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Original Article

Validation of a prediction model for post-chemotherapy fibrosis in nonseminoma patients

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Objective

To validate Vergouwe's prediction model using the Swedish and Norwegian Testicular Cancer Group (SWENOTECA) RETROP database and to define its clinical utility.

Materials and methods

Vergouwe's prediction model for benign histopathology in post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND) uses the following variables: presence of teratoma in orchiectomy specimen; pre-chemotherapy level of alpha-fetoprotein; β-Human chorionic gonadotropin and lactate dehydrogenase; and lymph node size pre- and post-chemotherapy. Our validation cohort consisted of patients included in RETROP, a prospective population-based database of patients in Sweden and Norway with metastatic nonseminoma, who underwent PC-RPLND in the period 2007–2014. Discrimination and calibration analyses were used to validate Vergouwe's prediction model results. Calibration plots were created and a Hosmer–Lemeshow test was calculated. Clinical utility, expressed as opt-out net benefit ($NB^{opt\text{-}out}$), was analysed using decision curve analysis.

Results

Overall, 284 patients were included in the analysis, of whom 130 (46%) had benign histology after PC-RPLND. Discrimination analysis showed good reproducibility, with an area under the receiver-operating characteristic curve (AUC) of 0.82 (95% confidence interval 0.77–0.87) compared to Vergouwe's prediction model (AUC between 0.77 and 0.84). Calibration was acceptable with no recalibration. Using a prediction threshold of 70% for benign histopathology, $NB^{opt\text{-}out}$ was 0.098. Using the model and this threshold, 61 patients would have been spared surgery. However, only 51 of 61 were correctly classified as benign.

Conclusions

The model was externally validated with good reproducibility. In a clinical setting, the model may identify patients with a high chance of benign histopathology, thereby sparing patients of surgery. However, meticulous follow-up is required.

Keywords

clinical decision rules, lymph node excision, forecasting, neoplasms, germ cell and embryonal, nonseminomatous germ cell tumour, testicular neoplasms

Introduction

Post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND) for metastatic nonseminoma, with residual retroperitoneal lymph nodes of ≥10 mm in longest axial (transversal) diameter, is a challenging procedure. During the last decades, the aim has been to decrease the burden of complications following surgery by modifying the surgical templates, introducing nerve-sparing techniques, and centralizing surgery to tertiary high-volume surgical centres [1–3]. Nevertheless, in up to 50% of patients who undergo PC-RPLND, the histopathology results reveal necrosis/fibrosis, and the surgery performed was therefore excessive [4]. To address these issues, prediction models have been introduced to select patients for surgery [5–8]. Two of the prediction studies included fewer than 340 patients [5,6] and, to date, Vergouwe's prediction model for fibrosis/necrosis in retroperitoneal lymph nodes after chemotherapy is the best studied prediction model [7]. The original model was created in 1995, updated in 2001 and finalized in 2007. The model uses presence of teratoma in orchiectomy specimen, pre-chemotherapy levels of alpha-fetoprotein (AFP), β-Human chorionic gonadotropin (β-HCG) and lactate dehydrogenase (LDH), and pre- and post-chemotherapy lymph node size as variables to predict benign outcome [7,9].

The early version of the prediction model has been validated by the Vergouwe group [10–12]. Since the final version was published in 2007, two groups, one from Canada and one from Germany, have independently validated the prediction model [13,14]. However, the implementation of the model in clinical practice is challenging because of the risk of leaving teratoma or viable cancer in residual retroperitoneal lymph nodes. The aim of this study was to validate Vergouwe's prediction model in the population-based RETROP dataset of patients, and evaluate its possible clinical use.

Materials and Methods

Patients with testicular nonseminomatous germ cell tumour in Sweden and Norway who underwent PC-RPLND between 1 September 2007 and 1 September 2014 were prospectively included in the RETROP database. RETROP was linked to the population-based Swedish and Norwegian Testicular Cancer Group (SWENOTECA) register [15]. The patients were treated according to the SWENOTECA guidelines. SWENOTECA IV guidelines (1995–2012) recommended that patients with initial clinical stage ≥ II B retroperitoneal lymph node metastases underwent PC-RPLND, regardless the size of the residual tumour. PC-RPLND could be omitted for patients with initial clinical stage IIA and complete remission on chemotherapy. [16] However, after 2012, only patients with a residual tumour of ≥10 mm underwent surgery, while patients with a residual tumour <10 mm were followed with surveillance [15]. Patients who developed a growing mass in the retroperitoneum while on surveillance were considered to have a recurrence and were not included in this study. The patients underwent surgery with an open transperitoneal technique at six university hospitals in Sweden and at four university hospitals in Norway. The PC-RPLND templates

Table 1 Baseline characteristics of patients in the RETROP cohort.

