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Review – Testis Cancer

Testicular Tumour Size and Rete Testis Invasion as Prognostic Factors for the Risk of Relapse of Clinical Stage I Seminoma Testis Patients Under Surveillance: a Systematic Review by the Testicular Cancer Guidelines Panel

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Abstract

Context: Patients with clinical stage I (CS I) seminoma testis with large primary tumours and/or rete testis invasion (RTI) might have an increased risk of relapse. In recent years, these risk factors have frequently been employed to decide on adjuvant treatment.
Objective: To systematically review the literature on tumour size and RTI as risk factors for relapse in CS I seminoma testis patients under surveillance.
Evidence acquisition: Relevant databases including Medline, Embase, and the Cochrane Library were searched up to November 2016. Randomised controlled trials (RCTs) or quasi-RCTs, prospective observational studies with controls, retrospective matched-pair studies, and comparative studies from well-defined registries/databases were included. The primary outcome was the rate of relapse and relapse-free survival (RFS). The risk of bias was assessed by the Quality in Prognosis Studies tool.
Evidence synthesis: After assessing 3068 abstracts and 80 full-text articles, 20 studies met the inclusion criteria. Although evidence to justify a cut-off of 4 cm for size was lacking, it was the most frequently studied. The reported hazard ratio (HR) for the RFS for tumours >4 cm was 1.59–2.8. Accordingly, the reported 5-yr RFS ranged from 86.6% to 95.5% and from 73.0% to 82.6% for patients having tumours ≤4 and >4 cm, respectively. For tumours with RTI present, the reported HR was 1.4–1.7. The 5-yr RFS ranged from 86.0% to 92.0% and 74.9% to 79.5% for patients without versus those with RTI present, respectively. A meta-analysis was considered inappropriate due to data heterogeneity.
Conclusions: Primary tumour size and RTI are associated with the risk of relapse in CS I seminoma testis patients during surveillance. However, in the presence of either risk

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factor, the vast majority of patients are cured by orchiectomy alone and will not relapse. Furthermore, the evidence on the prognostic value of size and RTI has significant limitations, so prudency is warranted on their routine use in clinical practice.

Patient summary: Primary testicular tumour size and rete testis invasion are considered to be important prognostic factors for the risk of relapse in patients with clinical stage I seminoma testis. We systematically reviewed all the literature on the prognostic value of these two postulated risk factors. The outcome is that the prognostic power of these factors in the published literature is too low to advocate their routine use in clinical practice and to drive the choice on adjuvant treatment in clinical stage I seminoma testis patients.

1. Introduction

Testicular cancer is a rare malignancy with a rising incidence in the Western world (three to 10 in 100 000 males/yr) [1]. The vast majority of patients presents with clinical stage I (CS I) disease both for nonseminomatous or seminomatous histology. Patients with metastatic seminoma of the testis have a good prognosis with a 5-yr survival rate of 86% for good and 72% for intermediate prognosis patients [2]. CS I seminoma testis patients (70% of all seminoma testis) have a very good prognosis with an overall survival rate of 98%. For CS I seminoma testis patients, the standard management following inguinal orchiectomy is close surveillance, but long-term follow-up is warranted as approximately 5% of relapses occur after 5 yr and even very late relapses (>10 yr) might occur [3]. The majority of recurrences, however, occur within 2 yr after diagnosis. Identification of CS I seminoma testis patients who are at a high risk of recurrence has largely been based on two prognostic factors: primary testicular tumour size, and the presence or absence of rete testis invasion (RTI). Warde et al [4] were the first to show that patients having one or both risk factors present in the pathological specimen were at a higher risk of relapse than patients without those risk factors. The relapse rate in the absence of both risk factors was only 6% for a surveillance policy [5]. Therefore, in patients having one or both risk factors, adjuvant treatment, such as one cycle of carboplatin or radiotherapy to the retroperitoneum, has been advocated in order to reduce the risk of relapse [6–8]. However, the rather weak correlation between the presence of these risk factors and the risk of recurrence is subject to debate. In addition, the possibility of late negative effects of carboplatin or radiotherapy, such as secondary malignancies or cardiovascular disease [9], must be taken into account when considering adjuvant treatment for CS I seminoma patients [10]. In addition, the reported second relapse rate is higher in relapsing patients initially treated with adjuvant carboplatin than those relapsing under surveillance [11,12].

If primary tumour size and RTI are being considered as important factors to guide clinical decision making on adjuvant treatment in CS I seminoma testis patients, their prognostic value for the risk of recurrence needs to be clarified and potentially be improved. With this aim, we performed a systematic review of all the relevant literature to establish the prognostic value of tumour size and RTI in CS I seminoma testis under surveillance.

2. Evidence acquisition

2.1. Data acquisition and search strategy

This review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [13]. The review protocol was published in PROSPERO database (http://www.crd.york.ac.uk/PROSPERO; registration number CRD42017056975).

A literature search was conducted using the electronic databases Medline (Ovid) (1950 to 28 November 2016) and Embase (1980 to 28 November 2016), the Cochrane Central Register of Controlled Trials (to Issue October 2016), and Cochrane Database of Systematic review (2005 to 23 November 2016) from 1980 onwards (see Supplementary material, search strategy). Studies in children, case reports, letters, and meeting abstracts were excluded. Searches were limited to English language. The search was complemented by the reference lists of included studies and additional reports identified by the European Association of Urology (EAU) Testicular Cancer Guideline Panel. Two reviewers (J.L.B. and J.MdC) screened all abstracts and full-text articles independently. Disagreement was resolved by discussion, and when no agreement was reached, a third independent party acted as an arbiter (L.M.).

