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Original research

Validation of nomogram for disease free survival for colon cancer in UK population: A prospective cohort study

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HIGHLIGHTS

- We externally validated a nomogram for colon cancer disease free survival.
- The accuracy of the nomogram was acceptable to predict colon cancer recurrence.
- The nomogram is recommended for use in conjunction with AJCC TNM staging system.

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ABSTRACT

Aims: To externally validate the MSKCC nomogram in a UK population, and determine if it could be used in our practice here in the UK.
Methods: The colon cancer database from a district general hospital in England was used to extract all patients who had a curative colon cancer resection. Inclusion criteria were all patients who had curative elective colon cancer resection between 01/01/1998 and 31/12/2003. Patients were followed up for up to ten years. Five and ten year predictions were calculated for each patient, and plotted against the actual recurrence using a ROC curve, and AUC was calculated for both the five and ten year nomogram.
Results: 138 patients were included in the study. Overall five year recurrence rate was 26.8% with a mean follow up of 60.24 months (SD = 38.6). 118 patients were included in the five year nomogram validation, and 102 patients were included in the ten year nomogram validation. A ROC curve was plotted for both the five and ten year nomogram and AUC was calculated. For the five year nomogram AUC was 0.673, and for the ten year nomogram AUC was 0.687. Two cut off points were identified for each nomogram and this divided the cohort into low, medium and high risk groups for recurrence. Cox regression showed there was significant difference between all groups for both nomograms.
Conclusion: The MSKCC colon cancer nomogram was validated in our cohort, but it is recommended to be used in conjunction with AJCC TNM staging system.

1. Introduction

According to the Office of National Statistics (ONS), 281,118 new cancers were registered in England in 2012. Colon cancer was the third most common cancer in both males and females, affecting 19,286 males (13.4% of all cancers in men) and 15,036 females (10.9% of all cancers in women) [1].

Medical professionals have traditionally used their own clinical judgement to plan their patients' treatment, however it has been recognised that the use of clinical judgement alone to estimate specific outcomes is difficult and will suffer from personal bias – clinicians viewpoints are affected by their previous experiences and knowledge of similar patients [2,3].

Taking a multidisciplinary team approach (MDT), and adding predictive tools like risk grouping to plan the management of cancer patients is one way to reduce the personal bias. However, this process will still rely on clinical judgement, and the usefulness of risk grouping is limited by the fact it assigns equal risk to each member of the group, and cannot assess the individual risk of any single patient within the group [4–6].

Over the last few years there has been greater emphasis on personalising the treatment of colon cancer, with new drugs and

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agents being developed and new regimens created to treat patients. There are still areas, however, where uncertainty exists, and where clinical decision-making could be enhanced by the application of statistical models. Identifying high-risk stage II patients who may benefit from adding adjuvant chemotherapy, and identifying patients with advanced colorectal cancer who may benefit from adding anti-EGFR agents are two examples of clinical challenges that have played a role in driving the development of predictive tools to improve the management of colon cancer.

The MSKCC (Memorial Sloan Kettering Cancer Centre) colorectal cancer nomogram-post surgery [7,8], was published in 2007. Its main aim is to predict five and ten year disease free survival after curative colon cancer resection. Collins et al. [9], validated the MSKCC five year disease free nomogram only as part of validating two predictive tools in colon cancer.

In this study our aim will be to externally validate the MSKCC colon cancer nomogram using a cohort of patients from a district general hospital in England. We will be validating both the five and ten year disease free survival prediction tools.

By validating the nomogram, we will help to add another tool for clinicians to use during the process of assessing and planning treatment for colon cancer patients.

2. Patients and methods

Our cohort was from patients treated in a district general hospital (DGH) in England. The colorectal team in the hospital kept an Access based data set between 1998 and 2003 for all patients who had surgical treatment for colorectal cancer in the hospital undertaken by the team.

Inclusion criteria was all patients who had curative elective colon cancer resection between 01/01/1998 and 31/12/2003. The exclusion criteria were: emergency surgery, rectal cancer, evidence of metastatic disease in the preoperative assessment or intra-operatively, and missing any variables essential for calculating the probability of disease free survival using the nomogram.

