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Research Article

External validation of nomograms for prediction of survival outcome in retroperitoneal sarcoma using the North East England patient cohort

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ABSTRACT

Introduction: Retroperitoneal sarcoma is a rare tumour that does not present nor progress in a manner typical for other soft tissue sarcomas. As a result of this the conventional AJCC staging manual for peripheral STSs is not applicable to RPS and does not allow for stratification of patient groups. This has been recognised by other research groups and has led to their development of nomograms, incorporating statistically significant clinical characteristics on retrospective multivariate analysis of patient cohorts. We applied two of these nomograms to the North East England (NEE) RPS database.

Methods: Nomograms published by Gronchi et al. (to predict 7 year overall and disease-free survival) and Anaya et al. (to predict 3 year and 5-year overall survival) were applied retrospectively to the 79 patients in the NEE RPS database. Statistical analysis was performed by use of concordance index to assess capacity to correctly predict an expected outcome.

Results: The nomogram for predicting 3-year OS published by Anaya et al. gave a concordance index of 0.792 (95% CI 0.70-0.89), p-value <0.001. For 5-year OS, the model has a concordance index of 0.803 (95% CI 0.70 - 0.91), p-value <0.001. The nomogram published by Gronchi et al. to predict 7-year OS was also applied to our cohort and produced a concordance index of 0.539 (95% CI 0.34-0.74), p value 0.70. No patients in our cohort were disease free at 7 years and so analysis could not be performed.

Conclusion: The nomogram published by Gronchi et al. was not able to accurately predict the seven-year survival outcome for patients in the NEE RPS database however the nomogram published by Anaya et al. provided an accurate prediction of 3 and 5 year survival in our cohort. This warrants further external validation of this cohort using a larger cohort and incorporating a version of this nomogram into the next edition of the AJCC Staging Manual should be considered.

Introduction

Retroperitoneal sarcoma (RPS) is a rare and highly heterogenous group of tumours which account for less than 1% of all adult malignancies and fewer than 15% of all sarcomas [1]. Despite the centralised management of RPS in specialist treatment centres, patients continue to experience poor survival outcomes [1, 2]. This is for several reasons including the difficulty of surgery due to anatomical location, commonly late

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presentation, limited availability of adjuvant therapies and frequent local recurrence after index operation [3, 4]. Some promising results in laboratory research and early clinical trials involving use of novel anticancer therapies have yet to translate into improved survival [5].

To best manage this rare disease, it is important to be able to predict likely outcome based on patient-specific factors. Likely prognosis is currently evaluated based on stage of disease. The current accepted staging system for RPS is the American Joint Committee on Cancer (AJCC) Staging Manual. This was developed from large cohorts of patients with sarcoma, however very little data came from truncal or retroperitoneal sarcoma cohorts5. This system is effective in staging extremity sarcoma, but there are several issues when applying it to RPS tumours, namely key differences in the characteristics in size of tumour at presentation and the prognostic relevance of nodal spread and presence of metastases. These discrepancies have been highlighted in several publications [6-8].

The interest in improving prognostication for RPS has led several groups to produce their own nomograms to predict patient-specific disease free and overall survival [7,9]. These nomograms have been created from retrospective analysis of patient cohorts and have incorporated statistically significant clinical variables. The role for nomograms in the management of patients with cancer is increasingly being recognised, and this is reflected in their incorporation in the 8th edition of the AJCC Staging Manual [10].

In 2010 Anaya et al published a nomogram to predict three- and five-year overall survival (OS) based on a retrospective analysis of 343 patients at their centre at the University of Texas MD Anderson Cancer Centre [7]. In 2013 Gronchi et al published a nomogram to predict seven-year disease-free (DFS) and seven-year OS, based on 523 patients across three institutions [9]. Both research teams performed univariate and multivariate analysis of patient characteristics and included statistically significant variables in a nomogram. They ascribed points to each variable according to significance to give a total score to predict survival. The Gronchi nomogram has recently been externally validated in two publications, one in a multiinstitution European publication, and the other in an Asian study [11, 12].

