ONCOLOGY

Actual frequency of imaging during follow-up of testicular cancer in Israel—a comparison with the guidelines

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Abstract

Objectives Computed tomography (CT) examinations are frequent in follow-up care of testicular cancer (TC) but may increase the risk for other cancers. We wanted to assess the actual number of CT and X-ray examinations within the first 5 years after a diagnosis of TC in Israel during 2003–2007.

Methods The database of Maccabi Healthcare Services, Israel, was searched for TC patients diagnosed in 2003 to 2007 by direct linkage with the Israel National Cancer Registry. Data on diagnostic imaging examinations (CT of chest, abdomen, or pelvis, unspecified sites; X-ray of chest) were extracted during a 5-year follow-up for 226 incident patients. The actual number of CT and X-ray examinations was compared to the National Comprehensive Cancer Network (NCCN) guideline. We tabulated the median with 10th and 90th percentiles (P10, P90) for the number of CTs and X-rays considering histology, stage, and adjuvant strategy.

Results The number of abdomen or pelvis CTs for TC patients receiving chemo- or radiotherapy was in accordance with the NCCN guideline. The median of abdomen or pelvis CTs for surveillance patients was 8.5 (P10, P90: 3; 13) for nonseminoma and 5.0 (P10, P90: 5; 13) for seminoma patients compared to 14 to 17 CTs recommended. The number of chest X-rays was lower than recommended in the guideline for all adjuvant strategies.

Conclusions The NCCN guidelines regarding CTs were met for TC patients treated with chemo- or radiotherapy but fell below recommendations for surveillance. Guidelines from 2011 and 2012 were updated in favor of fewer CTs during surveillance.

Key Points
• *The number of CTs followed the NCCN guidelines in patients treated with chemo- or radiotherapy.*
• *Surveillance patients received fewer CTs and X-rays than recommended in the NCCN guidelines from 2005.*
• *The number of applied CT examinations corresponded to a radiation dose that did not substantially raise the lifetime risk for cancer.*

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Abbreviations

ALARA	As low as reasonably achievable
AYAS	Adolescents and young adults
BEIR	Biological Effects of Ionizing Radiation
CI5C	Cancer in Five Continents
CT	Computed tomography
CTX	Chemotherapy
EAU	European Association of Urology
FDG-PET	Fluorodeoxyglucose positron emission tomography
ICD-O	International Classification of Diseases for Oncology
INCR	Israel National Cancer Registry
IQR	Interquartile range
LAR	Lifetime attributable risk
MHS	Maccabi Healthcare Services
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
RTX	Radiotherapy
TC	Testicular cancer
US	Ultrasound

Introduction

The incidence of testicular cancer (TC) has substantially increased during the last decades in the industrial nations of Europe and Israel, as well as in Australia and North America [1–3]. The highest age-specific incidence rates are observed in the age group of 15–44 years where TC is the most frequent malignancy, involving about 15% of all newly arising cancers in men. According to population-based cancer registries and hospital data, roughly 70% of patients with TC have clinical stage I [4, 5].

During the last decade, evidence-based international guidelines for treatment of TC have increasingly recommended a postorchiectomy surveillance strategy for stage I disease instead of applying traditional adjuvant therapy [6–9]. The relevance of surveillance in the follow-up is apparent considering the young age of many TC patients together with the potentially carcinogenic late sequelae of chemotherapy (CTX) and radiotherapy (RTX). Most surveillance strategies include physical examination, measurement of tumor markers, computed tomography (CT) of abdomen, and examinations of the chest and pelvis in selected patients.

Studies of the atomic bombs survivors show that even small red bone marrow doses of radiation, i.e., corresponding to the exposures given during repeated diagnostic CT (3 mGy per exposure at age 20), may result in an increased risk of cancer [10, 11]. Some recent large cohort studies from the U.S., U.K., and Australia have shown an increased long-term risk of cancer due to diagnostic CT radiation [12, 13]. The risks are of particular concern for younger patients [14, 15].