2.2. Types of studies and participants

Prospective or retrospective studies investigating the independence of the association between tumour size and/or RTI in the relapse of CS I seminoma testis were included. Studies reporting on patients diagnosed with CS I seminoma testis, who were surveyed after radical orchiectomy without adjuvant treatment, were included, whereas patients receiving adjuvant treatment were not eligible for this analysis. Studies including patients having spermatocytic seminoma, nonpure seminomatous tumours, or bilateral testicular tumours were not included in the analysis. If there were multiple publications using the same cohorts and reporting the same outcome, the most recent publication was used for data extraction and analysis. If different outcomes were reported in different publications derived from the same cohort, information from all relevant publications was extracted.

2.3. Prognostic factors evaluated

The size of the primary tumour (either as a continuous variable or as a categorical variable using different cut-off

points) and/or the presence or absence of RTI (as a categorical variable) at the radical orchiectomy specimen analysis was evaluated. In addition, information on how tumour size and RTI were assessed and what definition of RTI was used was captured.

2.4. Types of outcome measures included

The primary outcome measure was disease relapse rate (as absolute number of events) at different time points. Radiological or pathological diagnoses were accepted. Relapse based on biochemical recurrence only was not accepted, because biochemical recurrences without radiological evidence are extremely rare and restaging by imaging in 6 wk is warranted. Secondary outcome measures were estimates of relapse-free, disease-free, and overall survival at 5 and 10 yr, as assessed by the Kaplan–Meier method.

2.5. Measures of association

Estimates of the primary and secondary outcomes, and unadjusted (univariate) and adjusted (multivariable) measures of association were extracted from the included studies. Effect sizes were converted, as necessary, to a common measure in order to avoid possible selection bias and allow us to use the data from as many studies as possible. Either relative or absolute differences were used as the common measure of the relationship between tumour size, RTI, and relapse rate. Relative differences were based on either relative risks or odds ratios (ORs) for categorical outcomes, and on hazard ratios (HRs) for time to event outcomes. For consistency, associations were recalculated to be in the same direction, as necessary, with estimates >1 indicating a worse prognosis relative to the best prognosis group. Absolute differences were calculated based on the difference at a given point in time or the difference in the overall percent of patients experiencing an event.

2.6. Assessment of risk of bias

The risk of bias in the included studies was assessed using the Quality in Prognosis Studies tool for six domains: participants, attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting [14]. Two reviewers (J.L.B. and MdC) assessed the overall risk of bias. Disagreement was resolved by discussion, and when no agreement was reached, a third independent party acted as an arbiter (L.M.). Important potential confounding factors for the risk of relapse were identified a priori in consultation with content experts of the EAU guideline panel on testicular cancer. Confounding factors taken into account were age, race, pathological T-stage, lymphovascular invasion, and molecular markers (CKIT, M2A, and OCT3/4).

2.7. Data synthesis

For data analysis, descriptive statistics were used to summarise baseline characteristics. Meta-analyses were planned if valid data were available assessing the association between tumour size, RTI, and relapse rate from sufficiently homogeneous studies in terms of population, prognostic factor, definition and outcome. Important heterogeneity between series led us to abandon the intention to perform a meta-analysis, and a narrative synthesis was performed instead.

3. Evidence synthesis

3.1. Quantity of evidence identified

The search strategy identified a total of 3068 studies, which were screened. Of these, 80 studies were selected for full-text screening, and finally, 20 studies (including 9185 patients) were eligible for inclusion in the systematic review [3–5,15–31]. The study selection process is outlined in the PRISMA diagram (Fig. 1).

3.2. Risk of bias and quality assessment

The risk of bias assessment is depicted in Supplementary material (Risk of bias assessment). The risk of bias across the six domains was moderate to high for 18 studies; only two studies were with a low risk [21,28]. Important heterogeneity was found between series, and frequently relevant information describing population, patient selection, and methodology was lacking.

3.3. Analysis of RTI as a prognostic factor for recurrence

Fourteen studies [5,15–21,23,24,26,28,30,31] (see Table 1 for the characteristics of the 20 studies included in the analysis) included data on RTI and 12 studies [5,15,16,18–20,23,24,26,28,30,31] assessed the correlation of RTI and the risk of relapse. Only one study provided a clear definition of RTI [30]. The reported median follow-up varied from 2.5 to 15.1 yr, and the median age of the patients from 34 to 40 yr. The proportion of RTI present varied from 15.2% to 67%, whereas the proportion of missing data on RTI varied from 0% to 50%. In general, all patients had a full staging assessment at the time of diagnosis, including tumour markers, and chest and abdominal imaging. Eight series had complete raw data on RTI and the relapse rate available (Table 2) [15,16,18–20,26,28,31], enabling the calculation of ORs and to construct a simple Forest plot (Fig. 2). The OR for RTI was statistically significant in two series [26,28].

In 1993, von der Maase et al [28] were the first to report on the prognostic significance of size and RTI in CS I seminoma testis patients. The 4-yr relapse-free survival (RFS) was 80% for the total population ($n = 261$, including four patients having spermatocytic seminoma). With a median follow-up of 4 yr, RTI was significant only in the univariable analysis ($p = 0.04$, log rank). However, no estimates of RFS were given for RTI-positive versus RTI-negative patients. In 2014 and 2016, the same group reported on 1954 and 2000 patients, respectively, including the patients from 1993, but no data on RTI as a prognostic factor were provided [3,16].

