Greater Manchester Cancer

GMCA GREATER MANCHESTER COMBINED AUTHORITY

NHS in Greater Manchester

Greater Manchester Cancer

Risk Stratified Follow-up Protocol following Curative-intent Radiotherapy for Lung Cancer

Introduction

International lung cancer guidelines universally recommend follow up after curative intent treatment for lung cancer. The purpose of this follow-up is to:

- **Monitor and treat underlying co-morbidities** *(including tobacco addiction)*
- **Provide patient support and information**
- **Prevent acute crisis admissions**
- **Manage treatment-related complications**
- **Detect treatable relapse of cancer**
- **Detect second primary cancers that could undergo further curative-intent treatment**

However, international guidelines also universally acknowledge a paucity of high quality evidence on which to make specific recommendations on the type and intensity of both imaging surveillance and clinical review. Therefore, clinical teams in Greater Manchester have led a multi-centre study across the UK to inform a risk stratified protocol for follow-up after curative intent radiotherapy for lung cancer. This study included approximately 900 patients and investigated multiple clinical and cancer related factors to devise and validate risk prediction models for disease recurrence and survival.

Key outcomes

- **36% of patients suffered disease recurrence within the first two years**
- **The pattern of disease recurrence was local 30%, nodal 8% and distant 62%**
- **The commonest management strategy for disease recurrence was best supportive care (58%)**
- **Treatment for disease recurrence was palliative in 38% and radical in 4%**
- **4% of patients developed a metachronous primary lung cancer**
- **67% of metachronous primary tumours were stage 1 and 60% treated radically**
- **41% of patients died within the first two years**
- **Death was attributed to lung cancer in 65% & co-morbidity related in 32%**

Risk Stratification for disease recurrence:

The ASSENT Score

Multivariable analysis identified 6 variables as having independent associations with disease recurrence within 2 years (**A**ge, performance **S**tatus, **S**moking status, staging **E**BUS, **N**-stage and **T**-stage). From this final model, a scoring system (the ASSENT score, Table 1) was produced using the regression coefficients. Scores range from 0 to 6, categorised as follows:

- ***Low-risk (Score ≤3, 44% of study population, 2yr recurrence rate 20%)***
- ***Moderate-risk (Score 3-4, 37% of study population, 2yr recurrence rate 46%)***
- ***High-risk (Score ≥4, 19% of study population, 2yr recurrence rate 64%)***

The AUROC for Total score in the derivation cohort was 0.712 (95%CI: 0.671-0.753) and 0.72 (95%CI: 0.65-0.789) in the validation cohort. Log rank tests for difference between survival curves was significant across the two cohorts (p<0.001) confirming a consistent, statistically significant difference in survival between the three risk groups.

