Clinical and Translational Radiation Oncology 16 (2019) 28–33

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Original Research Article

Anemia is a poor prognostic factor for stage I non-small cell lung cancer (NSCLC) patients treated with Stereotactic Body Radiation Therapy (SBRT)

Rima S. Pathak [a,1], Jason R. Pantarotto [a], Graham Cook [a], Oliver Holmes [b], Peter Cross [a], Robert M. MacRae [a,*]

[a] Division of Radiation Oncology, The University of Ottawa, Ottawa, ON, The Ottawa Hospital Cancer Centre, Canada
[b] Discipline of Oncology, Dr. H. Bliss Murphy Cancer Centre, St. John's, Newfoundland and Labrador, Canada

ARTICLE INFO

Article history:
Received 3 January 2019
Accepted 9 January 2019
Available online 24 January 2019

1. Introduction

Stereotactic Body Radiation Therapy (SBRT) is now accepted as a standard of care for medically inoperable early stage non-small cell lung cancer (NSCLC) [1,2]. Long term results of retrospective series show excellent local control rates but poor survival with higher rates of distant metastasis despite early stage at presentation [3–6]. Development of a prognostic tool to recognize factors can allow for stratification to test treatment strategies in future trials and selection of risk appropriate treatment strategies. These prognostic factors could be the bridge from empirical to individualized treatments for this patient population.

Previous studies have recognized patient, tumor and treatment related factors associated with overall survival (OS) or distant metastases free survival (DMFS) like the age at presentation, tumor size, histology, radiation dose, maximum standardized uptake value (SUVmax) of the primary tumor and various hematologic parameters [7,8]. Many studies have evaluated the role of absolute leucocyte, neutrophil, monocyte, lymphocyte or platelet count, ratios of various parameters like neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio among others and found conflicting results and a variety of threshold values with prognostic importance [9–14]. However, most of these studies have evaluated patients with advanced stage or medically operable early stage NSCLC who underwent surgery. There are very few studies evaluating their role in stage I NSCLC undergoing SBRT [15,16]. Most of these studies have limited their blood values measured within the 3 month period prior to initiating therapy [9–13,15,17]. Moreover, none of the studies have evaluated the changes in the values of the hematological parameters between pre-SBRT and post-SBRT. Therefore, in our study we evaluated the role of hematologic and other known prognostic factors including the trends of change in the hematological parameters between pre-SBRT and post-SBRT in early stage NSCLC patients treated with SBRT for various survival end points. We included CBC values that were produced within 6 months prior to and after SBRT in order to evaluate if these values show prognostic significance like that of the values within 3 months in other studies.

2. Material and methods

We reviewed 752 consecutive biopsy-proven stage I NSCLC patients (867 lesions) in an ethics-approved single institution retrospective study. Each patient underwent FDG PET-CT for staging at baseline as per the institutional policy. Of the 752, 487 patients received SBRT with a biologically equivalent dose (BED) >100 Gy_{10} from January 2009 to January 2016. In brief, all patients underwent standardized positioning with or without abdominal compression. A 4DCT was acquired and an ITV was created using the maximum intensity projection. A risk adapted approach was used for deciding the dose fractionation where central tumors were treated with a more protracted fractionation as compared to peripheral tumors [18,19].

These patients were followed up with 3-monthly clinical examination and a contrast enhanced CT-scan of the chest for up to 2 years and then every 6 monthly to 5 years. The overall survival (OS), local recurrence-free survival (LFS) and DMFS were calculated

* Corresponding author at: Box 903, The Ottawa Hospital, 501 Smyth Road, Ottawa, Ontario K1H 8L6, Canada.
E-mail addresses: drrimapathak@gmail.com (R.S. Pathak), jpantarotto@toh.ca (J.R. Pantarotto), gcook@toh.ca (G. Cook), oliver.holmes@medportal.ca (O. Holmes), pcross@toh.ca (P. Cross), rmacrae@toh.ca (R.M. MacRae).
[1] Current affiliation: Department of Radiation Oncology, Tata Memorial Centre & Homi Bhabha National Institute, Mumbai, Maharashtra 400012, India.

https://doi.org/10.1016/j.ctro.2019.01.003

using the Kaplan Meier method. The OS was defined as the time from the date of biopsy to death from any cause. The LFS was defined as the time from the RT completion to the date of local recurrence (within the radiation field). The DMFS was defined as time from the date of biopsy to the development of distant metastases. The definition of recurrence was based on the joint decision of the multi-disciplinary team including the treating physician mostly based on the clinical and radiologic assessment and occasionally after biopsy. If a patient had both local and distant failure they counted as events for both local and distant failure.

The Fig. 1 shows the consort diagram for this study explaining the number of patients with their CBC values available for this study at different time points before and after SBRT. Of the 487 patients treated with SBRT, 464 had their blood drawn for testing complete blood count (CBC) in the 6 months leading up to the first fraction, with 304 patients having additional blood work available in the 6 months post-SBRT. Of the 464 patients 324 patients, 225 had blood drawn within 3 months of pre and post SBRT. Duration between the date of drawing blood sample and radiation therapy starting was also noted. This information was retrieved retrospectively from patient charts and community reports. As described above various parameters like the hemoglobin level (Hb), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), total platelet count (TPC), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) both prior to and post-SBRT were noted for their prognostic significance. We then categorized the hematological values as 'Normal' and 'Abnormal' where the values for Normal hematological parameters were obtained from the reference values published by the Royal College of Physicians and Surgeons of Canada and are shown in Table 1 [20]. Comparisons were made between the pre-SBRT and post-SBRT values to evaluate the trends of change due to the treatment or otherwise. For this study a change in ANC or ALC of $\geq 0.2 \times 10^9$/L was considered significant and was reported as an increment/decline whereas, changes smaller than that were labelled as unchanged.