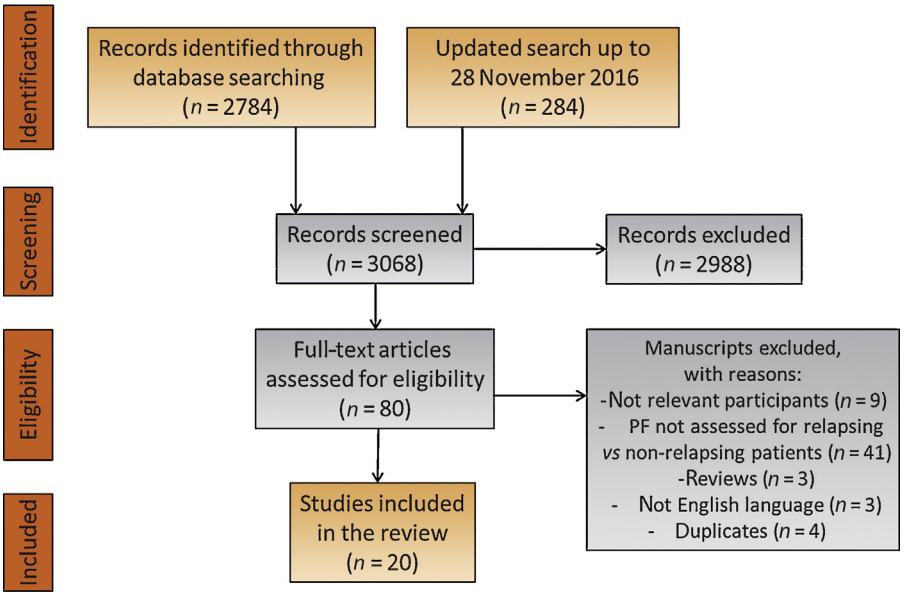

Fig. 1 – PRISMA flow diagram of the study. PF = prognostic factor.

The Princess Margaret Cancer Center reported on 150 patients recruited from 1981 to 1993 [23], and found a 10-yr relapse-free rate of 92% versus 75% ($p = 0.05$) for patients with RTI absent versus those with RTI present. Later, the series was pooled with patients from Denmark and the UK ($n = 638$ patients) [30]. Although no central pathology was done, RTI was clearly defined as an extension of tumour into the testicular mediastinum without necessarily involving the tubular lumen. With a median follow-up of 7.0 yr, the 5-yr RFS was 86.3% versus 76.7% ($p = 0.003$) for RTI-negative versus RTI-positive patients. Moreover, the prognostic value of RTI in addition to size was assessed; the HR for the risk of relapse of patients having both RTI present and a tumour size of >4 cm (95 patients) was 3.4 (2.0–6.1) as compared with patients without risk factors (176 patients). On the contrary, a recent retrospective analysis of prospectively collected databases of the same institutions failed to show the prognostic significance of RTI in a population of 685 patients [18]. Eighty-eight patients relapsed (median time to relapse: 12 mo) and 116 patients had RTI present. The reported HR for RTI was 1.36 (95% confidence interval [CI]: 0.81–2.28; $p = 0.25$).

The Spanish Germ Cell Cancer Group published an update [5] of two previous reports [15,16] on 396 patients under surveillance. The primary end point was the cause-specific disease-free survival, but only relapses were considered events. With a median follow-up of 6.7 yr, the 5- and 10-yr RFS values were, respectively, 90.6% and 88.6% for patients without RTI versus 74.9% and 64.5% for patients with RTI present ($p < 0.0001$).

A prospective study by the Swedish and Norwegian Testicular Cancer Group (SWENOTECA) performed a risk-adapted approach of one course of adjuvant carboplatin versus surveillance [26]. Patients were eligible to participate if they had pure seminoma, no spermatocytic seminoma, no lymph nodes >1 cm, and normal alpha-fetoprotein. For the 422 patients under surveillance, the overall relapse rate was 7.5%. Although no individual data on the prognostic significance of RTI were reported, the combination of size (cut-off of 4 cm) and RTI was presented and the relapse rate increased from 4% (no risk factors present) to 16.7% (both risk factors present). A previous study by SWENOTECA did not contain data on the prognostic significance of RTI [25].

A German registry of 130 centres recruited 256 CS I seminoma patients between 2008 and 2013 [19]. No information was provided on the eligibility criteria, and patients were assessed and followed up according to clinical practice and not by a predefined follow-up schedule. Kaplan–Meier estimates of relapse over time were constructed, but no differences were seen between RTI-positive and RTI-negative patients ($p = 0.472$, log rank; no RFS reported). In addition, raw data on the association of the relapse rate and RTI also failed to show any difference between the presence and absence of RTI (Fig. 2).

Lastly, smaller series on retrospective cohorts were identified. Soper et al [24] reported 5-yr RFS of 89.8% versus 79.5% ($p = 0.049$, log rank) for RTI-positive versus RTI-negative patients ($n = 94$). Howard et al [20] recruited 52 patients of whom 17.3% relapsed and the OR for RTI was 1.06, but neither CI nor a p value was provided. A series by Yoshida et al [31] on 64 patients (no eligibility criteria stated) found a relapse rate of 12.3%, and central pathology review showed the proportion of RTI to be 18.9%. Both the diagnostic assessment and the follow-up were according to a defined protocol, and raw numbers on RTI and the rate of relapse were provided. However, RTI did not correlate with the risk of relapse ($p = 0.46$, log rank). Arai et al [17] stated that presence of RTI did not correspond with the rate of relapse in a cohort of 70 patients ($p = 0.057$), but no further information was provided.