Table 1: The ASSENT Score

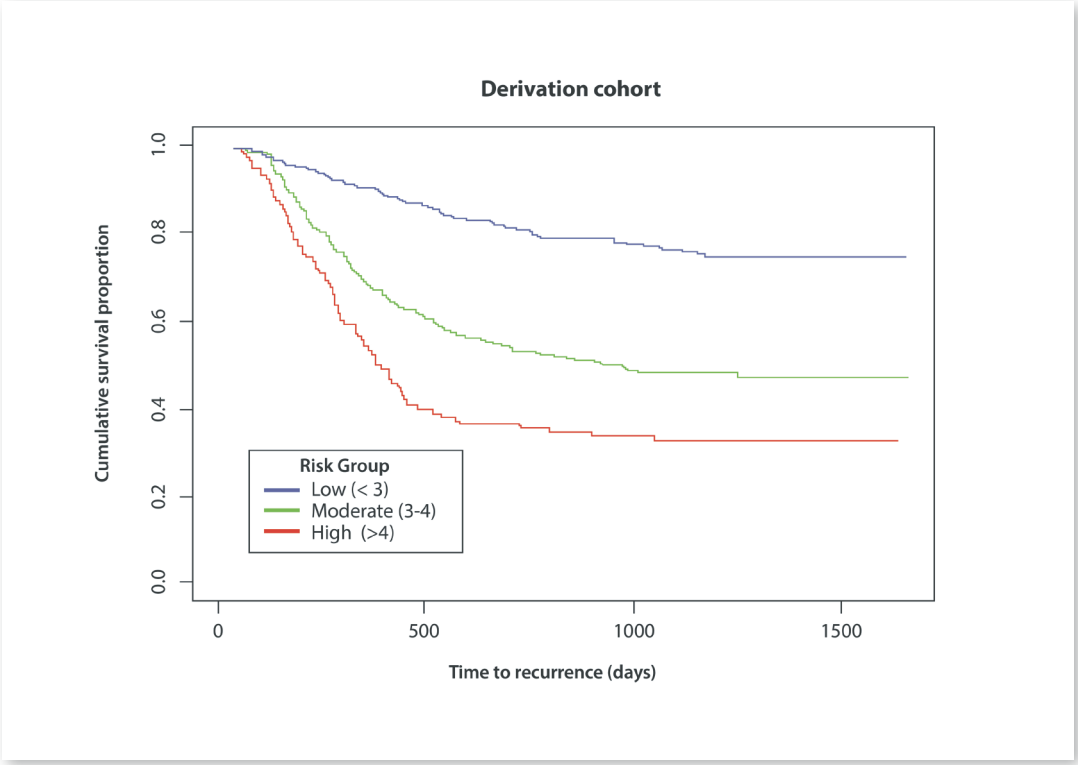
Variable		Score
Age	<75yrs	0.5
	≥75yrs	0
Performance **S**tatus	0	1
	1	0.5
	2	0.5
	3	0
Smoking Status	Never	0
	Ex-smoker	1
	Current	1
Staging **E**bus performed	No	0
	Yes	0.5
N-Stage (clinical staging)	N0	0
	N1	1
	N2	1
	N3	1
T-Stage (clinical staging)	T1a-c	0
	T2a-b	1
	T3	1
	T4	2
Overall Risk Score	**Low**	**≤3**
	Moderate	**3 - 4**
	High	**≥4**

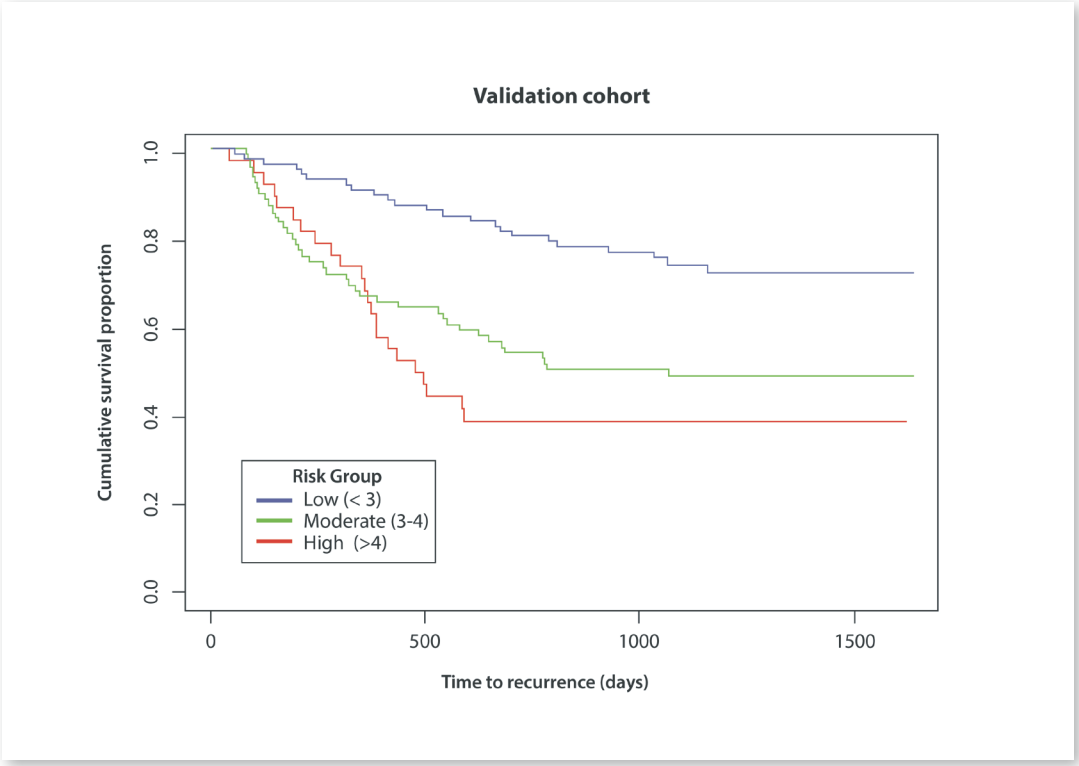
Risk Stratification for disease recurrence:

