

# Non-Guideline-concordant Treatment of Testicular Cancer Is Associated With Reduced Relapse-free Survival

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## Abstract

**The treatment of testicular cancer (TC) requires a multimodal approach. We retrospectively evaluated the diagnostic work-up, treatment, and outcomes of 131 patients with respect to the European Association of Urology guidelines. Of 131 patients, 18% had received non-guideline-concordant treatment, with undertreatment having a negative effect on relapse-free survival. Thus, implementation of guidelines is needed to decrease the mortality of TC.**

**Introduction:** The management of testicular cancer (TC) requires a complex multimodal therapeutic approach. Despite the availability of regularly updated guidelines, non-guideline-concordant treatment of TC still occurs. The purpose of the present study was to evaluate the compliance patterns in diagnosis and therapy and their potential effects on patient outcomes with respect to the guidelines of the European Association of Urology. **Patients and Methods:** We performed a retrospective analysis of 131 patients diagnosed with TC who had been referred to our department from September 2015 to October 2016. Patient characteristics were compared with European Association of Urology guideline recommendations. **Results:** Of the 131 primary treated patients, 23 (18%) had received a non-guideline-concordant treatment. The most common error was undertreatment ( $n = 12$ ; 52%), mainly due to missing chemotherapy cycles. Overtreatment occurred in 30% of patients ( $n = 7$ ); however, inappropriate treatment ( $n = 2$ ; 9%) and misdiagnosis ( $n = 2$ ; 9%) were rarely observed. In salvage therapy, non-guideline concordant treatment was observed less frequently compared to patients receiving primary therapy (12% vs. 18%). Of the 131 patients, 35 developed a relapse, 23 of whom were treated correctly and 6 of whom were undertreated. Undertreatment of patients resulted in significantly reduced relapse-free survival compared with guideline-concordant management in primary treated patients ( $P = .005$ ). **Conclusion:** Despite the standardization of treatment by interdisciplinary guidelines, its integration into daily practice remains limited. Undertreatment of TC patients is associated with significantly reduced relapse-free survival and should thus be avoided.

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## Introduction

Management of testicular cancer (TC), the most common cancer in young men, requires a complex multimodal therapeutic

approach.<sup>1,2</sup> Depending on the patients' clinical status, which is defined by the presence and localization of metastases and tumor marker profiles, the potential treatment options include surveillance, chemotherapy, radiotherapy, and surgery. For standardized management of TC, different national and international guidelines on TC are available and regularly updated, including the widely used European Association of Urology (EAU) guidelines for TC treatment.<sup>1,3</sup>

A recently reported study suggested that integration of interdisciplinary guidelines significantly reduced therapeutic mistakes from 28% to 8% in a tertiary referral center, leading to decreased patient mortality.<sup>4</sup> Despite the available guidelines, the translation of the recommended treatment into clinical practice has remained inadequate among institutions, which could affect patient outcomes.<sup>5,6</sup>

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## Association of Non-Guideline Treatment of TC and RFS

The German second-opinion network, which aims to improve the quality of care for TC patients by providing advice to requesting urologists, reported a discrepancy between the first and second opinions in 39.5% of cases.<sup>7</sup> Moreover, a recently reported study revealed non-guideline-directed care for 30% of patients with TC in the United States. In that study, non-guideline-concordant treatment was most frequently caused by inappropriate imaging studies and overtreatment, leading to delayed definitive therapy, greater morbidity, and greater rates of relapse.<sup>8</sup>

In Europe, only limited data on guideline conformity for treatment of TC, especially with respect to patient outcomes, is available. In the present study, we performed a retrospective investigation of frequently occurring mistakes in the diagnosis of and therapy for TC in consideration of the current EAU guidelines. We hypothesized that non-guideline-concordant treatment of TC might still be a major problem in various TC-treating institutions and might have a negative effect on patient outcomes.

### Patients and Methods

#### Study Population

In our study, we retrospectively analyzed the TC database at the University Hospital of Cologne as an observational cohort study. We identified 147 patients with a diagnosis of TC (International Classification of Disease, 10 revision, code C62) who had been referred to our department from September 2015 to October 2016. Patients with benign testicular tumors, non-germ cell tumors, or testicular masses from nontesticular primary tumors were excluded from the present study ( $n = 15$ ). Patients with insufficient medical records were also excluded ( $n = 1$ ), for a total of 131 patients enrolled in the present study. We collected data on age, histologic findings, clinical stage, and International Germ Cell Cancer Collaborative Group risk classification. Moreover, the treatment type, treatment duration, and follow-up analysis results were included. Disease recurrence was defined as in- or outfield lymph node metastases and distant metastases. Survival data were not available for 5 of the analyzed patients. The year of diagnosis is listed in [Supplemental Table 1](#) (available in the online version), and the patient characteristics are listed in [Table 1](#). The local ethics committee approved the present study, which complied with the Declaration of Helsinki.

#### Definition of Guideline Concordance

The patients' treatment was compared with the current EAU guidelines for TC.<sup>1</sup> The EAU guidelines for TC were initially published in 2001 and have been regularly updated, including major changes in the diagnosis and treatment of germ cell tumors.<sup>3</sup> Non-guideline-concordant treatment was defined as treatment that was not in line with the EAU guidelines. It was further subdivided into overtreatment, undertreatment, inappropriate treatment, and misdiagnosis, similar to the categories used in a recent study.<sup>8</sup> Modified treatment, defined as a planned modification of guideline-concordant treatment because of chemotherapy side effects or thrombosis, another simultaneous tumor burden or an atypical histologic type, was classified as correct treatment. The members of the TC working group of our department manually reviewed the data from all the patients included in the present study using the following standardized

**Table 1** Patient Characteristics of Study Population ( $n = 131$ )

Characteristic	n (%)
Age (y)	
Median	35
IQR	28-49
Age distribution	
<20 y	4 (3)
20-30 y	42 (34)
31-40 y	32 (26)
40-50 y	20 (16)
>50 y	25 (21)
Histologic type	
Nonseminoma	74 (57)
Seminoma	47 (37)
Extragonadal	4 (3)
Bilateral	4 (3)
Clinical stage	
1	55 (43)
2	52 (40)
3	22 (17)
IGCCCG risk classification	
Good	103 (80)
Intermediate	15 (12)
Poor	10 (8)
Treatment	
Surveillance/follow-up	25 (19)
Orchiectomy	5 (4)
Chemotherapy	44 (33)
RT	4 (3)
RPLND	0 (0)
Chemotherapy plus RPLND	48 (37)
Chemotherapy plus RT	1 (1)
Chemotherapy plus RPLND plus RT	4 (3)
RPLND field	
Unilateral modified	19 (53)
Bilateral	17 (47)
Chemotherapy cycles (n)	
Median	3
IQR	3-4
Follow-up (mo)	
Median	9
IQR	4-22
Relapse until follow-up end	
No	91 (72)
Yes	35 (28)
Relapse treatment	

classification and subclassification in accordance with the EAU guidelines (see [Tables 2](#) and [3](#)). Overtreatment was defined as unintended and/or too intense treatment, including unnecessary high dosages of chemotherapy or radiotherapy, the performance

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