The primary end point was evidence of distal or local recurrence. The secondary end point was death from a non-cancer reason before completing five or ten years follow up.

All variables required for the nomogram were retrieved for each patient. These variables included: age, sex, tumour location, Pre-operative Carcinoembryonic Antigen (CEA) levels, T stage, positive lymph nodes, negative lymph nodes, tumour differentiation, lymphovascular invasion, perineural invasion and whether post-operative chemotherapy was given.

We used outpatient correspondence, histology, imaging reports and the biochemistry reporting system to identify all variables and reduce the number of missing variables. Histology reports were reviewed and we used TNM seventh edition [10] to stage our patients, as the dataset used the previous version in the coding process.

The MSKCC nomogram was accessed online and the variables for each patient were processed, giving each patient a five and ten year probability of recurrence free survival. This was documented and used in the process of validating the nomogram.

Our results were reported in line with STORBE criteria [11], and this study is registered with the Research Registry and the unique identifying number is: researchregistry655.

2.1. Statistical analysis

Statistics for the Social Sciences version 17.0 statistical package (SPSS Inc, Chicago, IL) was used for the statistical analysis in this study.

Descriptive statistics were used to give an overall look at the variables. Logistic regression was used to assess the relationship between different variables and risk of recurrence or death at five and ten years. The relationships presented as an odds ratio, with 95% Confidence Intervals (95% C.I) calculated and $P < 0.05$ considered statistically significant.

We produced a Receiver Operator Characteristic (ROC) curve for each prediction produced by the nomogram (five and ten years), and then calculated the Area Under the Curve (AUC) for each one. We also reported the standard error and 95% confidence intervals. $P < 0.05$ was considered statistically significant.

A ROC curve is a graph representing sensitivity (Sn) on the y-axis and 1- specificity on the x-axis for different cut off points of test value [12]. A ROC curve shows the inverted relationship between sensitivity and specificity (Sp), so as the test sensitivity increases its specificity decreases and vice versa [13]. The purpose of a ROC curve is to help identify the best cut off point for a test at which it shows the most discriminatory result [12].

The AUC represents the performance of a test and its ability to distinguish between patients who have or do not have a disease [12]. The larger the AUC the better the performance of the test, and as the AUC gets smaller the performance of the test reduces [14].

For the validation process we excluded patients who did not complete the full length of follow up without recurrence. We opted for this option rather than including all patients in the validation process to reduce both selection bias and comorbidity bias, as the nomogram does not take comorbidities into account.

3. Results

3.1. Study cohort

431 patients were identified as a potential cohort from the dataset, out of these patients only 138 had all the required variables for the nomogram predictions to be calculated (Fig 1). The clinical and pathological characteristics of our cohort are described in (Table 1).

The cohort mean follow up was 60.24 months (SD = 38.6). Overall five years recurrence rate was 26.8% (37 patients), and two patients developed recurrence after five years (after 64 and 84 months). Overall five years survival was 64.5% and overall ten years survival was 50%. Only 2 patients were reported to have perineural invasion, this most likely reflects the underreporting of this feature during the period the specimens were examined.

20 (14.49%) patients died from non-cancer causes in the first five years post-surgery, and a further 16 patients died from non-cancer causes before completing ten years follow up. During the first five years 21% (29) patients died secondary to cancer recurrence, and a further four died due to cancer recurrence in the second five years of follow up (Fig 2).

3.2. Validating the nomogram

3.2.1. Validating the five year nomogram

Patients who died from non-cancer causes before they completed five years follow up were excluded from this analysis (n = 20) and the total number included in the analysis was 118 patients.

To validate the model we used a ROC curve and calculated the AUC for the five years recurrence free survival predictions of the nomogram against the actual recurrence free survival of our cohort. A ROC curve was plotted (Fig 3) and AUC was calculated (AUC = 0.673, 95% C.I = 0.565–0.781, $P = 0.003$, null hypothesis area = 0.5).

The nomogram produces the estimated probability of a patient being recurrence free at a specified time interval, five or ten years.