We evaluated the ability to predict survival outcome for both the Anaya and the Gronchi nomograms using the North East England RPS cohort based at the Freeman Hospital, NewcastleUpon-Tyne, to determine their accuracy when applied to a relatively small cohort in England.

Methods

All patients receiving a histological diagnosis of RPS and treated at the Freeman Hospital between March 1997 and March 2013 were included in a database (the North East England [NEE] cohort), which was retrospectively analysed. The database consists of 79 patients who have undergone a total of 90 resections; 79 index operations and 11 secondary resections. Further analysis of this cohort has been published previously.

The demographics included in the Gronchi nomograms (age at presentation, size of tumour, Fèdèration Nationale des Centres de Lutte Contre le Cancer [FNCLCC] grade, histological subtype, multifocality, extent of resection) and the Anaya nomograms (age at presentation, primary or recurrent tumour, size of tumour, multifocality, extent of resection, histological subtype) were collected for each of the patients in the North East England cohort. In the case of the Gronchi nomogram each patient was only entered once, based on their index operation. As the Anaya nomogram accounts for primary tumours vs recurrence each patient was entered for each operation with a different score.

A score and a survival prediction were calculated for each patient using both nomograms following the published guidance. Statistical analysis was performed primarily by use of a concordance index (representing the area under the receiver operating characteristic [ROC] curve) to assess capacity to correctly predict patient survival at a given interval. The ROC curves were produced with the assumption that the survival predictions of the nomograms follow a binomial distribution.

A concordance index score below 0.5 indicates a test has no value in predicting outcome. A score 0.6-0.7 has minimal value, 0.7-0.8 has good prognostic value and is a strong predictive model, 0.8-0.9 is a very strong model and 0.9-1.0 is an almost perfect predictor of outcome. Statistical significance was set at a p-value<0.05. SPSS version 22 was used to perform statistical analysis.

Results

Full analysis of this database has already been published in detail in 20163. In total 79 patients underwent 90 resections with overall five-year disease-free survival (DFS) and overall survival (OS) rates of 24.8% (95% confidence interval [CI]: 19.2-30.4%) and 55.3% (95% CI: 49.9-60.7%). Mean age at presentation was 60 years, with a range of 27 to 87. Mean maximal size of tumour was 205mm, range 50-560mm. The cohort data for the other demographics included in the nomograms are in (Table 1).

The nomogram for predicting 3-year OS published by Anaya et al. gave a concordance index of 0.792 (95% CI 0.70-0.89), p-value <0.001. For 5-year OS, the model has a concordance index of 0.803 (95% CI 0.70 - 0.91), p-value <0.001.

The nomogram published by Gronchi et al. to predict 7-year OS was also applied to our cohort and produced a concordance index of 0.539 (95% CI 0.34-0.74), p value 0.70. No patients in our cohort were disease free at 7 years and so DFS analysis could not be performed.

Discussion

The AJCC staging system is incapable of differentiating between patients with RPS and is not useful to provide an accurate prognosis. The focus on tumour size, nodal spread and metastasis is not appropriate for RPS. The benefits of an improvement in prognostic capabilities are several fold; it allows clinicians to more confidently give a likely life expectancy to patients; it allows for patterns in improvement in survival to be easily analysed; it allows cohort stratification for clinical trials, and furthermore a standardised and accepted staging system makes meta-analysis to combine results from multiple independent studies easier and more reliable.

Table 1: Clinical features of patients included in the North East Retroperitoneal Sarcoma database

		N (%)
Resection clearance	R0/1	88 (88.9%)
	R2	10 (11.1%)
	Piecemeal	23 (25.6&)
FNCLCC grade	1	35 (38.9%)
	2	17 (18.9%)
	3	38 (42.2%)
Histology	Well differentiated liposarcoma	34 (37.8%)
	Dedifferentiated liposarcoma	26 (28/9%)
	Leimyosarcoma	12 (13/3%)
	Sarcoma not otherwise specified	8 (8.9%)
	Other	7 (7/8%)
Focality	Unifocal	55 (61.1%)
	Multifocal	35 (38.9%)
Disease resected	Primary	63 (70%)
	Recurrent	27 (30.0%)

Several publications have highlighted both the need for, and the benefit of, an additional prognostic tool. Anaya et al and Gronchi at al subsequently developed nomograms to predict three and fiveyear OS, and seven-year DFS and seven-year OS respectively.

