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Retroperitoneal Lymph Node Dissection with No Adjuvant Chemotherapy in Clinical Stage I Nonseminomatous Germ Cell Tumours: Long-Term Outcome and Analysis of Risk Factors of Recurrence

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Abstract

Background: The best management for patients with clinical stage I (CS1) nonseminomatous germ cell tumours (NSGCT) is still under debate.
Objective: We evaluated the long-term oncologic outcome of retroperitoneal lymph node dissection (RPLND) in patients with CS1 NSGCTs and reevaluated the traditional predictors of recurrence in a set of patients not undergoing adjuvant treatment.
Design, setting, and participants: Between 1985 and 1995, 322 consecutive CS1 NSGCT patients underwent primary RPLND not followed by adjuvant chemotherapy in a single referral centre. Patients were followed until relapse for a median time of 17 yr.
Measurements: We estimated the crude cumulative incidence of any recurrence. Categories pN and pT, vascular invasion (VI), percentage of embryonal carcinoma, and presence of teratoma were evaluated as 2-yr recurrence predictors of event in a binary logistic model.
Results and limitations: Fifty patients had a recurrence (46 in $\leq$2 yr and only 4 [1.2%] in >2 yr). The 10-yr recurrence incidence was 15.2%. Significant predictors of recurrence at multivariable analysis were pN+, pT >1, and the presence of VI. However, the discriminative ability of the model was modest (Harrell C = 0.74); only 9% and 3% of patients had a predicted recurrence probability >30% and >50%, respectively.
Conclusions: RPLND alone could prevent recurrence in 85% of patients and minimise late relapses to 1.2%. Most patients could avoid the immediate and late toxicity of chemotherapy. Prognostic parameters combined into the multivariable model appeared of limited use in identifying a subset of patients at high risk of recurrence.

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1. Introduction

Patients with clinical stage I (CS1) nonseminomatous germ cell tumours (NSGCTs) have an approximately 30% risk of micrometastases and a very favourable cure rate approaching 100% [1–6]. Ease of use, costs, acute and late toxicity of therapy, and limitations of a second therapy are the factors that have contributed to the current treatment at this stage. Retroperitoneal lymph node dissection (RPLND) is gradually being replaced by surveillance or adjuvant chemotherapy that is proposed according to risk factors, essentially vascular invasion (VI) [7]. Risk-adapted treatments have avoided overtreatment in many patients and a second therapy in others [8,9]. But recent scientific debate has raised the question about the poor evidence supporting risk-adapted treatments [10]. Few centres still pursue RPLND, and Albqami and Janetschek are evaluating laparoscopy [11].

Since the early 1980s, we have been treating CS1 patients with RPLND followed by surveillance until relapse [12]. The long-term outcome of RPLND alone was the main objective of this study. Our evaluation also allowed us to reconsider the prognostic values of the best known traditional predictors of metastatic disease when RPLND is the exclusive primary treatment.

2. Patients and methods

Between 1985 and 1995, 322 consecutive CS1 patients with NSGCT underwent RPLND alone at the Fondazione IRCCS Istituto Nazionale dei Tumori of Milan [13]. Unilateral RPLND was performed as previously reported [14]. In the case of intraoperative suspicious lymph nodes, frozen sections were required. A modified bilateral RPLND was performed in the case of metastatic nodes. No patient received any adjuvant treatment following surgery. Nerve-sparing techniques were introduced in 1988. We do not report data about the preservation of antegrade ejaculation.

Pathologic category (pT) was classified according to the 1987 TNM Union Internationale Contre le Cancer staging system (4th edition), in which VI had not yet been included.

The follow-up program provided eight visits in the first 2 yr, three in the third year, four in the fourth and fifth year, and every year thereafter. An abdominal imaging was provided every second visit, but patients actually underwent three to four computed tomography (CT) scans during the first 3 yr. Follow-up was updated in June 2008. The median follow-up was 17.3 yr (interquartile range [IQR]: 14.9–19.9 yr).

2.1. Statistical methods

The study end point was tumour recurrence, including distant and abdominal metastases. We estimated the crude cumulative incidence (CCI) of recurrence, that is, the probability of developing recurrence as the first event in the presence of a contralateral tumour and death from an unrelated cause (competing events). Time to event was computed from the date of RPLND to the first occurrence of the event, with censoring at final follow-up for event-free patients.

A multivariable analysis was performed using a binary logistic model, in which the response variable was recurrence as first event at 2 yr from RPLND, at which time only one patient was lost to follow-up. Based on the findings of Vergouwe et al [7], the following variables were chosen: pT, VI, percentage of embryonal carcinoma (%ECa; modelled as a continuous covariate using a three-knot restricted cubic spline [15] to obtain a flexible fit), teratoma (T), and nodal metastasis at RPLND (pN). The missing values were "filled in" by applying a multiple imputation (MI) procedure, following the approach of Clark and Altman [16].

The logistic model performance focused on the aspects of internal calibration, which was explored graphically by calibration plots, and discriminative ability, quantified by the C statistic, which corresponds to the area under the receiver operating characteristic curve (the higher towards 1, the better) [17]. The latter estimate was adjusted for optimism, which is a common problem of the models fitted using small data sets such as ours, by applying a bootstrap procedure [18].

Table 1 – Patient and disease characteristics

	n	%
Age at surgery, yr		
≤30	216	67
>30	106	33
Median (IQR)	27 (22–32)	
Pre-orchiectomy AFP (IU/ml)		
Normal (<15)	94	29
Elevated (≥15)	156	49
Not available	72	22
Preorchiectomy β-hCG (IU/ml)		
Normal (<5)	131	41
Elevated (≥5)	109	34
Not available	82	25
Interval between orchiectomy and RPLND, d		
≤30	34	11
>30, ≤60	97	30
>60	191	59
Median (IQR)	66 (47–82)	
RPLND extension		
Modified unilateral	289	90
Modified bilateral	33	10
T category*		
pT1	201	62
pT2	19	6
pT3	7	2
Not available	95	30
Vascular invasion		
Absent	131	41
Present	72	22
Not available	119	37
Embryonal carcinoma		
Absent	56	17
Present	258	80
Median (IQR)	40 (6–85)	
Not available	8	3
Teratoma		
Absent	130	40
Present	192	60
Yolk sac tumour		
Absent	173	54
Present	149	46
Pathologic N stage at RPLND†		
pN0	262	81
pN+	60	19
Pathologic stage IIA	41	13
Pathologic stage IIB	19	6

AFP = α-fetoprotein; hCG = human chorionic gonadotropin; IQR = interquartile range; RPLND = retroperitoneal lymph node dissection.
* 1987 TNM Union Internationale Contre le Cancer classification.
† Pathologic stage IIA: nodal metastases <2 cm, no extranodal spread; pathologic stage IIB: nodal metastases ≥2 cm and/or microscopic extranodal spread [12].