	RETROP
Number of patients	284
Year of PC-RPLND	2007–2014
Median (IQR) age, years	29 (24–35)
Royal Marsden clinical stage, *n* (%)	
II	165 (60)
III	21 (7)
IV	98 (34)
Abdominal stage, *n* (%)	
A	32 (11)
B	160 (56)
C	62 (22)
D	30 (11)
IGCCCG prognostic group, *n* (%)	
Good	184 (65)
Intermediate	56 (20)
Poor	44 (15)
Less than standard chemotherapy*, *n* (%)	
1–2 cycles BEP, PEI or EP	6 (2)
Standard-dose chemotherapy, *n* (%)	
3–4 cycles BEP	217 (77)
3–4 cycles PEI	6 (2)
4 cycles EP	4 (1)
Intensified-dose chemotherapy, *n* (%)	
1–4 BEP + 1–3 PEI/BEP-if	37 (13)
1–4 BEP + 1–3 TIP	6 (2)
Intensified-dose chemotherapy and HD, *n* (%)	
2–3 BEP + 2–3 PEI/BEP-if + 1–2 HD	4 (1)
2–3 BEP + 1–2 TIP + 2 HD	3 (1)
1 PEI + 3 HD	1 (1)

*Standard chemotherapy was 3–4 cycles of BEP, EP or PEI. Intensified therapy was TIP or PEI/BEP-if. Abdominal stage A: retroperitoneal lymph nodes <20 mm; B: 20–49 mm; C: 50–99 mm; D: ≥100 mm. BEP, bleomycin, etoposide, cisplatin; BEP-if, bleomycin, etoposide, cisplatin, ifosfamide; EP, etoposide and cisplatin; HD, high-dose chemotherapy; IGCCCG, International Germ Cell Cancer Collaborative Group; PC-RPLND, post-chemotherapy retroperitoneal lymph node dissection; PEI, cisplatin, etoposide, ifosfamide; TIP, paclitaxel, ifosfamide, cisplatin. *Patients received less than standard chemotherapy due to toxicity.*

used for the patients included in the study are described in detail elsewhere [3,4].

Patients included in this study had normalized tumour markers after chemotherapy and no history of previous RPLND. From the SWENOTECA register, RETROP and medical records, we collected information on the presence of teratoma in the orchiectomy specimen, lymph node size pre- and post-chemotherapy on CT, tumour marker levels before start of chemotherapy, type of chemotherapy given, modified Royal Marsden clinical stage [17], prognostic group according to the International Germ Cell Cancer Collaborative Group (IGCCCG) [18], and histopathology results from PC-RPLND. No central review of the CT scans or the histopathology was performed.

Definitions

The outcome was histopathology result from the PC-RPLND, defined as either benign (fibrosis/necrosis), or tumour (teratoma/cancer). The variables used to predict outcome in Vergouwe's prediction model were: teratoma in orchiectomy specimen, categorized as present or absent; AFP and β-HCG levels before start of chemotherapy, classified as either elevated or normal; LDH level at start of chemotherapy as a continuous variable; change in longest axial lymph node diameter on CT before and after chemotherapy; and longest axial lymph node diameter on CT after chemotherapy. Change in lymph node mass size was calculated using the formula in Vergouwe's prediction model [7].

Statistical Analysis

The outcome, histopathology from PC-RPLND, was coded as: 0 = malign/teratoma and 1 = benign. For each variable, bivariate odds ratios (ORs) with 95% CI were estimated using complete-case analysis. For multivariable analysis, missing values were imputed using 10 imputations (see Appendix for details). Calculations to find the linear predictor (lp) were performed according to the 2007 manuscript by Vergouwe et al. with the corrections pointed out by Punjani et al. [7,19,20]. The linear predictor was thus calculated using the formula: (lp = −1.2 + 1.13 × teratoma in orchidectomy [0 = present, 1 = absent] + 1.11 × AFP [0 = elevated, 1 = normal] + 0.72 × HCG [0 = elevated, 1 = normal] + 0.82 × [log {LDH/upper level of normal value of LDH}] − 0.27 × sqrt [size post-chemotherapy] + 0.14 × [percent change in mass size/10]), where lp is the linear predictor. Individual probabilities of benign outcome were calculated using (prob = 1/[1 + exp{−lp}]). Discrimination was estimated using concordance statistics with 95% CI, and an area under the receiver-operating characteristic curve (AUC) curve was plotted. Calibration was assessed using a calibration plot and a Hosmer–Lemeshow test.