For the North East cohort, the nomograms published by Anaya et al., which predict 3- and 5-year OS, were 'strong' and 'very strong' predictors of outcome respectively according to the correlation statistic, and as such can be considered of value when predicting survival of patients at the time of index operation. The nomograms for 7-year OS and DFS published by Gronchi et al. we're not of value when predicting outcome for the patients in our cohort. No patients were disease free at 7 years which either suggests our analysis was underpowered or that the characteristics of the two cohorts are very different, for example in the nature of surgery. The prognostic capacity was also found to be poor for the OS nomogram.

There are several differences between the two nomograms, most notably the difference in the level of detail. Some variables in the Anaya nomogram are used to stratify patients in a 'digital' yes/no manner, whereas the Gronchi nomogram offers further gradations and allows greater stratification. As an example, the Anaya nomogram separates age in a 'digital' manner, giving points based on patient age being over 65 or under 65. In contrast the Gronchi nomogram gives points for a range of ages and takes into account that outcome is poorer at both extremes of age.

Tumour size in the Anaya nomogram is awarded points based on size greater or smaller than 15cm, however the Gronchi nomogram has more gradations of size, taking into account the subtle but important changes in survival outcome based on their retrospective analysis. The Gronchi nomogram also awards slightly fewer points to the very largest tumours (50cm, 80cm), in recognition that the tumours which are largest at presentation are often the slowest growing and most indolent, with a slightly lower rate of recurrence. The Anaya nomogram does not allow for this. Other variables, such as completeness of resection and multifocality, remain 'digital' variables in both nomograms and are awarded points in a similar way.

There are also some differences in the way points are ascribed to histology and size of tumour at presentation. In the case of histology, well-differentiated liposarcoma (WD LPS) gives a better outcome than de-differentiated liposarcoma (DD LPS) in the Anaya nomogram. This might be intuitive, as WD LPS are more alike to normal tissue and better outcome is experienced with WD LPS than with DD LPS in other sarcomas. However, the points are reversed in the Gronchi nomogram; an explanation for this is not given.

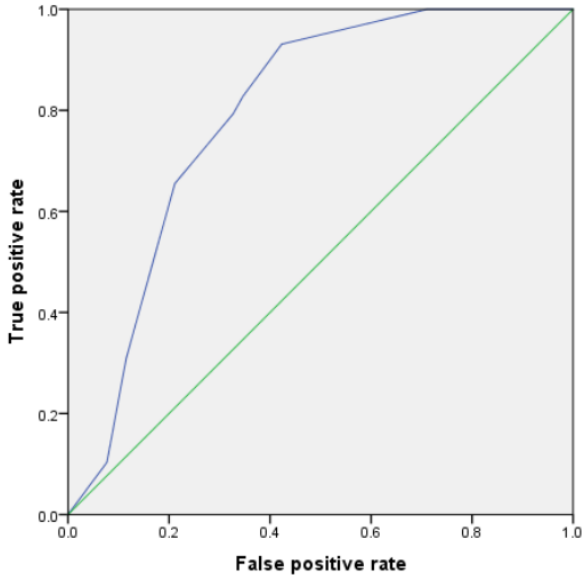

Figure 1 - Receiver operating characteristic curve for 3-year survival

Two groups have recently published the finding that the Gronchi nomogram could be applied to their cohorts with impressive accuracy 11,12. This finding was not replicated when applying the nomogram to our cohort. In the North East England cohort nine patients were still alive at seven years and no patients were disease free at seven years. As a result, no meaningful analysis of the data was possible. Different approaches to surgical management between centres may explain some of this variation. Notably surgeons at the Freeman Hospital do not

perform complete compartmental resection (CCR), a more radical approach to resection involving removal of a larger number of organs, which is associated with an improvement in DFS13. The five-year OS of this cohort is 55.3% (95% CI: 49.9-60.7%) which is similar to other figures quoted in the literature14, suggesting that a variable other than patient management is underlying the different effects seen when using this nomogram. Our cohort may be too small to identify a significant predictive value of the Gronchi nomogram.

