Development of a prediction model on disease recurrence for low-risk resected stage I lung adenocarcinoma with high prevalence of EGFR mutations

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BACKGROUND:

Except for stage IB disease with high-risk features, complete surgical resection alone is the treatment of choice for stage I non-small cell carcinoma of lung (NSCLC). Although excellent 5-year survival rate is expected, early disease recurrence will nevertheless occur in some of these patients. An accurate and dedicated survival prediction model can help inform clinicians on appropriate follow-up strategy and may form a more refined basis for future adjuvant treatment selection.

METHODS:

We conducted a retrospective single-center cohort study to formulate a risk prediction model on disease-free survival (DFS) in consecutive patients with stage I adenocarcinoma of lung without high-risk features (e.g., lymphovascular invasion, visceral pleural involvement, poor tumor differentiation, unknown lymph node status) who have undergone curative resection in Queen Mary Hospital from 2013 to 2017. Weibull survival model and Cox regression analysis was used to assess median DFS and hazard ratio (HR) for potential risk factors. A tree-based method was then employed to partition the combinations of any interacting demographic profile into groups with distinct DFS outcome and generate their stepwise risk ratio (RR). These covariates were then included in a multivariate model to build a scoring system to predict disease recurrence. An external validation using a 2011 – 2012 cohort form Queen Mary Hospital was finally performed for the model.

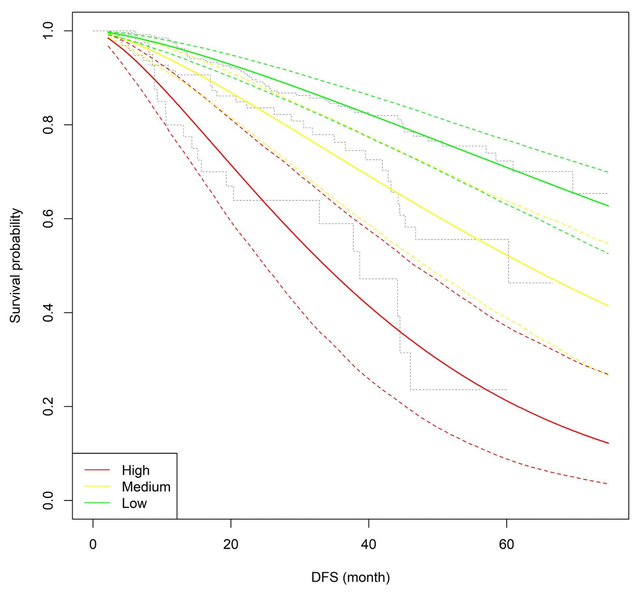
RESULTS:

This study included 408 patients with mean follow-up of 40.5 months. Analysis by Weibull survival model and Cox regression identified non-smoking status, stage IA disease, EGFR mutants and female gender as factors for better DFS [hazard ratio of 0.468 (p = 0.000), 0.620 (p = 0.005), 0.660 (p = 0.048) and 0.663 (p = 0.005) respectively]. The tree-based survival model confirmed that, after consideration of the interacting nature of the four identified risk factors, only 8 cohorts with distinct survival outcome remained. By multivariate model analysis, it was confirmed that only 3 of the covariates (namely smoking status, disease stage and gender) were necessary to build a scoring system. Three risk group with distinct DFS were identified [low risk 99.4 months (95% CI 78.3 – 125.3), medium risk 62.9 months (95% CI 48.2 – 82.0), high risk 33.7 (95% CI 24.6 – 46.1), p < 0.005]. External validation of the scoring system yielded an area under the curve (AUC) by receiver operating characteristic (ROC) analysis of 0.863 (95% CI 0.755 – 0.972).

CONCLUSIONS:

A tree-based model was formulated to predict median DFS based on smoking status, staging, gender and mutation profile in conventional low-risk resected stage I lung adenocarcinoma. The new scoring system could separate these patients into 3 distinct risk groups based on readily available clinical information, which may potentially guide subsequent follow-up strategy and adjuvant treatment after curative resection.

Figure 1: Median DFS comparing patients in three different risk groups by Kaplan Meier method



Risk group	Median DFS (95% CI)	p-value
Low risk	99.4 (78.3 – 125.3)	0.0132 (vs. medium)
Medium risk	62.9 (48.2 – 82.0)	0.0094 (vs. high)
High risk	33.7 (24.6 – 46.1)	<0.0001 (vs. low)

* p-value after Bonferroni correction

Figure 2: Risk ratio (RR for each level with reference to the whole cohort) based on the subtree model. The arrow (↑/↓) indicated whether the additional factor increases / decreases the risk ratio when added to the previous layer.

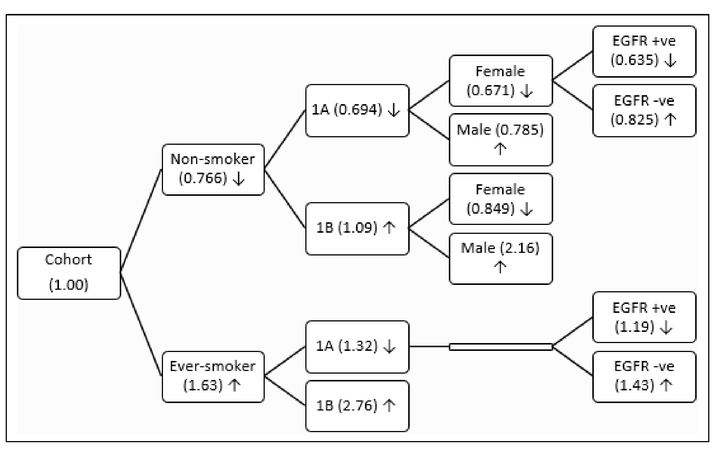


Table 1: Prediction scores for recurrence after resection for stage I adenocarcinoma of lung

Prognostic factors	Score
Staging and sex	
Stage IB AND Male	5
Stage IB AND Female	2
Stage IA AND Male	1
Stage IA AND Female	0
Smoking status	
Ever-smoker	3
Nonsmoker	0

Table 2: Risk group stratification and corresponding DFS

Risk group		DFS (95% CI), months	p-value*
Low risk	0 – 2	99.4 (95% CI 78.3 – 125.3)	0.0132 (vs. medium)
Medium risk	3 – 4	62.9 (95% CI 48.2 – 82.0)	0.0094 (vs. high)
High risk	5 - 8	33.7 (95% CI 24.6 – 46.1)	<0.0001 (vs. low)

* p-value after Bonferroni correction

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