International guidelines vary widely regarding frequency and extent of CT examination in the management of TC [16–18]. In Israel, physicians usually apply guidelines of the U.S. National Comprehensive Cancer Network (NCCN). These guidelines result in up to 16 abdomen or pelvis CTs in the first 5 years of the surveillance strategy [17]. Remarkably, despite concerns that even surveillance may have negative health consequences because of the radiation exposure from CT, to our knowledge only two population-based studies assessed the actual number of CT examinations employed during follow-up care of TC [19, 20]. The aim of this study is to review the actual number of CTs within the first 5 years after a diagnosis of TC in Israel during 2003–2007 and to compare them to the recommendations from the NCCN guidelines. Furthermore, we will estimate the lifetime risk of cancer due to radiation doses from CT examinations.

Material and methods

We utilized computerized data of Maccabi Healthcare Services (MHS), the second largest publicly funded health maintenance organization in Israel. MHS is one of four health maintenance organizations in Israel, serving 24% of the total population (2.1 million members). The proportion of Jews at MHS is higher than in the total population of Israel. The MHS central database retains historical records of patient demographic data, physician data, diagnostic imaging data, laboratory results, and filled prescription information. Major advantages of MHS data include a relatively large and stable population of members and the availability of direct linkage with the Israel National Cancer Registry (INCR) using the unique national identifying number, given to all newborns or immigrants to Israel by name, sex, and date of birth.

Established in 1960, the INCR collects information on diagnosed cancer patients from all medical institutions in the country with a completeness of above 93.5% for solid tumors [21]. All cancer patients are classified according to the International Classification of Diseases (for Oncology) (ICD(-O)) including histologic findings and stage [22]. We extracted incident TCs coded as C62 according to ICD-10 from the cancer registry. Moreover, histology had to be coded as either seminoma (9060, 9061, 9062, 9064) or nonseminoma including mixed germ cell tumors (9065, 9070–9072, 9080–9085, 9100–9102). Spermatocytic tumors (9063) were not in the data set. The stage was initially

classified according to the Surveillance, Epidemiology, and End Results Program Summary Staging Manual and we collapsed it to three stages according to the American Joint Committee on Cancer (Supplementary Table 1) [23].

By use of the MHS and INCR data, we were able to detect 233 incident patients of TC for the period 2003–2007. Regarding the representativeness of the MHS sample, we compared the age-standardized incidence rate based on the MHS sample by using World Standard Population with the nationwide incidence rate of TC from the INCR data for the Jewish Israeli population in Cancer Incidence in Five Continents (CI5C) [24, 25]. For 226 patients with a complete 5-year follow-up period, we extracted data on CT examinations of the chest, abdomen, pelvis, and unspecified sites from the MHS computerized database (Supplementary Table 2). Furthermore, data on alternative diagnostic imaging examinations including magnetic resonance imaging (MRI), ultrasonography (US), and fluorodeoxyglucose positron emission tomography (FDG-PET) were received as well as X-ray of the chest. The number of diagnostic imaging examinations was added up for the time span between 4 weeks before registered diagnosis and 5 years after date of diagnosis. Hence, initial staging examinations are included. The number of diagnostic imaging examinations classified by the chest, abdomen, or pelvis and unspecified sites were tabulated in terms of mean, standard error (SE), median, interquartile range (IQR), and 10th and 90th percentiles (P10, P90). The number of observed CT and X-ray examinations was compared with the number recommended in the NCCN guideline from 2005 added up for 5 years considering histology, stage, and adjuvant strategy [7]. Since prognosis and treatment of TC depends on the histology, analyses were stratified by seminoma and nonseminoma. Adjuvant therapy was defined as a therapy starting within the first 3 months after date of diagnosis. Surveillance patients did not receive any therapy during that time. The NCCN guideline recommended different numbers of CTs during follow-up for adjuvant therapies and surveillance. The lowest number was recommended for seminoma patients treated with RTX and the highest for surveillance patients. The number of recommended CTs decreased with increasing duration of the follow-up (Table 1).