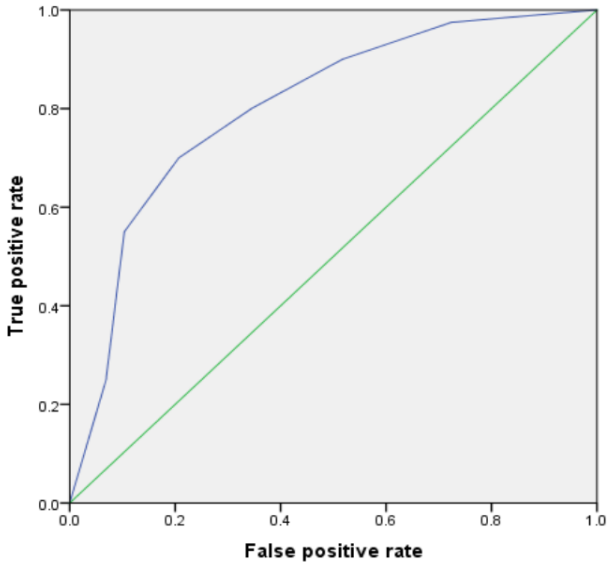

Figure 2: Receiver operating characteristic curve for 5-year survival

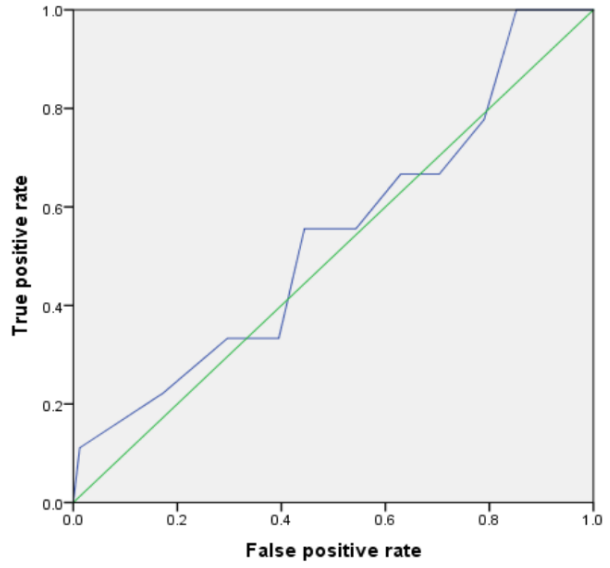

Figure 3: Receiver operating characteristic curve for 7-year survival

Limitations

This is a relatively small cohort, which may be the reason for the poor predictive power of the nomograms for 7-year OS and DFS.

Conclusion

The AJCC Staging Manual is not appropriate for use in RPS. Other groups have formed their own nomograms as alternative systems. Despite recent successful external validation in two recent publications, a nomogram published by Gronchi in 2013 for the prognostication of patients with RPS was not appropriate for use with the North East England RPS database because too few patients were alive at 7 years to allow meaningful data interpretation. This was reflected in the poor strength of the concordance index. However, another alternative nomogram published by Anaya et al in 2010 focusses on the shorter-term outcome of survival at three and five years. These nomograms were strong predictors of outcome of the patients in the North East England RPS cohort.

It would be of interest to produce a nomogram with the level of detail and further gradations that the Gronchi nomogram has to offer, but for three- and five-year survival as this may offer more accurate prediction of survival whilst also offering a prognosis for more patients. To the authors' knowledge at the time of publication there has been no external validation of the nomograms published by Anaya et al. These nomograms applied more readily to the North East RPS cohort with strong concordance results, and these findings warrant their application to larger cohorts from other centres. If universally strongly predictive then the authors suggest that this nomogram should be adopted as the accepted system for outcome prediction, coupled with an appropriate confidence range, for RPS patients at index operation.

Declarations

This work has previously been partially presented at the British Sarcoma Group conference in Manchester in March 2016.

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