Table 1 – Study characteristics of the 20 studies included in the systematic review

Study ID	Institution	Enrolment period	Patients under surveillance (*n*)	Eligibility criteria for surveillance	Mean and median [a] age (range), yr	Median follow-up (range), yr
Tandstad (2016) [26]	Swedish and Norwegian Testicular Cancer Study Group	2007–2010	422	Pure seminoma, no spermatocytic seminoma, normal AFP, LN <1 cm	NR	5.4 (NR)
Nayan (2016) [22]	Princess Margaret Cancer Center, University of Toronto, Canada	1980–2014	893	NR	NR	7.4[a] (4.3–10.2)
Mortensen (2016) [3]	Danish Testicular Cancer Study Group	1984–2007	2000	NR	37 (NR)	15.0 (9.0–21.0)
Dieckmann (2016) [19]	German Testicular Cancer Group	2008–2013	256	NR	NR	2.5 (0.5–5.0)
Chung (2015) [18]	Princess Margaret Cancer Center, University of Toronto, Canada	1998–2005	685	NR	40 [a] (20–75)	3.85 (0.1–10.3)
Howard (2014) [20]	Dana Faber Cancer Institute, Boston, MA, USA	1997–2010	52	NR	36 [a] (16–82)	NR (>2.0)
Mortensen (2014) [21]	Danish Testicular Cancer Study Group	1984–2008	1954	No history of testicular cancer, no synchronous testicular tumour, no levels of hCG >200 IU/l	36.4 (22–67)	15.1 (0.6–28.7)
Soper (2014) [24]	Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA, USA	1990–2010	94	Pure seminoma, no evidence of nodal or distant disease	37 [a] (16–82)	5.2 (0.1–17.7)
Aparicio (2014) [5]	Spanish Germ Cell Cancer Group	1994–2008	396	NR	38 (NR)	6.6 (2.0–17.0)
Arai (2012) [17]	National Cancer Center Research Institute, Tokyo, Japan	NR	70	NR	NR	NR
Aparicio (2011) [16]	Spanish Germ Cell Cancer Group	2004–2008	153	Pure seminoma, tumour-free resection margins	NR	2.8 (0.1–5.3)
Tandstad (2011) [25]	Swedish and Norwegian Testicular Cancer Study Group	2000–2006	512	Pure seminoma, no spermatocytic seminoma, normal AFP, no extragonadal germ cell tumour	NR	5.0 (0.3–10.1)
Yoshida (2009) [31]	Osaka Medical Center for Cancer and Cardiovascular diseases, Osaka, Japan	1982–2005	64	NR	37 [a] (18–86)	10.3 (1.5–25.2)
Tyldesley (2006) [27]	British Columbia Cancer Registry, Canada	1992–2002	93	NR	35 [a] (21–62)	2.8 [b] (NR); 3.5 [c] (NR)
Aparicio (2003) [15]	Spanish Germ Cell Cancer Group	1994–1999	143	Pure seminoma, tumour-free resection margins	36 [a] (21–81)	NR
Warde (2002) [30]	Princess Margaret Cancer Center, University of Toronto, Canada; Royal Mardsen and Royal London Hospital, London, UK; Danish Testicular Cancer Study Group	1981–1997	638	NR	NR	7.0 (0.02–17.5)
Parker (2002) [23]	Princess Margaret Cancer Center, University of Toronto, Canada	1981–1993	150	No spermatocytic seminoma	NR	9.4 (2.4–16.5)
Warde (1997) [29]	Princess Margaret Cancer Center, University of Toronto, Canada	1981–1993	201	NR	NR	6.1 (1.3–12.3)
Von der Maase (1993) [28]	Danish Testicular Cancer Study Group	1985–1988	261	NR	34 [a] (20–86)	4.0 (0.5–5.6)
Warde (1993) [4]	Princess Margaret Cancer Center, University of Toronto, Canada	1984–1991	148	Pure seminoma, tumour-free resection margins, no evidence of nodal or distant disease, normal postoperative AFP and hCG, no concomitant or previous malignancy except bcc or scc of the skin, patients available for and consent to close follow-up	NR	3.9 (0.6–7.3)

	Mean and median [a] tumour size (range, SD), cm	pT stage	Proportion of RTI present/missing (%)	Relapse rate (%)	Overall risk of bias	Frequency of follow-up visits
Tandstad (2016) [26]	2.6 [a] (NR, NR)	NR	15.2/4.7	15.5	Moderate risk	Year 0–2: 3×/yr; year 3–4: 2×/yr; year 5–10: 1×/yr
Nayan (2016) [22]	3.8 (NR, 2.2)	pT1: 73.9% pT2: 24.8% pT3: 0.9% pT4: 0.4%	NR/NR	7.5	High risk	Year 0–3: Abd and pelvic CT 2×; year 4, 5, 7, and 9: Abd CT

Table 1 (*Continued*)