The ASSENT Score

Figure 1: Kaplan-Meier survival curves for low, moderate and high risk of disease recurrence groups

(ASSENT Score) in (A) derivation and (B) validation cohorts





Risk Stratification for death:

The STEPS score & post-treatment NLR/ALC

Multivariable analysis identified 5 variables as having independent associations with death within 2 years (**S**ex, **T**-stage, staging **E**BUS, **P**erformance status, N-**S**tage). From this final model, a scoring system (the 'STEPS' score) was produced using the regression coefficients (Table 2). Score range from 0 to 8.5, categorised as follows:

- ***Low-risk (Score <1, 15% of study population, 27% 2 year morality)***
- ***Moderate-risk (Score 1-2.5, 60% of study population, 40% 2yr mortality)***
- ***High-risk (Score >2.5, 35% of study population, 63% 2yr mortality)***

The AUROC for Total score in the derivation cohort was 0.625 (95%CI: 0.581-0.669) and 0.607 (0.53-0.684) in the validation cohort. The Kaplan-Meier survival curves for the derivation and validation cohorts are provided in Figure 2. Log rank tests for difference between survival curves was significant across the two cohorts (p<0.001) confirming a consistent, statistically significant difference in survival between the three risk groups.

Table 2: The STEPS Score

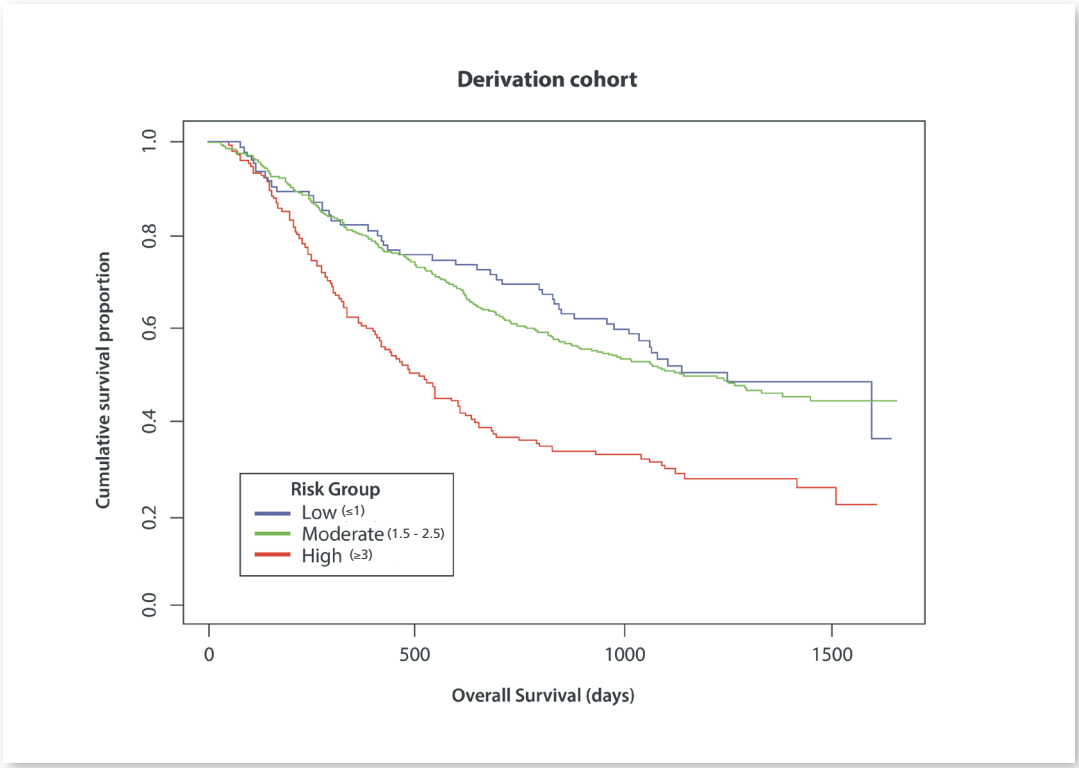
Variable		Score
Sex	Female	0
	Male	1
T-Stage	T1	0
	T2	0.5
	T3	1
	T4	3
Staging Ebus performed	No	0
	Yes	0.5
Performance Status	0	0
	1	0
	2	1
	3	1
N-**S**tage	0	0
	1	0
	2	1
	3	1
Overall Risk Score	**Low**	**≤1**
	Moderate	**1.5 - 2.5**
	High	**≥3**

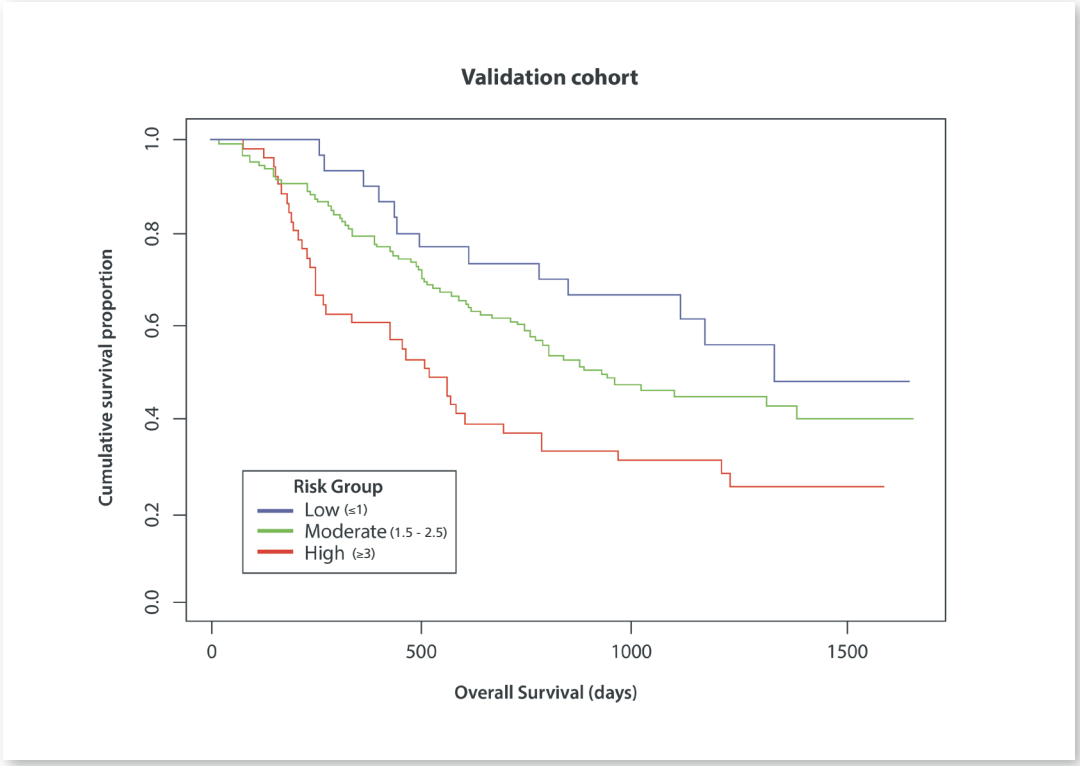
Risk Stratification for death:

