ELSEVIER

Urologic Oncology: Seminars and Original Investigations ▮ (2017) ▮▮▮–▮▮▮

UROLOGIC ONCOLOGY

Review article

Prognostic factors for tumor recurrence in patients with clinical stage I seminoma undergoing surveillance—A systematic review

Friedemann Zengerling, M.D.[a,e,*], Frank Kunath, M.D.[b,e], Katrin Jensen, Ph.D.[c], Christian Ruf, M.D.[d], Stefanie Schmidt, Ph.D.[e], Annabel Spek, M.D.[e,f]

[a] *Department of Urology, University Hospital of Ulm, Ulm, Germany*
[b] *Department of Urology, University Hospital of Erlangen, Erlangen, Germany*
[c] *Institute of Medical Biometry and Informatics, University of Heidelberg, Heidelberg, Germany*
[d] *Department of Urology, Federal Armed Forces Central Hospital of Koblenz, Koblenz, Germany*
[e] *UroEvidence@Deutsche Gesellschaft für Urologie, Berlin, Germany*
[f] *Department of Urology, University Hospital of Munich, München, Germany*

Received 23 January 2017; received in revised form 19 April 2017; accepted 14 June 2017

Abstract

Objective: To systematically evaluate evidence on prognostic factors for tumor recurrence in patients with clinical stage I seminoma undergoing surveillance.

Methods: Systematic literature search conducted of Medline, Web of Science, Cochrane Library, and the conference proceedings of the ASCO, AUA, and EAU meetings (last search: October 2016), according to our prospectively registered protocol (PROSPERO registration number CRD42014009434). Identified records were reviewed according to the Cochrane Method Group of Prognosis Reviews recommendations and the PRISMA reporting guideline. Study quality was appraised with the Quality in Prognosis Studies (QUIPS) tool.

Results: Nineteen studies reporting on 26 potential prognostic factors were included in our analysis. Among the most frequently reported factors, tumor size (continuous or dichotomized) was significantly associated with relapse in 10/14 studies with a hazard ratio (HR) ranging from 1.33 (95% confidence interval [CI]: 1.14–1.56) to 3.17 (95% CI: 1.08–9.26). Rete testis invasion was significantly associated with relapse in only 4/13 studies with a HR ranging from 1.18 (95% CI: 0.92–1.51) to 1.36 (95% CI: 0.81–2.28). Lymphovascular invasion, young age, and preoperative HCG level had no association with relapse. Our findings are limited by heterogeneity of study designs, potential reporting bias, and moderate-to-poor study quality.

Conclusion: In stage I seminoma, tumor size is the most valuable prognostic factor on which to base relapse risk and to counsel patients about adjuvant treatment. Large tumor size was defined quite inhomogenously among the included studies, so no distinct cutoff value for tumor size can be recommended. Other potential prognostic factors including rete testis invasion play a minor role in stage I seminoma.

Keywords: Seminoma; Recurrence; Rete testis invasion; Tumor size; Surveillance; Prognostic factor

1. Introduction

Testicular cancer is the most common cancer in young men. The primary treatment of testicular cancer is inguinal orchiectomy. Pathology reveals seminoma in approximately 60% of the cases, and the incidence appears to be increasing [1]. To determine metastatic disease, patients undergo further staging procedures including tumor markers and radiologic examination of the chest, abdomen, and pelvis. Approximately 80% of the diagnosed seminomas exhibit no tumor-suspicious abnormalities and are therefore classified as clinical stage I. Data from large case series of 1954 patients show that despite the absence of pathologic findings at the initial staging,

* Corresponding author. Tel.: +49-731-5005-8004; fax: +49-731-5005-8002.
E-mail address: friedemann.zengerling@uniklinik-ulm.de (F. Zengerling).

http://dx.doi.org/10.1016/j.urolonc.2017.06.047
1078-1439/

approximately 15% to 20% of patients with stage I seminoma develop tumor recurrence in follow-up [2].