Table 2 Predictors of benign histopathology in the RETROP and Vergouwe datasets.

	Values	RETROP		Vergouwe	
		Benign/All (%)	OR (95% CI)	Benign/All (%)	OR (95% CI)
Overall		130/284 (46)		425/1094 (39)	
Teratoma elements in orchiectomy specimen	Present	32/126 (25)	1	146/591 (25)	1
	Absent	98/157 (62)	4.9 (2.9–8.2)	279/503 (55)	3.8 (2.9–4.9)
Missing data		1		–	
AFP serum level	Elevated	65/171 (38)	1	225/755 (30)	1
	Normal	58/98 (59)	2.4 (1.4–3.9)	200/339 (59)	3.4 (2.6–4.4)
Missing data		15		–	
β-HCG serum level	Elevated	63/179 (35)	1	241/716 (34)	1
	Normal	59/90 (66)	3.5 (2.1–6.0)	184/378 (49)	1.9 (1.4–2.4)
Missing data		15		–	
LDH serum level	Normal	30/102 (29)	1	87/260 (33)	1
	1–2× normal	54/94 (57)	3.2 (1.8–5.9)	130/303 (43)	1.5 (1.1–2.1)
	>2× normal	34/67 (51)	2.5 (1.3–4.7)	132/258 (51)	2.1 (1.5–3.0)
Missing data		21		273	
Axial size of residual lymph node on CT	0–19 mm	75/132 (57)	3.5 (1.6–7.8)	214/344 (62)	7.2 (5.1–10.2)
	20–49 mm	44/110 (40)	1.8 (0.8–4.0)	146/399 (37)	2.5 (1.8–3.6)
	>49 mm	11/40 (28)	1	65/351 (19)	1
Missing data		2		–	
Decrease in axial size of residual lymph node on CT scan before and after chemotherapy	Increase	1/29 (3)	–	10/133 (8)	0.2 (0.1–0.4)
	0–49%	67/145 (46)	1	119/444 (27)	1
	50–69%	33/68 (49)	1.1 (0.6–2.0)	129/267 (48)	2.6 (1.9–3.5)
	>70%	26/33 (76)	4.3 (1.9–11.4)	167/250 (67)	5.5 (3.9–7.7)
Missing data		9		–	

For each predictor, the total number of benign histopathology cases is specified with rate in parenthesis. ORs calculated with bivariate logistic regression for each variable and the outcome of benign disease. Tumour markers analysed pre-chemotherapy. AFP, alpha-fetoprotein; LDH, lactate dehydrogenase; OR, odds ratio; β-HCG: β-human chorionic gonadotropin.

To estimate clinical utility, net benefit (NB) and decision curve analyses were used [21]. For these analyses, outcome was coded in reverse (0 = benign, 1 = malign/teratoma) as well as probabilities (probability of malignant disease = 1 − probability of benign disease). As PC-RPLND is the standard procedure in patients with residual tumour of ≥10 mm, an opt-out strategy was used, where surgery in all patients was considered to have an NB of 0 [22]. The difference in NB between classification using the model vs PC-RPLND in all cases was reported for different decision thresholds of 90%, 80%, 70%, 60% and 50% chance of benign histopathology.

The Vergouwe study suggested a 70% threshold for benign histopathology, therefore, a subgroup analysis was performed using a threshold of 70% for benign disease and subgrouping by residual lymph node size of 0–9 mm, 10–19 mm, 20–49 mm or ≥50 mm following chemotherapy.