	Mean and median [a] tumour size (range, SD), cm	pT stage	Proportion of RTI present/ missing (%)	Relapse rate (%)	Overall risk of bias	Frequency of follow-up visits
Mortensen (2016) [3]	NR		NR/NR	17.8	Moderate risk	NR
Dieckmann (2016) [19]	2.5 [a] (NR, NR)	NR	17.6/NR	24.1	Moderate risk	NR
Chung (2015) [18]	3.0 [a] (0.2–13, NR)	NR	16.9/30.2	12.9	Moderate risk	NR
Howard (2014) [20]	3.1, 2.0 [a] (0.5–10.0, 2.5)	NR	30.8/15.4	17.3	Moderate/high risk	NR
Mortensen (2014) [21]	3.5 [a] (0.1–15.0, NR)	NR	33.9/23.5	18.9	Low risk	Tumour markers/2 mo, CT/6 mo the 1st year; tumour markers/3 mo, CT/6 mo the 2nd year; tumour markers/6 mo and a final CT at 60 mo
Soper (2014) [24]	3.8 [a] (NR, NR)	pT1: 76.6% pT2: 20.2% pT3: 1.1% pT4: 1.1%	18.1/NR	11.7	High risk	Median first review 5 mo. Median in 2 yr, 3× CT
Aparicio (2014) [5]	NR	pT1–2: 90.2%	13.4/0.5	12.9	Moderate risk	Tumour markers and chest Rx/3 mo, CT/6 mo
Arai (2012) [17]	NR	NR	67.1/0	12.9	High risk	NR
Aparicio (2011) [16]	NR	pT1: 82.1% pT2: 17.2% pT3: 0.7%	16.3/0	9.8	Moderate risk	NR
Tandstad (2011) [25]	NR	NR	NR/NR	12.7	Moderate risk	20 in 10 yr
Yoshida (2009) [31]	NR	pT1: 53.1% pT2: 39.1% pT3: 7.8%	18.8/0	12.3	Moderate risk	2 mo chest Rx and tumour markers for 2 yr, CT/4 mo 2 for yr
Tyldesley (2006) [27]	NR	NR	NR/NR	17.2	High risk	NR
Aparicio (2003) [15]	NR	pT1: 100%	18.9/1.4	16.1	Moderate risk	Chest Rx and tumour markers at 3, 6, 9, 12, 18, 26, 36, 48, 60, 72 mo and CT at 6, 12, 18, 26, 36, 48, 60, 72 mo
Warde (2002) [30]		NR	27.6/25.5	16.1	Moderate risk	Every 2–6 mo the first 2–3 yr
Parker (2002) [23]	NR	NR	24.7/50.0	19.0	Moderate risk	Evolved during study: year 0–3 3×; year 4–7 2×; year 8–10 1×; tumour markers and CT every visit, chest Rx alternate
Warde (1997) [29]	NR	NR	NR/NR	20.0	High risk	Year 0–3: 3× tumour markers and CT; year 4–7 2× markers and CT; year 8–10 1× markers and CT; chest Rx at alternate visits
Von der Maase (1993) [28]	NR	NR	37.5/NR	15.4	Moderate risk	Year 0–1: 6× tumour markers + chest Rx; year 1–2: 3× markers + chest Rx; year 2–5: 2× markers and chest Rx; year 0–2: 3× CT; year 3–5: 2× CT
Warde (1993) [4]	NR	NR	NR/NR	19.0	Moderate risk	Year 0–2: 6× tumour markers; year 2–3: 3× tumour markers; year >3: 2× tumour markers; year 0–3: 4× CT; year 4–7: 2× CT; year 8–10: 1× CT

Abd CT = computerised tomography of the abdomen; AFP = alpha-fetoprotein; bcc = basal cell carcinoma; chest Rx = X-ray of the thorax; CT = computed tomography; hCG = human chorionic gonadotropin; LN = lymph node; NR = not reported; pT stage = pathological T stage; RTI = rete testis invasion; scc = squamous cell carcinoma; SD = standard deviation.

[a] For nonrelapsing patients.

[b] For relapse.

[c] For survival.

3.4. *Analysis of tumour size as a prognostic factor for recurrence*

Tumour size was evaluated as a risk factor in 17 studies [3–5,15,16,18–26,28–30], both as dichotomous ($n = 15$) [5,15,16,18–20,22–26,28–31] and a continuous variable ($n = 8$) [5,18,20,21,24,28–30]. Size was assessed by the pathology specimen in all but four studies [16,17,27,31]. Detailed information on how tumour size was exactly measured, however, was not provided. Warde et al [4] were the first to use a cut-off point of 4 cm, because it was the median tumour size in their series. Since then, it has been the most frequently addressed cut-off point, although 3 [18,22,28], 6 [23,28,29], and 7 cm [31] have also been reported. The median tumour size, which was provided in seven series, varied from 2 to 4 cm, and in six out of the seven series it was ≤4 cm [18–21,24,26]. Of note, in only four series central pathology review was done [22,28,29,31].

On multivariable analyses, size was identified as an independent prognostic factor for RFS in five series with reported HR ranging from 1.59 to 2.8 [18,21,23,29,30] (Table 3). The largest series by Mortensen et al [21] ($n = 1954$) reported a statistically significant HR of 1.59 (95% CI: 1.31–1.92; $p < 0.0001$) for size as a continuous variable. This study partly overlapped with that of Chung

Table 2 – Results of studies reporting on the prognostic significance of rete testis invasion in CS I seminoma testis patients

Study ID	Institution	Patients (*n*)	Method for reporting prognostic significance	Univariate analysis of results	Method reporting multivariate analysis	multivariate Analysis of results
Howard (2014) [20]	Dana Faber Cancer Institute, Boston, MA, USA	52	Raw numbers	OR [a] = 1.06 (0.22–5.18)	NR	NR
Chung (2015) [18]	Princess Margaret Cancer Center, University of Toronto, Canada	685	3-yr RFR (log rank)	81.6% (RTI present) vs 86.5% (RTI absent) $p = 0.232$	Cox proportional hazard model	HR = 1.36 (95% CI: 0.81–2.28, $p = 0.25$)
Dieckmann (2016) [19]	German Testicular Cancer Study Group	256	Raw numbers Actuarial relapse rate over time (log rank)	OR [a] = 1.49 (95% CI: 0.52–4.31) $p = 0.471$	NR	NR
Yoshida (2009) [31]	Osaka Medical Center for Cancer and Cardiovascular diseases, Osaka, Japan	64	Raw numbers Relapse rate	OR [a] = 1.88 (95% CI: 0.32–11.1) $p = 0.46$ [b]	NR	NR
Von der Maase (1993) [28]	Danish Testicular Cancer Study Group	261	Raw numbers RFS (log-rank)	OR [a] = 1.93 (95% CI: 0.99–3.75) $p = 0.04$	Cox regression	Not significant (HR not reported)
Tandstad (2016) [26]	Swedish and Norwegian Testicular Cancer Study Group	422	Raw numbers [b]	OR [a] = 2.44 (95% CI: 1.06–5.63)	NR	NR
Aparicio (2011) [16]	Spanish Germ Cell Cancer Group	153	Raw numbers Relapse rate (χ^2 test) Actuarial 3-yr DFS	OR [a] = 2.95 (95% CI: 0.91–9.54) $p = 0.061$ 78.3% (RTI present) vs 93.5% (RTI absent and size <4 cm) $p = 0.067$	NR	NR
Aparicio (2003) [15]	Spanish Germ Cell Cancer Group	143	Raw numbers	OR [a] = 3.01 (95% CI: 1.11–8.16)	NR	NR
Parker (2002) [23]	Princess Margaret Cancer Center, University of Toronto, Canada	150	10-yr relapse-free rate (log rank)	75% (RTI present) vs 92% (RTI absent) $p = 0.05$	NR	NR
Warde (2002) [30]	Princess Margaret Cancer Center, University of Toronto, Canada; Royal Mardsen and Royal London Hospital, London, UK; Danish Testicular Cancer Study Group	638	5-yr RFS (log rank)	76.7% (RTI present) vs 86.3% (RTI absent) $p = 0.003$	Cox regression	HR = 1.7 (1.1–2.6), p value not reported
Aparicio (2014) [5]	Spanish Germ Cell Cancer Group	396	5-yr RFS (log rank) 10-yr RFS (log rank)	74.9% (RTI present) vs 90.6% (RTI absent) 64.5% (RTI present) vs 88.6% (RTI absent) $p < 0.0001$	Cox proportional hazard model	HR = NR, $p < 0.001$
Soper (2014) [24]	Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA, USA	94	5-yr RFS (log rank)	79.5% (RTI present) vs 89.8% (RTI absent) $p = 0.049$	Cox regression	Not significant (HR not reported)