To reduce the risk of relapse, radiation therapy and chemotherapy are adjuvant therapy options for patients with stage I seminoma. Both irradiation of the equilateral retroperitoneal lymphatic tissue and the one-time intravenous administration of carboplatin AUC7 have been shown to lower the relapse risk to less than 5% [3,4]. Successful oncological outcomes are bought with long-term side-effects, which have gained greater awareness recently [5,6]. Surveillance, that is, close follow-up without active medical intervention, is therefore a reasonable option for patients with seminoma stage I. In North America, surveillance is the preferred clinical strategy for stage I testicular cancers, whereas in other countries, the situation is more ambiguous.

Given the risk of adverse effects with adjuvant therapy, prognostic factors that can stratify risk and thus guide treatment would be ideal. The first prognostic factors were histopathological characteristics of the primary tumor specimen. In 2002, Warde et al. [7] published the results of a retrospective study and found a tumor diameter greater than 4 cm, and infiltration of the rete testis were associated with tumor recurrence. The same group, however, was unable to validate these 2 risk factors in a prospective study [8]. Further prospective studies on tumor diameter and rete testis infiltration revealed conflicting results [9,10].

In nonseminoma patients, the decision for or against adjuvant therapy is easier, as there is pT $\geq$ 2 stage considered as a well-validated broadly accepted risk factor for stage I patients. In contrast, for patients with seminoma stage I, the evidence on prognostic factors is limited. Guidelines of the National Comprehensive Cancer Network (NCCN), the European Association of Urology (EAU), and the European Society of Medical Oncology (ESMO) do not clearly recommend tumor size or rete testis infiltration as prognostic factors for the decision on adjuvant treatment for patients with stage I seminoma because of limited and inconclusive evidence [11,12].

Novel biomolecular markers, using primary tumor specimens or patient peripheral blood samples, have been investigated. Unfortunately, their usefulness has often been hampered by retrospective study design, small patient numbers, poor methodology, and lack of validation studies. None of these potential biomolecular markers have so far entered routine use of clinical decision-making or the clinical guidelines.

Owing to the lack of consistent prognostic factors for stage I seminoma, our aim was to summarize the available evidence on the association of prognostic factors with the risk of disease recurrence in patients with clinical stage I seminoma undergoing surveillance.

2. Methods

We followed the recommendations of conducting systematic reviews of prognostic studies, provided by the PRISMA reporting guidelines, in general, for systematic reviews [13] and by the Cochrane Prognosis Methods Group especially for systematic reviews on prognosis [14].

2.1. Study hypothesis

The question to be addressed in this systematic review was whether there are reliable prognostic factors that are associated with recurrence in patients with clinical stage I seminoma undergoing surveillance.

2.2. Search strategy

We conducted a systematic literature search in MEDLINE, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) without setting any language or time restrictions. Our search was complemented by additional hand-searching of the conference proceedings of American Society of Clinical Oncology (ASCO), the Annual Meeting of the European Association of Urology (EAU), and the American Urologic Association (AUA) from 2008 onwards. The search of all databases was initially conducted in January 2016 and was updated in October 2016. Additionally, we reviewed the reference lists of the included studies. The complete search strategy and detailed methodology are attached as Supplementary material (Appendix).

2.3. Inclusion criteria

We included studies reporting on potential prognostic factors that predict disease recurrence in patients with clinical stage I seminoma undergoing surveillance. Studies were eligible for inclusion if they reported on patients diagnosed with a stage I tumor, who received no adjuvant therapy, and provided data on the association of any prognostic factors with disease recurrence with a minimum follow-up (median or mean) of 24 months. We included prospective and retrospective longitudinal observational studies as well as intervention studies, if the results in the surveillance group were reported separately. Exploratory studies as well as confirmatory studies were considered [15]. Reviews, case reports, editorials, and comments were excluded.

Our a priori defined primary outcome of interest was disease recurrence during follow-up. Recurrence was assessed as reported by the study authors, regardless of the mode of diagnosis (radiologic finding, histologic specimen, and tumor marker elevation) at the described time points.

2.4. Methodology

Articles were selected for inclusion by title and abstract and afterwards full-text review performed by 2 authors independently (F.Z. and A.S.). Discrepancies were resolved