates, for patients with clinical stage I testicular cancer (CSITC) undergoing NRAS. Secondary objectives included assessment of short- and long-term side effects of therapy, and comparative outcomes of risk-adapted management strategies.

2.2. Search strategy and selection criteria

The methods for this systematic review follow the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement [4]. MEDLINE (PubMed), Embase, the Cochrane Central Register of Controlled Trials, and guideline statements from professional organizations were searched from January 1, 1987 through January 1, 2017. The search strategy included the following medical subject headings: "<testicular cancer> AND (<clinical stage I> OR <stage I>) AND (<active surveillance> OR <surveillance>)." The search strategy revealed 740 records, and subsequent title and abstract screening revealed 148 studies for review. Each article was reviewed, and additional relevant articles were selected from authors' bibliographies. Given limitations of the literature and subsequent data abstraction and synthesis, this manuscript is reported as a critical review and summary of the data as strict systematic review methodologies cannot be applied rigorously.

A total of 39 studies (Table 1 and Supplementary Table 1) and four guidelines statements [5–8] were identified through the search strategy and included in the critical review. One randomized study evaluated different AS protocols and was included in the critical review [9]. Seventeen nonrandomized, comparative studies [10–26] and 21 single-arm studies [27–47] were also included. Twenty studies included patients with nonseminomatous germ cell tumor (NSGCT) [9–13,27–41] and 25 included patients with seminoma [14–26,28,35,36,38–40,42–47]; six overlapping studies included patients with both NSGCT and seminoma [28,35,36,38–40]. Supporting data from additional studies, including those from authors' bibliographies, are included throughout the manuscript where appropriate.

Relevant data were abstracted and synthesized for the report. Duplicate datasets are reported as such. Risk of bias was evaluated using the Cochrane Collaboration Tool for Controlled Studies and the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI) [48,49]. The risk of bias was determined to be *moderate* based on the few randomized studies, and the bias in selection of patients into each retrospective study and each study arm. Strength of evidence was considered among five domains—study limitations, directness, consistency, precision, and reporting bias, and classified as high, moderate, low, and insufficient.

2.3. Statistical analysis

Owing to heterogeneity of data, heterogeneity of study design, and significant overlapping datasets, a formal meta-analysis was not achievable. Data were synthesized and reported according to the following topics related to NRAS: rationale, oncologic/clinical outcomes, AS protocols, comparative efficacy of risk-adapted AS management, and research gaps.

Table 1 – Studies included in the critical review

	NSGCT	Seminoma
Randomized study	AS protocol (one study/414 patients) [9]	
Nonrandomized, comparative studies	AS vs CT vs RPLND (one study/4040 patients) [10] AS vs CT (three studies/1178 patients) [a] [11–13]	AS vs CT vs RT (5 studies/9065 patients) [14–18] AS vs CT (six studies/2475 patients) [a] [19–24] AS vs RT (2 studies/837 patients) [25,26]
Single-arm AS studies	(15 studies/6458 patients)[a] [27–41]	(12 studies/7799 patients) [a] [28,35,36,38–40,42–47]
Guideline statements	(Four guidelines) [6–8,87]	

AS = active surveillance; CT = chemotherapy; NSGCT = nonseminomatous germ cell tumor; RPLND = retroperitoneal lymph node dissection; RT = radiation therapy.
[a] Significant redundancy in patient population among studies and overlap of study populations among studies. Greater details regarding the studies identified in the search strategy are reported in Supplementary Table 1.

Please cite this article in press as: Pierorazio PM, et al. Non–risk-adapted Surveillance for Stage I Testicular Cancer: Critical Review and Summary. Eur Urol (2018), https://doi.org/10.1016/j.eururo.2017.12.030