The STEPS score & post-treatment NLR/ALC

Figure 2: Kaplan-Meier survival curves for low, moderate and high risk of death groups

(STEPS Score) in (A) derivation and (B) validation cohorts





Risk prediction for death:

Neutrophil-Lymphocyte Ratio (NLR) & Absolute Lymphocyte Count (ALC)

There is an increasing body of research demonstrating that inflammation in the solid tumour microenvironment promotes proliferation, survival and migration of the neoplastic process (1). Peripheral circulatory blood cells like neutrophils and lymphocytes can be used as surrogate markers which reflect the equilibrium between pro and anti-inflammatory cytokines in the tumour microenvironment. Neutrophils promote tumourogenesis by various mechanisms whereas lymphocytes promote anti-tumour immunity by stimulating apoptosis and suppressing the proliferation and migration of tumour cells.

Greater Manchester clinical teams have led a further retrospective study of 425 patients who underwent curative-intent RT for NSCLC across 9 sites in the UK from 01/10/2014 to 01/10/2016, performing a multivariate analysis of the ability of pre-treatment NLR/ALC, post-treatment NLR/ALC and change in NLR/ALC, adjusted for co-founding factors using the Cox proportional hazards model, to predict overall survival (OS) within 2 years of treatment. Complete outcome data for survival was available for 89% (379/425) of patients. 45% (170/379) of patients died within 2 years of curative intent RT.

The following parameters were independent predictors of overall survival when adjusted for cofounding variables including age, stage, and performance status (Figure 2):

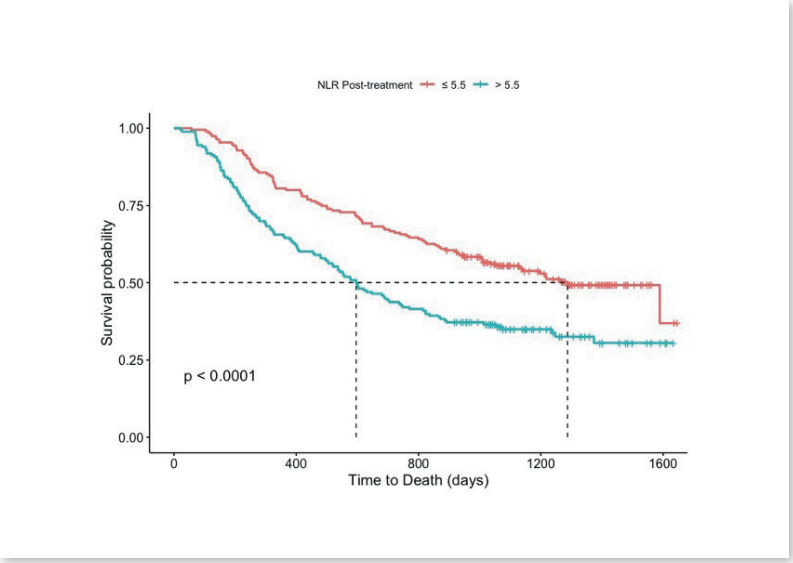
- **Post-treatment NLR >5.5:** OR 2.36 95%CI 1.49-3.76, p<0.001, median overall survival 1287 versus 596 days, p=<0.001.
- **Change in NLR from pre to post treatment >3.6:** OR 2.41 95%CI 1.5-3.91, p<0.001, median overall 1214 versus 553 days, p=<0.001.
- **Post-treatment ALC <0.8:** OR 2.86, 95%CI 1.76-4.69, p<0.001, median overall survival 1287 versus 594 days respectively (Figure 2).