Risk models based on the Biological Effects of Ionizing Radiations (BEIR) VII Report and organ-specific radiation doses were used to estimate the lifetime attributable risk (LAR) of radiation-induced cancer from CT examinations. The BEIR VII report includes data for the LAR of cancer incidence from a 100-mSv organ equivalent dose for different age groups, sex, and organs [26]. As per Sodickson et al, we assigned an effective dose per CT examination based on covered regions (chest 8 mSv, abdomen alone 7.5, pelvis alone 7.5, abdomen and pelvis combined 15 mSv). For unspecified sites, we assumed an effective dose of 2 mSv [27]. Based on the BEIR VII model, the LAR of a colon cancer for a 30-year-old male who received a 100-mSv radiation dose is 125 patients per 100,000 persons. Therefore, the LAR from a 10-mSv dose is $(10/100) \times (125/100,000) = 0.000125 = 12.5$ per 100,000 persons [15, 27]. All statistical analyses were run in SAS® version 9.4 (SAS Inc.). The study protocol was approved by the Maccabi Healthcare Services Research Committee and the Assutas Hospitals' Institutional Review Board with waiver of informed consent.

Results

From 2003 to 2007, there were 233 incident patients of TC among MHS members giving an age-standardized incidence rate of 5.2 per 100,000 person years (SE 0.4). For the Jewish Israeli population, CI5C reported an age-standardized incidence rate of 4.7 per 100,000 person years (SE 0.2) during the same time span [25].

A total of 226 patients had a complete follow-up of 5 years, five patients died, and two left MHS. For 222 patients, the tumor histology was available. For 65% of these patients, the histologic subtype was seminoma. The median age was 35 (IQR 31–41) and 30 (IQR 24–34) years for seminoma and nonseminoma patients, respectively. Overall, 206 patients were coded as stage I TC. The proportion of patients on surveillance was slightly higher in seminoma than in nonseminoma patients. About 25% of seminoma patients received an adjuvant therapy not mentioned in the NCCN

Table 1 Number of CTs recommended per year in the NCCN guideline from 2005 for stage I patients according to histology and adjuvant strategy

Histology	Adjuvant strategy[a]	CT diagnosis	CT during follow-up					CT total
			Year 1	Year 2	Year 3	Year 4	Year 5	
Seminoma	Radiotherapy	1	1	1	1	0	0	4
	Surveillance	1	3–4	3–4	3–4	2	2	14–17
Nonseminoma	Chemotherapy	1	2	1–2	1	1	1	7–8
	Surveillance	1	4–6	3–4	3	2	1	14–17

[a] Version 1.2005 did not yet include chemotherapy for seminoma patients

Table 2 Patient characteristics of 222 newly diagnosed seminomatous and nonseminomatous germ cell tumors of the testis from Maccabi Healthcare Services, Israel, 2003–2007 with a 5-year follow-up

Characteristic	Histological subgroups	
	Seminoma	Nonseminoma
Newly diagnosed patients by year (N)		
2003	29	20
2004	37	12
2005	30	15
2006	21	15
2007	27	16
Total (N, %)	144 (65.0)	78 (35.0)
Age at diagnosis in years (median, IQR)	35 (31, 41)	30 (24, 34)
Stage at primary diagnosis (N)		
Missing	4	4
I	138	68
II	2	3
III	0	3
Adjuvant strategies		
Chemotherapy only (N, %)	38 (26.4)	44 (56.4)
Radiation therapy only (N, %)	32 (22.2)	0
Chemo- and radiotherapy (N, %)	7 (4.9)	0
Surveillance (N, %)	67 (46.5)	34 (43.6)

IQR interquartile range (25th and 75th percentiles)

guidelines for stage I, namely CTX before 2007 or a combination of CTX and RTX (Table 2).

Seminoma patients received a mean number of 7.0 CTs (SE 0.3) and nonseminoma patients a mean number of 11.3 CTs (SE 0.9) during 5 years of follow-up. Almost 45% of CT examinations were applied during the first year after diagnosis. For seminoma patients, 44% of all CTs were performed during the first year after diagnosis compared to 34% according to the distribution of CTs in the NCCN guideline. CTs performed in nonseminoma patients show a fair to good agreement with the schedule given in the NCCN guideline (Fig. 1).