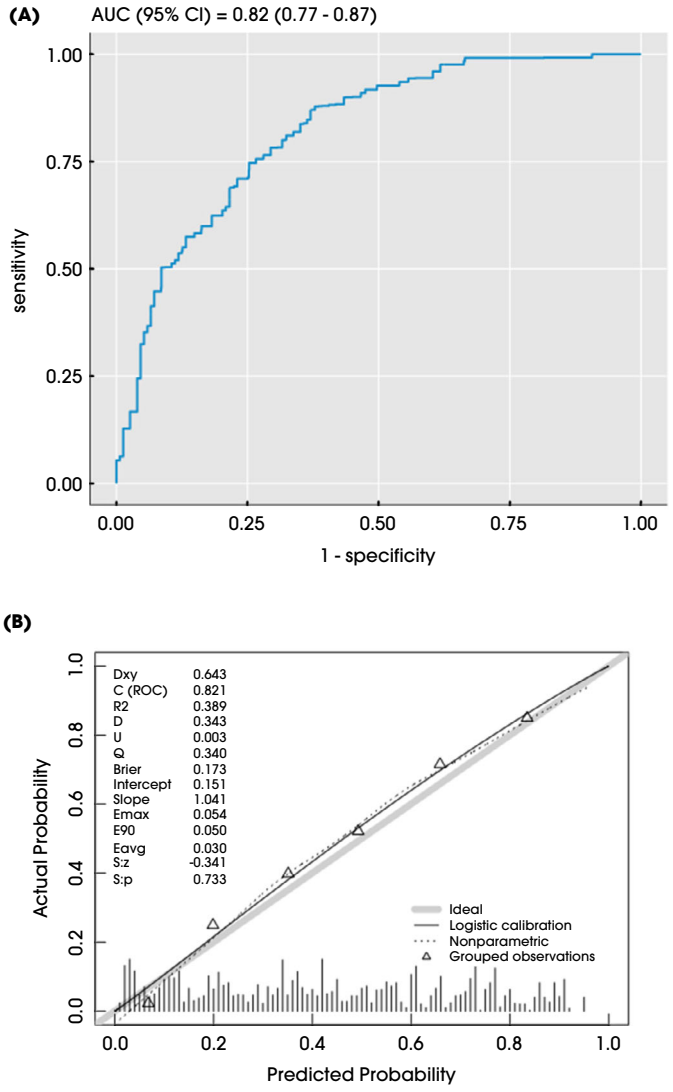
Results

A total of 284 patients were included. Of these, 130 patients (46%) had necrosis/fibrosis/benign lymph nodes, 126 patients (44%) had teratoma and 28 (10%) patients had viable disease on PC-RPLND histopathology. Most of the patients (85%) belonged to the good or intermediate prognostic group according to IGCCCG grading, and 80% received standard chemotherapy (three to four cycles of bleomycin, etoposide, cisplatin [BEP], etoposide and cisplatin (EP) or cisplatin, etoposide, ifosfamide [PEI]; Table 1). The median (interquartile range [IQR]) time from completion of chemotherapy to PC-RPLND was 5 (4–8) weeks.

In bivariate analyses, the highest OR for prediction of benign disease was absence of teratoma in the orchiectomy specimen and >70% lymph node shrinkage between pre- and post-chemotherapy CT scans. The case-mix was comparable to the Vergouwe study (Appendix S1). The distribution of outcome and predictors, with ORs, is shown in Table 2. In total, 12% of the cases had at least one missing value and these were imputed as described in the Appendix S1. Discrimination analysis showed good reproducibility, with an AUC of 0.82 (95% CI 0.77–0.87) and is presented in Fig. 1A. The dataset with imputed cases compared to the complete-case dataset did not change the AUC result (Fig. S1A). The calibration plot, presented in Fig. 1B, as well as the Hosmer–Lemeshow test (P = 0.37), showed acceptable calibration.

As suggested by Vergouwe, a 70% decision threshold level was selected for prediction of benign histopathology in PC-RPLND. Using a threshold level of 70%, the NB^{optout} was 0.098 compared to PC-RPLND in all patients. With this threshold, 61 patients would have been spared surgery and 51 of these patients would have had benign disease. The remaining 10 patients had either a teratoma (four patients) or viable cancer (six patients). Surgery would thus have been correctly avoided in 39% (51/130) of all patients with a