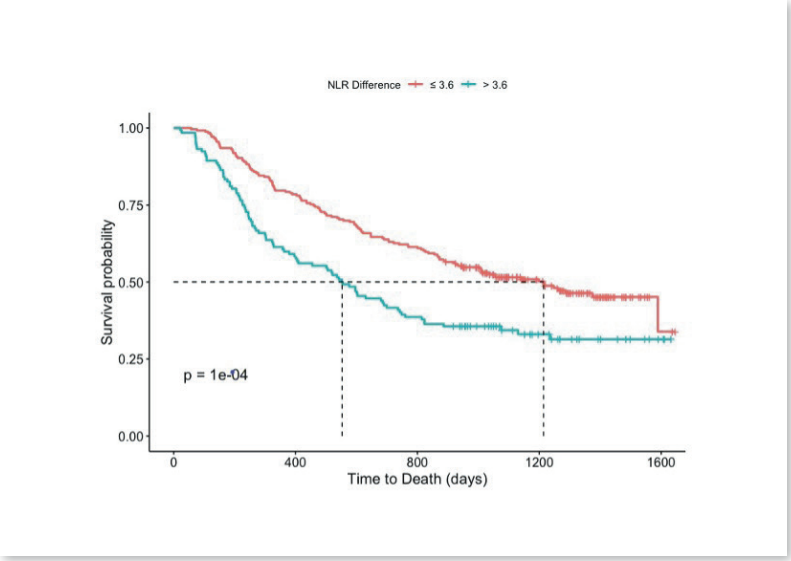
Risk prediction for death:

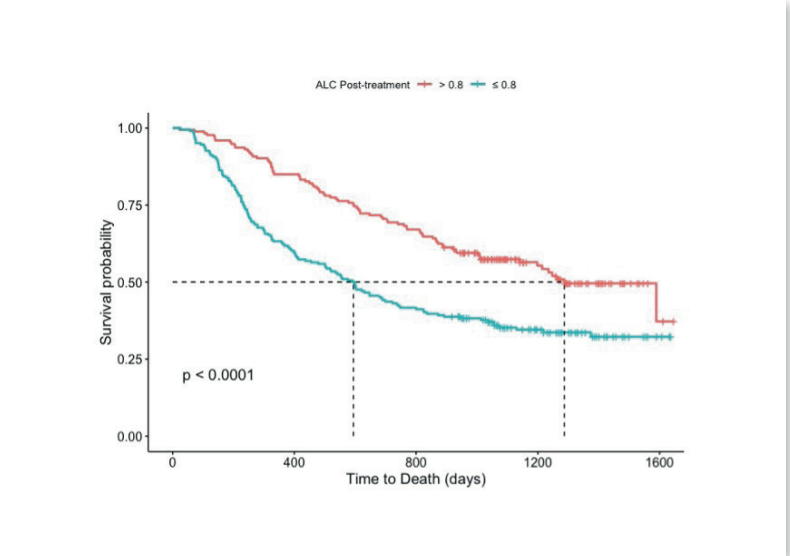
Neutrophil-Lymphocyte Ratio (NLR) & Absolute Lymphocyte Count (ALC)

Figure 2: Kaplan Meier Curves for overall survival stratified by high risk and low groups according to inflammatory cell parameters.