The number of CT and X-ray examinations stratified by adjuvant strategy is only displayed for stage I TC. The number of abdomen or pelvis CTs for seminoma patients receiving RTX was in accordance with the NCCN guideline, likewise for nonseminoma patients receiving CTX. The median number of abdomen or pelvis CTs for nonseminoma patients with surveillance was 8.5 (P10, P90: 3; 13) compared to 14 to 17 CTs recommended in the NCCN guideline. This difference is even more pronounced in seminoma patients. About 70% of seminoma patients received X-rays of the chest compared to 50% of nonseminoma patients. Seminoma and nonseminoma patients on surveillance received a median of 4.5 and 5.0 X-rays of the chest, respectively. The NCCN guideline recommended seven to nine X-rays of the chest for seminoma patients and 22 to 28 for nonseminoma patients on surveillance

during a 5-year follow-up (Table 3). A total of 135 patients with stage I TC received a median number of two ultrasounds of the abdomen or pelvis region regardless of histology or adjuvant strategy. Only two seminoma and three nonseminoma patients received a MRI of the abdomen or pelvis region; no patient received a FDG-PET.

The median effective dose of diagnostic radiation due to CT examinations was 88 mSv (P10, P90: 14; 183) for the complete duration of follow-up. For patients with stage I, we found a median effective dose of 80 mSv (P10, P90: 15; 167) and 95 mSv (P19, P90: 0; 215) for seminoma and nonseminoma patients, respectively. The median LAR of radiation-induced cancer incidence from CT examinations was 0.6% (P10, P90: 0.1%; 1.3%). The LAR for cancer incidence was higher among nonseminoma than seminoma patients (Table 4).

Discussion

This is the first study to assess data on both CT examinations and alternative imaging in the follow-up of TC patients according to histology and adjuvant strategy in a population-based sample. In Israel, the number of applied CT examinations in the follow-up of TC patients on surveillance was substantially lower than recommended in the NCCN guidelines. Alternative imaging examinations were hardly used and did

Fig. 1 Schedule of CT examinations during a 5-year follow-up by histology and collapsed over all adjuvant strategies for 206 incident testicular cancer patients with stage I from Maccabi Healthcare Services, Israel, 2003–2007 and comparison with NCCN guideline recommendations for stage I according to adjuvant strategies
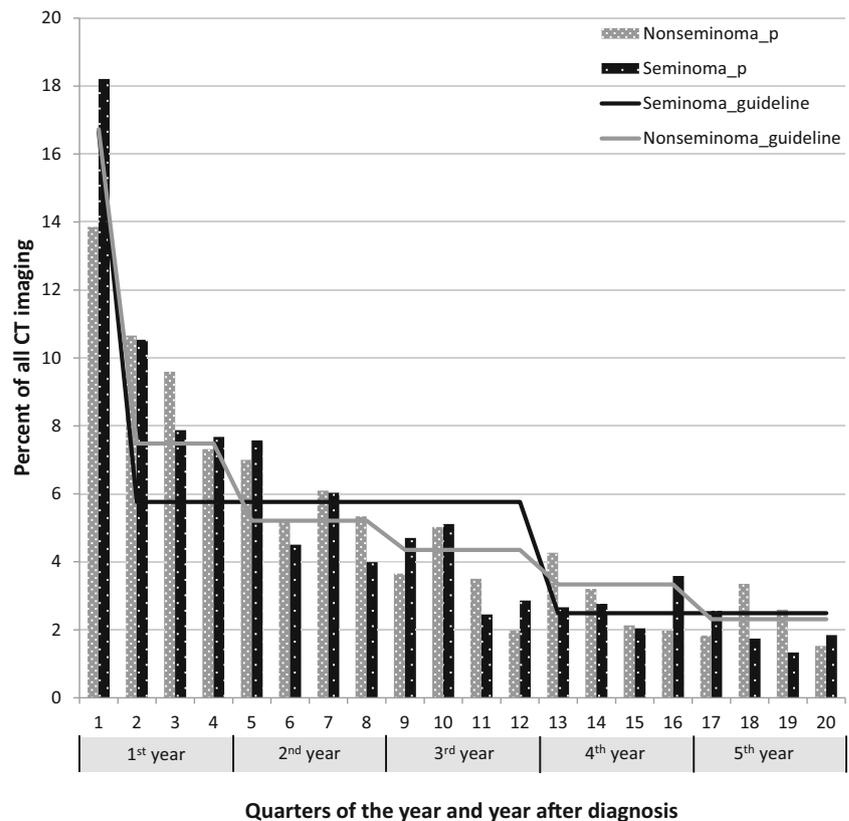
not compensate the underuse of CTs according to the guidelines. The risk of cancer from birth to the age of 80 is 33.6% for male Jews in Israel and was raised by 0.6% due to diagnostic CT radiation in patients from the MHS sample [28].