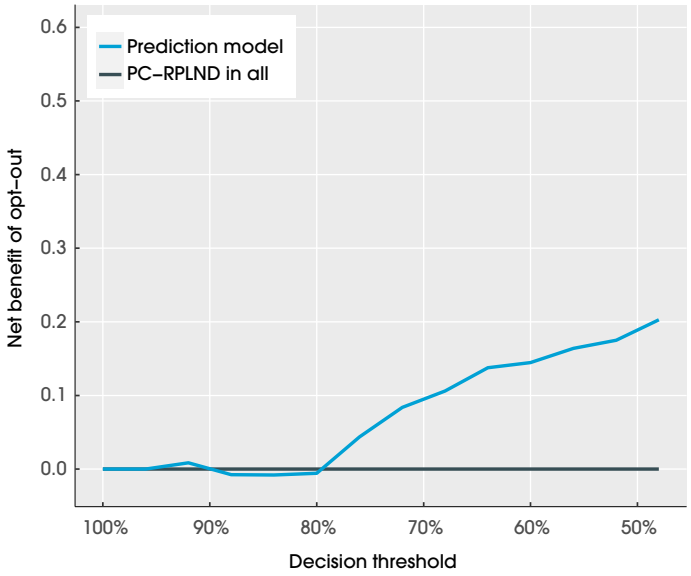
Fig. 1 (**A**) Discrimination plot for RETROP patients. Vergouwe et al. had an AUC between 0.77 and 0.84. (**B**) Calibration plot for RETROP patients. Hosmer–Lemeshow test (P = 0.37).



benign histopathology. On the other hand, teratoma would have been missed in 3% (4/126) of the patients with teratoma on PC-RPLND histopathology, and viable cancer would have been missed in 21% (6/28) of the patients with viable cancer on PC-RPLND histopathology. The decision analyses for the prediction model showed no difference in NB for decision thresholds above 70% between the current standard (PC-RPLND in all) and the use of the prediction model (Fig. 2).

In subgroup analyses, the patients were grouped depending on size of the residual tumour. Using a threshold level of 70% and a residual tumour of 10–19 mm, 24 patients with benign disease would have been omitted from surgery. This represents 51% (24/47) of all patients with benign disease in

Fig. 2 Decision curve analysis. Thresholds for prediction of benign post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND) histopathology and its corresponding net benefit (NB) compared to PC-RPLND in all patients. A decision threshold level needs to be selected to be able to use the prediction model. The figure shows the NB for different decision threshold levels of the prediction model and for PC-RPLND performed in all. An NB of zero means no clinical utility. The table describes the results for decision threshold levels between ≥50% up to ≥90%. For each level the corresponding PC-RPLND histopathology result is summarized for the patients that would be omitted from surgery. Avoiding PC-RPLND appropriately: the number of patients with benign histopathology that would be omitted from PC-RPLND out of all patients in RETROP with benign PC-RPLND histopathology (n = 130). Missing a teratoma/viable cancer: the number of patients with teratoma/viable cancer in histopathology that would be omitted from PC-RPLND out of all patients in RETROP with teratoma/viable cancer in PC-RPLND histopathology (teratoma, n = 26; viable cancer, n = 28). Opt-out NB vs PC-RPLND in all: the difference in NB for the prediction model and PC-RPLND in all.



Decision threshold level	Histopathological findings in those that would have been omitted from PC-RPLND (n=284)			Avoiding PC-RPLND appropriately (of n = 130)	Avoiding PC-RPLND inappropriately (n=154)		Opt-out net benefit vs PC-RPLND in all
	Benign	Teratoma	Cancer		Missing a teratoma (of n = 126)	Missing viable cancer (of n = 28)	
≥90%	8	1	0	8 (6%)	1 (1%)	0	-0.003
≥80%	23	2	4	23 (18%)	2 (2%)	4 (14%)	-0.006
≥70%	51	4	6	51 (39%)	4 (3%)	6 (21%)	0.098
≥60%	70	13	6	70 (54%)	13 (10%)	6 (21%)	0.145
≥50%	84	23	10	83 (64%)	23 (18%)	10 (36%)	0.178

this category. However, four patients would have been left with viable cancer in the retroperitoneum (Table 3).

The proportion of patients with benign histopathology changed after the introduction of SWENOTECA VIII in 2012. In the years 2007–2011, 50% (105/211) of the patients had benign histopathology. After omission of PC-RPLND for patients with residual lymph nodes <10 mm in 2012, only 34% (25/73) of the patients had benign histopathology at resection. This leaves fewer patients who would benefit from an opt-out strategy. This was also confirmed by the NB analysis, where the NB with a 70% cut-off was 0.098 for the whole study period, 0.111 for patients who underwent surgery in the period 2007–2011, and 0.059 for patients who underwent surgery after 2011. A complete subgroup analysis is found in the Appendix S1.