A: Post-treatment NLR (high risk >5.5),
B: Change in NLR (high risk >3.6),
C: Post treatment ALC (High risk <0.8)







Risk stratified follow-up protocol following curative intent radiotherapy:

Cross-sectional imaging protocol for disease recurrence

STEP 1: **Assess patient fitness, preferences & suitability for further treatment**

Assess if patient is fit for and would accept further work up and treatment of disease recurrence ***(noting low rate of active treatment following curative intent radiotherapy in our study).***

This assessment is complex and may take into account a number of factors:

- It may be considered that some patients may only be fit for targeted therapies in the event of distant relapse. In this case the clinical team may consider testing the pre-treatment histology for targetable mutations to help define the need for cross sectional imaging
- There may be new avenues of treatment for local recurrence post radiotherapy such as radiofrequency ablation and re-irradiation (noting that the re-irradiation service is a new & experimental service)

Good practice point: clinical teams should reassess the need for cross-sectional surveillance at every clinical encounter throughout the survivorship programme.

If CT surveillance not appropriate then plan intensity of clinical review according to POETS score & post-treatment NLR-ALC. Consider CXR at clinical appointments

STEP 2: **Risk stratify surveillance protocol according to ASSENT score**

Low Risk	Moderate Risk	High Risk
≤ 3	3 - 4	≥ 4

Follow risk stratified protocol according to risk category

Surveillance Protocol for first 2 years following Radiotherapy

	Months following treatments			
	6 months	12 months	18 months	24 months
Low Risk	Low dose CT Chest		Low dose CT Chest	
Moderate Risk	contrast-enhanced CT chest and upper abdomen	contrast-enhanced CT chest and upper abdomen	contrast-enhanced CT chest and upper abdomen	
High Risk	contrast-enhanced CT chest and upper abdomen +/- MR Brain*	contrast-enhanced CT chest and upper abdomen	contrast-enhanced CT chest and upper abdomen +/- MR Brain*	contrast-enhanced CT chest and upper abdomen

**Pending local agreement and resource dependent*

After completing 2 years of follow-up all patients reduce to an annual low dose CT of the chest starting at 30 months. The primary purpose of the annual low dose CT scan after 2 years of follow up moves away from detection of disease recurrence with more focus on detection of metachronous primary tumours that may be suitable for further curative intent treatment.

It may be the case that the clinical team conclude that a patient would only be suitable for treatment of a metachronous primary tumour and not suitable for treatment in the event of disease recurrence of the previously treated lung cancer. In this scenario the clinical team may elect NOT to calculate the ASSENT score and simply undertake annual low dose CT imaging from the outset.

Risk stratified follow-up protocol following curative intent radiotherapy:

Clinical review protocol for co-morbidity management & optimisation

STEP 1: **Risk stratify clinical review protocol according to STEPS score & NLR/ALC** (if available)*

Low Risk
Steps ≤1

Moderate Risk
Steps 1.5 - 2.5

High Risk
Steps ≥3

OR post-treatment NLR > 5.5, change in NLR >3.6, post-treatment ALC <0.8

*Pre-treatment bloods can be up to 6 weeks prior to XRT and post-treatment bloods should be taken up to 4 weeks post treatment

Clinical Review Protocol

	Months following treatments														
	3	4.5	6	7.5	9	10.5	12	13.5	15	16.5	18	19.5	21	22.5	24
Low															
Mod															
High															

Clinical Review

Telephone Review

After completing 2 years of follow-up all patients reduce to 6 monthly appointments with clinical review to tie in with annual low dose CT of the chest and telephone review for other appointments.

All patients should be provided with contact details for the survivorship team and informed to contact immediately with any concerning new symptoms.

Notes:

- An alternative protocol to this clinical review protocol would be patient reported symptoms via a patient portal with clinical review determined by these symptoms. If this service is available this would provide an alternate method for clinical review.
- One example of this is ePROMs (electronic Patient Reported Outcome Measures) which provides a robust method for patient centred follow-up that individualises follow up according to the needs of the patient.

When available ePROMs can inform the clinical follow-up post radiotherapy and could replace the above described protocol. In the absence of such platforms the above protocol can provide a standardised protocol for follow-up