Van Walraven et al found a median diagnostic radiation exposure of 110 mSv during 5 years of follow-up in TC patients from Ontario, Canada [19]. The median number of CT examinations was 10. However, patients who underwent a retroperitoneal lymph node dissection or RTX were excluded because they require no or few CT examinations during follow-up. In a study from two cancer care hospitals in Ireland, Sullivan et al found a median of 10 CTs per patient and a median cumulative effective dose of 125 mSv during an average follow-up of 4.4 years [29]. Stages II and III, for which the guidelines recommend up to 22 CTs during 5 years of follow-up for seminoma patients, were more frequent than in the MHS sample. The median diagnostic radiation exposure and the median number of CT examinations in both studies were higher than in the MHS sample. However, even the patients in the studies by van Walraven et al and Sullivan et al received fewer CTs than recommended in the guidelines. In a survey among Australian oncologists, Grimison et al found an even lower median number of eight abdomen CTs for seminoma patients and nine abdomen CTs for nonseminoma patients during a 5-year follow-up with surveillance. In contrast to recommendations, 62% of seminoma patients were treated with chemotherapy instead of surveillance

[30]. Interestingly, the median number of eight CT examinations (radiation dose of 90 mSv) for nonseminoma patients during 5 years in the MHS sample is comparable to the NCCN guideline recommendations from 2014 resulting in a minimum of eight CTs (estimated total effective dose of 112 mSv) during 6 years [31].

It could be argued that physicians might not be familiar with the guidelines but the concerns about secondary cancers from radiation during follow-up might have motivated physicians to reduce the number of CTs during follow-up. The updates of the NCCN guidelines from 2005 to 2012 resulted in a reduction of up to eight CT examinations for seminoma patients with stage I during a 5-year follow-up [32]. Moreover, the guideline from 2014 suggested 8 to 12 CTs, which is fewer than the minimum CT examinations recommended in the guideline from 2012 [31]. Besides reducing the number of CTs, during the last 10 years, efforts have been made to reduce radiation exposure in CT examinations by improving hardware and imaging software [33]. At any time, the ALARA (as low as reasonably achievable) principle should be followed. Furthermore, the societies of radiology and the associations for radiologic protection improved in informing patients and the general population about the different imaging methods, medical radiation, and their potential risks.

TC occurs in adolescents and young adults (AYAS) in contrast to many other cancers. In this age group, studies found a

Table 3 Cumulative number of CT examinations (thorax, abdomen or pelvis, and unspecified) and chest X-ray among 206 patients with newly diagnosed seminomatous and nonseminomatous germ cell tumors of the testis with stage I from Maccabi Healthcare Services, Israel, during 2003–2007 and over a follow-up of 5 years per patient and comparison with the National Comprehensive Cancer Network (NCCN) guideline from 2005