Discussion

Post-chemotherapy retroperitoneal lymph node dissection is a procedure with a high risk of complications. Almost half of the patients that undergo the surgery do not benefit from the procedure. In this study we used a population-based dataset, RETROP, to validate the prediction model used by Vergouwe et al. for predicting benign disease at PC-RPLND. The Vergouwe model has previously been externally validated by

Table 3 Observed frequencies of teratoma/viable cancer in post-chemotherapy retroperitoneal lymph node dissection histopathology.

Residual mass size	RETROP		Total
	Finding of teratoma/ viable cancer in patients classified as tumour (<70% probability of benign disease)	Finding of teratoma/ viable cancer in patients classified as benign (≥70% probability of benign disease)	
0–9 mm	10/20 (50%)	2/20 (10%)	12/40 (30%)
10–19 mm	43/66 (65%)	4/28 (14%)	47/94 (50%)
20–49 mm	63/98 (64%)	3/12 (25%)	66/110 (60%)
≥50 mm	28/39 (72%)	1/1 (100%)	29/40 (73%)

Observed frequencies of tumour in post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND) histopathology with a decision threshold of 70% for benign outcome. Subgroups created based on size of residual tumour following chemotherapy. Number and percentages of patients with teratoma/viable cancer in the group of patients predicted as tumour (<70%) or benign (≥70%). For example, 4/28 patients, with residual tumour size of 10–19 mm and predicted benign lymph nodes (≥70%), had teratoma/viable cancer in PC-RPLND histopathology. The tumour classification includes both viable cancer and teratoma.

two independent centres [13,14]. However, the study by Punjani et al. included only 51 patients and in the study by Paffenholz et al. the patients were from a single tertiary referral centre. The patients included in the study by Paffenholz et al. included more severe and complicated PC-RPLND cases, with a higher proportion of patients with poor prognosis and with a different proportion of the included variables compared to the study by Vergouwe et al. Our study is the first to use a population-based cohort to validate Vergouwe's prediction model for benign histopathology after PC-RPLND. The RETROP database used in this validation study is unique. The database includes all patients who underwent PC-RPLND during a 7-year period in Sweden and Norway.

Vergouwe's prediction model shows good reproducibility and discrimination when applied to the RETROP data and hence good validity, despite the 30 years that have passed since the first patient was included in the Vergouwe study. The diagnostics and therapy given for metastatic nonseminoma testicular cancer has developed over time. For example, since 1995, SWENOTECA has used dose-intensified treatment according to decline in tumour markers. In addition, prognostic group has been included in the treatment algorithm. Nevertheless, when comparing the outcome of benign histopathology in our study with the results from Vergouwe, they are almost similar. In RETROP, 46% of the patients had benign histopathology results compared to 39% in the Vergouwe cohort, indicating a similar case-mix. Even if the treatment protocol has changed over time for patients with insufficient tumour marker decline, the majority (80%) of the patients in the RETROP study received standard therapy with three to four cycles of cisplatin-based chemotherapy (BEP, PEI or EP). The standard therapy has not changed over time, except for patients with good prognosis who receive three cycles of BEP instead of the four cycles of BEP that was given historically [23]. Furthermore, the prediction results in our study are consistent with the Vergouwe dataset [7]. A limitation of this study is that 12% of the RETROP cases had missing values. However, the missing values that were imputed in this study did not change the outcome.

Excellent reproducibility, however, is not sufficient for launching this prediction model in the clinical setting. To use the algorithm in a clinical setting, its clinical utility needs to be established. In this study we chose NB as a decision tool to compare different thresholds for predicting benign disease at PC-RPLND. Previous studies have used opt-in NB [24] and found almost no NB. However, because surgery is the default option, we consider an $NB^{opt\text{-}out}$ calculation more appropriate [22]. Using this approach, a moderate NB (0.098) was estimated, at the threshold of 70%. With a 70% threshold, the number of patients with benign histopathology that would be selected for surgery declines from 46% to 35% and almost 40% of the patients with benign histopathology would be omitted from surgery using this cut-off level. However, 6% of the patients with viable cancer or teratoma would be omitted from surgery. For every 10% reduction in decision threshold level, the number of patients with viable cancer or teratoma omitted from surgery increases.