CI = confidence interval; CS I = clinical stage I; DFS = disease-free survival; HR = hazard ratio; NR = not reported; OR = odds ratio; RFR = relapse-free rate; RFS = relapse-free survival; RTI = rete testis invasion.

[a] Odds ratio calculated based on the raw numbers for RTI present versus absent in relapsing and nonrelapsing CS I seminoma testis patients.

[b] Statistical test used to calculate the differences in relapse rate not reported.

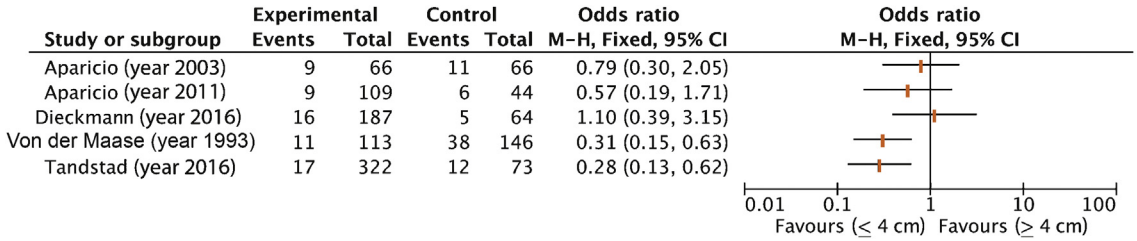

Fig. 2 – Simple Forest plot showing the relapse rate for CS I seminoma testis patients managed by surveillance having a tumour size of ≤4 versus >4 cm. CS I = clinical stage I; M–H = Mantel-Haenszel; CI = confidence interval; RTI = rete testis invasion.

et al [18] (n = 685), which evaluated various cut-off points but selected a cut-off of 3 cm with an HR of 1.87 (95% CI: 1.15–3.06; p = 0.01). In 2002, a series by Warde et al [30] on 638 patients reported an HR of 2 (95% CI: 1.3–3.2, p value not stated) for a cut-off of 4 cm. A smaller series of 150 patients by the same group used a cut-off of 6 cm and found an HR of 2.8 (95% CI: 1.2–6.5; p = 0.01) [23]. Lastly, an even earlier series by Warde et al [29] also reported an HR of 2.8 (95% CI: 1.6–6.6, p = 0.03) for the cut-off of 6 cm in 201 patients.

On univariable analyses, tumour size was correlated with different end points, such as the relapse rate, risk of relapse, and RFS (see Table 3). Only one series provided a significant OR of 1.34 (95% CI: 1.02–1.75) for size as a continuous variable [20]. However, six studies provided raw numbers on tumour size in relapsing versus nonrelapsing patients, enabling us to calculate the corresponding OR and construct a simple Forest plot (Fig. 3) [15,16,19,26,28,31]. It was found that in only two series the calculated OR for tumour size was statistically significant [26,28].

Various papers reported the estimated RFS at 3, 4, 5 (mainly), and 10 yr [4,5,16,18,22–24,28–30]. The reported 5-yr RFS ranged from 86.6% to 95.5% for patients having tumours <4 cm versus 73.0–82.6% for patients having tumours ≥4 cm, and the differences were shown to be statistically significant in almost all the series.

3.5. *Discussion*

Testicular tumour size and RTI are considered as important prognostic factors in CS I seminoma testis patients, and in clinical practice these factors are being used for guidance of decision making on adjuvant treatment. The results of this systematic review, however, show that the prognostic power of both tumour size and RTI is too weak to justify their routine use in clinical practice. Moreover, as the 5-yr RFS in all the series was >73% in the presence of RTI or tumour size ≥4 cm, this indicates that the vast majority of the patients are cured by orchiectomy alone and will not relapse. Advocating adjuvant treatment, which itself also does not provide a 100% relapse-free rate, based on these risk factors will result in a large proportion of overtreatment. This is in accordance with the findings of a very recent study, which was not included in the present review, on 473 CS I seminoma testis patients who had very large primary tumours (≥6 cm, median 7 cm, no data on RTI reported) [32]. The relapse rate (median follow-up 24 yr) of the 219 patients under surveillance was 32% versus 3% for the patients treated by adjuvant radiotherapy, showing that adjuvant radiotherapy led to overtreatment in approximately two-thirds of the patients, even in the presence of very large primary tumours. Importantly, up-front adjuvant treatment might lead to long-term adverse effects. Kvammen et al [33] recently showed a strong decline in the long-term relative survival of seminoma testis patients probably due to the late effects of adjuvant radiotherapy. Based on the findings of the present review and in accordance with current clinical guidelines [2,34] surveillance is a valid and safe option in all CS I seminoma testis patients, provided that high-risk patients adhere to a more stringent follow-up scheme.