Adjuvant strategy[a]	Seminoma					NCCN guideline	Nonseminoma					NCCN guideline
	N	Mean	SE	Median	P10; P90[b]		N	Mean	SE	Median	P10; P90[b]	
Chemotherapy												
Any CT	36	6.67	0.43	7.5	3.0; 10.0		37	11.32	1.18	9.0	4.0; 24.0	
Thorax CT	11	1.09	0.09	1.0	1.0; 1.0		7	4.29	1.69	2.0	1.0; 12.0	
Abdomen or pelvis CT	35	5.49	0.48	6.0	1.0; 8.0	0[c,d]	32	8.66	1.16	8.0	2.0; 18.0	7–8
Unspecified CT	14	2.57	0.40	2.5	1.0; 5.0		23	4.87	0.75	6.0	1.0; 8.0	
X-ray chest	27	5.15	0.79	5.0	1.0; 11.0	0[c,d]	23	5.17	0.77	5.0	1.0; 11.0	17–21
Radiotherapy												
Any CT	31	5.45	0.49	5.0	2.0; 10.0		0	–	–	–	–	
Thorax CT	7	2.00	0.53	1.0	1.0; 4.0		0	–	–	–	–	
Abdomen or pelvis CT	29	4.10	0.45	4.0	1.0; 8.0	4	0	–	–	–	–	0[c]
Unspecified CT	17	2.12	0.31	2.0	1.0; 4.0		0	–	–	–	–	
X-ray chest	20	4.25	0.99	3.0	1.0; 10.5	9–10	0	–	–	–	–	0[c]
Radio- and chemotherapy												
Any CT	7	6.14	1.34	5.0	3.0; 12.0		0	–	–	–	–	
Thorax CT	0	–	–	–	–		0	–	–	–	–	
Abdomen or pelvis CT	7	5.43	1.32	4.0	1.0; 11.0	0[c]	0	–	–	–	–	0[c]
Unspecified CT	4	1.25	0.25	1.0	1.0; 2.0		0	–	–	–	–	
X-ray chest	6	4.00	0.97	3.5	1.0; 8.0	0[c]	0	–	–	–	–	0[c]
Surveillance												
Any CT	58	8.17	0.66	7.0	2.0; 16.0		23	10.00	1.10	9.0	4.0; 16.0	
Thorax CT	12	3.50	1.03	2.5	1.0; 8.0		8	2.88	1.09	1.5	1.0; 10.0	
Abdomen or pelvis CT	56	6.45	0.55	5.0	2.0; 13.0	14–17	22	7.91	0.86	8.5	3.0; 13.0	14–17
Unspecified CT	29	2.45	0.42	1.0	1.0; 8.0		11	3.00	1.06	1.0	1.0; 7.0	
X-ray chest	48	5.38	0.58	4.5	1.0; 11.0	7–9	18	7.00	1.80	5.00	1.0; 16.0	22–28

SE standard error

[a] Applied therapy during the first 3 months after diagnosis

[b] P10, P90 = 10th/90th percentile

[c] This type of adjuvant therapy was not mentioned in the NCCN guideline from 2005

[d] Chemotherapy was introduced in the guideline in 2007 and recommendations were 14 to 17 CTs and 7 to 9 chest X-rays during a 5-year follow-up

lower adherence during cancer treatment and follow-up [34, 35]. Besides typical reasons for nonadherence like side effects or lack of symptoms, AYAS reported psychosocial and developmental concerns [36]. AYAS are not yet used to dealing with serious health issues and want to move on with their life giving priorities to raising children or building up a career instead of following an aftercare schedule.

The combination of concerns about radiation doses, unfamiliarity with the guidelines, and the low adherence of young men during follow-up leads to two scenarios. First, the physician chooses surveillance as adjuvant strategy and the number of CT examinations will stay below recommendations. Second, the physician chooses a more aggressive treatment with RTX that requires fewer CTs during follow-up. CTX with carboplatin came up as an alternative strategy for

seminoma patients with stage I and was incorporated in 2007 into the NCCN guidelines [37]. Hence, physicians had another option to treat patients with increased risk for relapse, leaving surveillance to patients with only a low risk for relapse and therefore a reduced need for frequent CT examinations.