Using a decision threshold of 70%, only one patient with a residual tumour ≥50 mm would be omitted from surgery. Furthermore, in the group of patients omitted from surgery, a higher proportion of viable cancer compared to teratoma was found. This might be explained by the variables used in the model. Patients with a limited residual tumour and absence of teratoma in orchiectomy histopathology will be selected in the prediction model as having a high probability of benign disease.

The challenge associated with use of the prediction model in a clinical setting is to determine the acceptable rate of patients left with retroperitoneal teratoma or viable cancer, and subsequent risk of recurrence. In this study, almost 30% of the patients in complete remission (<10 mm residual retroperitoneal lymph nodes and normal tumour markers following chemotherapy) at the time of PC-RPLND had teratoma or cancer. This is the same proportion as in

previous studies [25,26]. However, the current European Association of Urology guidelines and SWENOTECA guidelines recommend surveillance and not PC-RPLND in case of complete remission. The recurrence-free survival rate for this group of patients with complete remission is 92% if subjected to surveillance rather than surgery, and the cancer-specific survival rate is 98% [27,28]. Thus, even if teratoma or cancer is left untreated in patients with limited residual retroperitoneal lymph nodes, the patients will not always have a recurrence and a recurrence infrequently leads to testicular cancer death.

Clinical utility declined in patients treated according to SWENOTECA VIII (2012–2014) compared to patients treated according to SWENOTECA IV (2007–2011). This decline in clinical utility is explained by the omission of patients with a residual tumour of ≤10 mm after chemotherapy in SWENOTECA VIII. It is not only the NB that declined after introduction of the SWENOTECA VIII guidelines, in addition, the rate of benign histopathology dropped from 44% in SWENOTECA IV to 36% in SWENOTECA VIII. With this decline in benign histopathology, almost 65% of the patients will benefit from PC-RPLND. Thus, the prediction model has limited clinical value when omitting patients with little residual disease.

By combining the prediction model with close observation of the patients omitted from surgery, the patients with progressive disease post-chemotherapy might be identified at an early stage and managed accordingly. With MRI, radiology follow-up can be performed without increasing the radiation dose for the patient [29]. The SWENOTECA patients have follow-up with tumour markers every 3 months the first 2 years after completion of therapy and with MRI every 6 months. With improved diagnostic and follow-up methods, the decision threshold can be shifted to an even lower threshold level, so that more patients with necrosis/fibrosis in the retroperitoneal lymph nodes can be omitted from post-chemotherapy surgery. In the end, the decision whether to cope with the uncertainty and the risk of recurrence has to be made by the patient and the treating physician through a shared decision-making process, with regard to the risk of complications and side effects caused by PC-RPLND.

Vergouwe's prediction model is currently the most accurate model for predicting benign disease. New biomarkers and variables, such as microRNA miR-371a-3p [30], the use of volume of residual tumour instead of longest axial diameter on CT, magnetic resonance spectroscopy or radiomics might improve the prediction of benign histopathology further [31]. The effort to better identify patients who do not need PC-RPLND continues. However, every prediction model or test will be associated with the risk of leaving teratoma or viable cancer elements in the retroperitoneal lymph nodes when PC-RPLND is omitted.

In conclusion, approximately 50% of patients do not benefit from PC-RPLND. In this population-based RETROP study, Vergouwe's model for predicting benign disease has been externally validated. The prediction model is of limited use when excluding patients with <10-mm residual tumour from PC-RPLND. One could consider using the model in a clinical setting, but this needs to be combined with meticulous surveillance, preferably in a prospective study, in patients not selected for surgery.

Disclosure of Interests

None.

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Abbreviations: AFP, alpha-fetoprotein; AUC, area under the receiver-operating characteristic curve; BEP, bleomycin, etoposide, cisplatin; EP, etoposide and cisplatin; IGCCCG, International Germ Cell Cancer Collaborative Group; LDH, lactate dehydrogenase; NB, net benefit; NB^{optout}, opt-out net benefit; OR, odds ratio; PC-RPLND, post-chemotherapy retroperitoneal lymph node dissection; PEI, cisplatin, etoposide, ifosfamide; SWENOTECA, Swedish and Norwegian Testicular Cancer Group; β-HCG, β-Human chorionic gonadotropin.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Data management and imputation