Determination of both primary tumour size and RTI is greatly hampered by a lack of standardisation in the reported literature. Larger tumours confer a higher risk of recurrence and this correlation seems to be linear, but there is not enough evidence to justify the frequently used cut-off of 4 cm. The cut-off of 4 cm was described for the first time in 1993, because it was the median tumour size in the series by Warde et al [4]. Since then, however, seven series reported the median testicular tumour size and it was <4 cm in all series (range: 2.0–3.8 cm). Moreover, studies that addressed size as a continuous variable showed a clear significant correlation with the risk of relapse. Therefore, the use of a cut-off point for tumour size, if any, should be abandoned in clinical practice until solid evidence to support a certain cut-off point is provided. The new 2017 American Joint Committee on Cancer (AJCC) tumour, node, and metastasis classification on testicular cancer will subdivide pure seminoma testis into stage pT1a and pT1b using a cut-off of 3 cm and not 4 cm (Amin, M.B., Edge, S.B., Greene, F.L., et al. (Eds.) AJCC Cancer Staging Manual. 8th Ed. New York: Springer; 2017).

No study, except one, clearly described a definition of RTI. In addition, central pathology review was not performed in the vast majority of the series, and the proportion of missing data on RTI was substantial. No information on the number of slides to investigate the presence of RTI was available, which precludes the possibility of assessing RTI as a continuous variable, with tumours having more infiltration present being most likely more aggressive in biological behaviour than tumours with little infiltration. In addition, Pagetoid invasion of the rete testis, which is probably not a risk factor for relapse, was not reported in the series. This variation in reporting on RTI suggests possible differences in the interpretation of RTI by pathologists. As a prognostic

Table 3 – Results of studies reporting on the prognostic significance of tumour size in CS I seminoma testis patients

Study ID	Institution	Patients (*n*)	Size cut-off (cm)	Method for reporting prognostic significance	Univariate analysis of results	Method reporting multivariate analysis	Multivariate analysis of results
Dieckmann (2016) [19]	German Testicular Cancer Study Group	256	4	Raw numbers Actuarial relapse rate over time (log-rank)	OR [a] = 1.06 (95% CI: 0.39–3.15) $p = 0.8116$	Cox regression	Not significant (HR not reported)
Aparicio (2003) [15]	Spanish Germ Cell Cancer Group	143	4	Raw numbers	OR [a] = 0.79 (95% CI: 0.30–2.05)	NR	NR
Von der Maase (1993) [28]	Danish Testicular Cancer Study Group	261	4 <3; 3–<6; ≥6 cm Continuous	Raw numbers 4-yr RFS (log rank) RFS (log rank)	OR [a] = 0.31 (0.15–0.63) 94% vs 82% vs 64% $p < 0.001$	Cox regression	Significant (HR not reported)
Aparicio (2011) [16]	Spanish Germ Cell Cancer Group	153	4	Raw numbers Actuarial 3-yr DFS (log rank)	OR [a] = 0.57 (95% CI: 0.17–1.71) 93.5% (≤4 cm) vs 83.7% (>4 cm) $p = 0.067$	NR	NR
Tandstad (2016) [26]	Swedish and Norwegian Testicular Cancer Study Group	422	4	Raw numbers	OR [a] = 0.28 (95% CI: 0.13–0.62)	NR	NR
Yoshida (2009) [31]	Osaka Medical Center for Cancer and Cardiovascular diseases, Osaka, Japan	64	7	Raw numbers Relapse rate	OR [a] = 0.48 (95% CI: 0.10–2.38) $p = 0.43$ [b]	NR	NR
Howard (2014) [20]	Dana Faber Cancer Institute, Boston, MA, USA	52	Continuous	Logistic regression	OR = 1.34 (1.02–1.75) $p = 0.03$	NR	NR
Mortensen (2014) [21]	Danish Testicular Cancer Study Group	1954	Continuous	RFS	NR	Cox proportional hazard model	HR = 1.59 (95% CI: 1.31–1.92) $p < 0.0001$
Chung (2015) [18]	Princess Margaret Cancer Center, University of Toronto, Canada	685	3 4 Continuous	3-yr RFR (log rank) 3-yr RFR (log rank) 3-yr RFR (log rank)	90.6% (≤3 cm) vs 81.6% (>3 cm) $p = 0.012$ 87.8% (≤4 cm) vs 80.1% (>4 cm) $p = 0.047$ $p = 0.0006$	Cox proportional hazard model NR NR	HR = 1.87 (95% CI: 1.15–3.06, $p = 0.01$) NR NR
Warde (2002) [30]	Princess Margaret Cancer Center, University of Toronto, Canada; Royal Mardsen and Royal London Hospital, London, UK; Danish Testicular Cancer Study Group	638	4 Continuous	5-yr RFR (log rank) Relapse rate	86.6% (≤4 cm) vs 75.9% (>4 cm) $p = 0.003$ NR	Cox regression	HR = 2.0 (1.3–3.2), p value not reported NR

Table 3 (*Continued*)