Alternatively, other imaging techniques may have reduced the number of applied CTs in patients on surveillance. Despite a distinct use of ultrasound of the abdomen or pelvis region, the use in surveillance patients had to be much higher to fill the gap between applied CTs and the recommendations from the guidelines. MRI and FDG-PET were not used as alternatives to CT in Israel until 2012. Similarly, in the study by Sullivan et al, there was only little use of MRI and PET-CT [29]. Nevertheless, in recent years, the use of MRI and FDG-PET has been evaluated in several studies and is now

Table 4 Lifetime attributable risk of cancer incidence (LAR in %) due to CT examination during a 5-year follow-up after incident testicular cancer in 206 patients with stage I from Maccabi Healthcare Services, Israel, from 2003 to 2007

	N	LAR				
		Mean	SE	Median	P10[a]	P90[a]
Seminoma						
Lung cancer	138	0.09	0.01	0.08	0.02	0.17
Colon cancer	138	0.10	0.01	0.10	0.02	0.20
All solid cancers	138	0.49	0.03	0.48	0.09	0.94
All cancers	138	0.56	0.03	0.55	0.10	1.08
Nonseminoma						
Lung cancer	68	0.12	0.01	0.12	0.00	0.27
Colon cancer	68	0.15	0.01	0.14	0.00	0.31
All solid cancers	68	0.71	0.07	0.70	0.00	1.60
All cancers	68	0.81	0.08	0.79	0.00	1.78

SE standard error

[a] P10, P90 = 10th/90th percentile

recommended in the EAU Guidelines for certain scenarios [38–41]. The actual number of chest X-rays was also lower than recommended in the NCCN guidelines. However, the recommended number of 16 to 27 chest X-rays for nonseminoma patients is only classified as evidence category 2B and De La Pena et al rather pleaded for a combination of CT examinations and tumor marker information in the detection of relapse [42].

Considering the LAR of 0.6% due to CT examinations during surveillance, it has to be kept in mind that CTX and RTX also carry a risk for second cancers. Travis et al found relative risks for second cancers of 1.8 (95% CI 1.3, 2.5) and 2.0 (95% CI 1.9, 2.2) after CTX and RTX, respectively, compared to the general population [43]. However, studies comparing the late effects of adjuvant therapy and surveillance in TC patients under more current conditions are missing [44].

The strength of the study is the combination of cancer registry data and health insurance data. We could give a detailed description of applied CT, X-ray, and alternative imaging examinations for incident TC patients stratified by histology, stage, and adjuvant strategy. Nevertheless, there are factors limiting the interpretation of our results. First, our analyses are sensitive to the assumptions about treatment characteristics including our definition of surveillance. We assigned the patients to the adjuvant strategy that was started within the first 3 months after diagnosis, but individual courses of the disease may have caused misclassification regarding the assigned treatment. Second, the size and morphology of lymph nodes might be difficult to interpret resulting in misclassification of the stage [6]. With regard to stage distributions from the

Netherlands Cancer Registry 2000 to 2009 (73% had stage I, 16% had stage II, and 11% had stage III), a misclassification in favor of lower stages is probable [5]. Third, the estimation of the LAR is not based on the factual performed CT protocols but on estimates from the paper by Sodickson et al whose data date back to 1985 [27]. Because the radiation doses gradually decreased over time, the estimated LAR might be an overestimation of the actual risk. Finally, there was also no explicit code in the MHS database that indicated the occurrence of relapse.

Conclusion

The deviation from the recommended number of CT examinations in the NCCN guidelines depended on the type of adjuvant strategy. The guidelines were followed for patients treated with CTX or RTX but not for patients under surveillance. Updated guidelines from 2012 recommended fewer CTs during surveillance. From today's perspective, patients were not undersupplied with CTs but physicians quickly adapted new evidence from published studies before it was integrated into the guidelines. Accordingly, the radiation dose from actually applied CT examinations was rather low and did not substantially raise the lifetime risk for cancer.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Prof. Dr. med. Andreas Stang, MPH.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
• prospective
• observational
• performed at one institution

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