Study ID	Institution	Patients (*n*)	Size cut-off (cm)	Method for reporting prognostic significance	Univariate analysis of results	Method reporting multivariate analysis	Multivariate analysis of results
Warde (1997) [29]	Princess Margaret Cancer Center, University of Toronto, Canada	201	6 Continuous	5-yr RFS (log rank) Relapse rate	88% (≤6 cm) vs 67% >6 cm) $p = 0.004$ $p = 0.01$	Cox proportional hazard model	HR = 2.8 (1.2–6.6), $p = 0.03$
Parker (2002) [23]	Princess Margaret Cancer Center, University of Toronto, Canada	150	6	10-yr relapse-free rate (log rank)	82% vs 65% $p = 0.03$	Cox proportional hazard model	HR = 2.8 (1.2–6.5), $p = 0.01$
Nayan (2016) [22]	Princess Margaret Cancer Center, University of Toronto, Canada	863	3	5-yr conditional risk of relapse	87.8% (≤3 cm) vs 79.7% (>3 cm) p value NR	NR	NR
Aparicio (2014) [5]	Spanish Germ Cell Cancer Group	396	4 Continuous	5-yr RFS (log-rank) 10-yr RFS (log rank) NR	91.2%(≤4 cm) vs 82.6% (>4 cm) 89.3% (≤4 cm) vs 76.9% (>4 cm) $p = 0.016$ NR	Cox proportional hazard model	Not included as dichotomous variable $p = 0.052$
Tandstad (2011) [25]	Swedish and Norwegian Testicular Cancer Study Group	512	4	Relapse rate	14.1% (≤4 cm) vs 16.0% (>4 cm) $p = 0.186$	Cox proportional hazard model	Not included
Soper (2014) [24]	Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA, USA	94	4 Continuous	5-yr RFS (log rank) 5-yr RFS (log rank)	95.5% (≤4 cm) vs 78.5% (>4 cm) $p = 0.029$ Not significant, p value NR	Cox regression	Not significant (HR NR)
Warde (1993) [4]	Princess Margaret Cancer Center, University of Toronto, Canada	148	4	5-yr RFR (log rank)	88% (≤4 cm) vs 73% (>4 cm) $p = 0.12$	NR	NR

CS I = clinical stage I; DFS = disease-free survival; HR = hazard ratio; NR = not reported; OR = odds ratio; RFR = relapse-free rate; RFS = relapse-free survival; RTI = rete testis invasion.

[a] Odds ratio calculated based on the raw numbers for RTI present versus absent in relapsing and nonrelapsing CS I seminoma testis patients.

[b] Statistical test used to calculate the differences in relapse rate not reported.

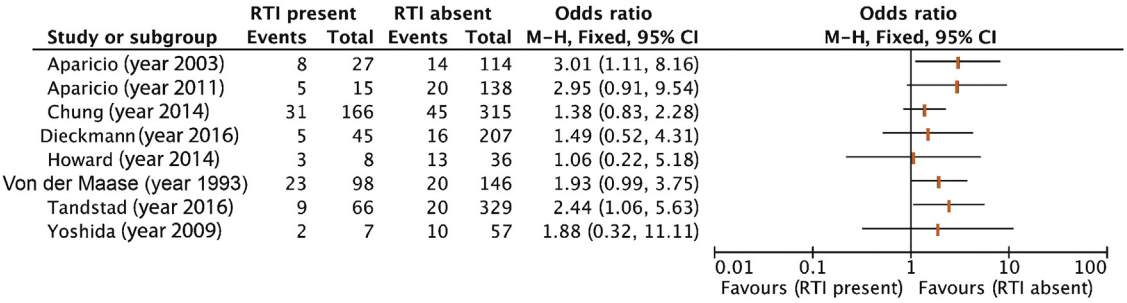

Fig. 3 – Simple Forest plot showing the relapse rate for CS I seminoma testis patients managed by surveillance in the presence versus the absence of rete testis invasion. CS I = clinical stage I; M–H = Mantel–Haenszel; CI = confidence interval.

factor that is nonstandardised or difficult to determine is not of universal use; we call for standardisation of the definition of RTI and incorporating central review in clinical studies by a pathologist who is experienced in testicular germ cell tumours. Lastly, hardly any information was provided in the studies on other possible histopathological risk factors, such as vascular invasion, invasion of the hilum of the testis, and the proportion of multifocal disease.

One of the strengths of the present review is the systematic approach that has been undertaken to address the prognostic significance of risk factors in CS I seminoma testis patients. The methodology of the review process included Cochrane reporting standards, such as PRISMA, and standardised tools to assess risks of bias. The principal findings of this review, however, are hampered by the heterogeneity of the populations of the studies included, the risk of overlapping populations, and the fact that the methodological quality of the studies greatly differed with moderate to high risk of biases in the majority of the studies. A way, at least partly, to overcome these limitations is to perform an individual patient data meta-analysis on the prognostic value of size and RTI in CS I seminoma testis patients under surveillance of the larger series incorporated in this review, such as the Spanish Germ Cell Cancer Group, SWENOTECA, the Danish Testicular Cancer Study Group, the German Testicular Cancer Group, and the Princess Margaret Cancer Center.

4. Conclusions

In CS I seminoma testis patients under surveillance, large testicular tumour size and RTI are associated with the risk of relapse. Tumour size seems to be linearly correlated with the risk of recurrence, but evidence is lacking to justify the use of a cut-off of 4 cm, which is most frequently studied. In addition, hardly any study provided a clear definition of RTI, and in the vast majority central pathology review was not carried out. Therefore, we conclude that the available evidence on the prognostic value of tumour size and RTI in CS I seminoma testis patients has significant limitations, and therefore their use in routine clinical practice is not recommended.

Author contributions: Joost L. Boormans had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Boormans.
Acquisition of data: Boormans, Mayor de Castro, Marconi, Yuan.
Analysis and interpretation of data: Boormans, Mayor de Castro, Laguna Pes, Albers, Bokemeyer, Nicolai, Algaba, Oldenburg, Marconi.
Drafting of the manuscript: Boormans, Mayor de Castro.
Critical revision of the manuscript for important intellectual content: Boormans, Mayor de Castro, Laguna, Albers, Bokemeyer, Nicolai, Algaba, Oldenburg, Marconi.
Statistical analysis: None.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Laguna, Albers, Marconi.
Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2017.09.025.

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