Univariate analysis was performed on multiple permutations (e.g. ratios) of hematologic parameters (both as continuous and categorical data where categorical data was obtained by dichotomizing continuous data based on various thresholds used in different studies) and known prognostic factors such as age, performance status, gender, Charlsons Comorbidity Index (CCI), smoking status, T-stage, SUVmax, interval between diagnosis and radiation therapy, radiotherapy dose and total treatment duration among others. A Cox regression model was used to analyze factors with a p value ≤ 0.1 on univariate analyses. Factors with a p-value of ≤ 0.05 and a 95% confidence interval (CI) of were considered statistically significant for the multivariate model.

Table 1
Reference Values that are considered Normal for adults as provided by the Royal College of Physicians and Surgeons of Canada.

Blood parameters	Males	Females
Hemoglobin	140–180 g/L	120–160 g/L
Absolute Neutrophil Count	$3–5.8 \times 10^9$/L	$3–5.8 \times 10^9$/L
Absolute Lymphocyte Count	$1.5–3 \times 10^9$/L	$1.5–3 \times 10^9$/L
Total Platelet Count	$150–400 \times 10^9$/L	$150–400 \times 10^9$/L

3. Results

3.1. Patient and treatment characteristics

The patient, treatment and tumor characteristics are shown in Table 2. The females (n = 284) outnumbered the males (n = 180) and only 4.4% of the study population were lifelong non-smokers. Majority of the study patients had a performance score of ≤ 1 (72.6%) and only 76 patients presented with a CCI of ≥ 4. Eighty patients had T2 tumors and the median tumor diameter was 2 cm (0.7–6.2 cm). The PET information prior to SBRT delivery was not available for 4.5% of the patients and for the rest the median SUVmax of the primary tumor was 4.7. All the patients were treated with SBRT with a mean duration of treatment of 7 days. Only 3 patients received doses with a BED <100 Gy_{10}.

3.2. Hematological parameters

There was minimal difference in the mean and median values of all the hematological parameters when comparing those recorded within 3 months to those within 6 months as seen in Table 3.

3.2.1. Changes between pre and post-SBRT within 6 months

The hematological parameters were measured within 6 months prior to SBRT and within 6 months post-SBRT. These values were compared to evaluate the trends of change due to treatment with

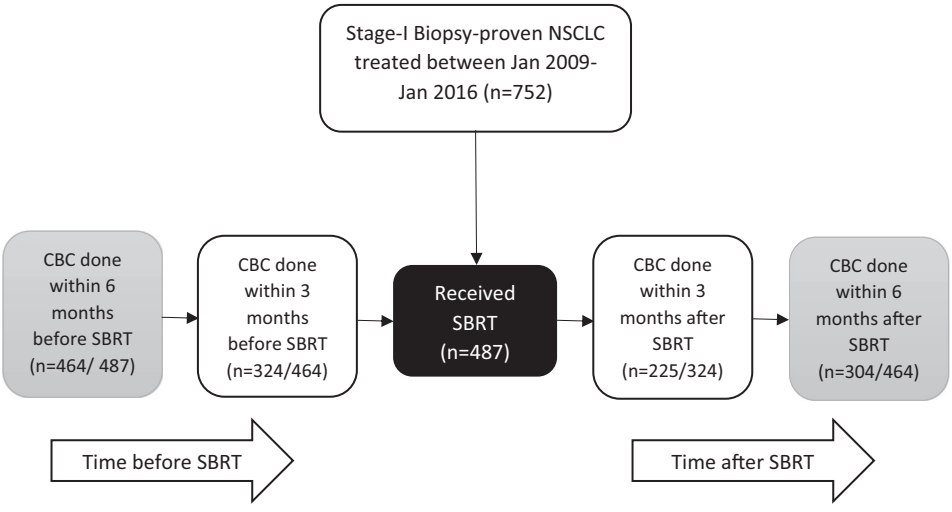

Fig. 1. CONSORT diagram.

Table 2
Patient, Tumor and Treatment Characteristics.

Variable		All patients n = 464 (%)
Median Age in years		76 (50–95)
Performance Status	0	157 (33.8%)
	1	180 (38.8%)
	2	116 (25%)
	3 or 4	11 (2.4%)
Median Charlsons Comorbidity Index		2 (0–8)
Ever Smoked (No/Yes)		20/434
T stage	T1	384 (82.8%)
	T2	80 (17.2%)
Histology	Adenocarcinoma	273 (55.6%)
	Squamous Carcinoma	102 (23%)
	NSCLC NOS[a]	89 (21.4%)
Median Tumor Diameter		2 cm (0.7–6.2)
Median GTV[b]		4.7 cc (0.4–100)
Median SUVmax[c]		4.7
Median Treatment time		7 (3–35)
Median BED[d]		132 (60–180)

[a] Non-Small Cell Lung Cancer, Not Otherwise Specified.
[b] Gross Target Volume.
[c] Maximum Standardized Uptake Value.
[d] Biologically Equivalent Dose.

SBRT. The median values of Hb, ALC, ANC and TPC declined post-SBRT as compared to the pre-SBRT level by 3 g/L (129 –26 g/L), 0.6×10^9/L (1.7 –1.1 $\times 10^9$/L), 0.3×10^9/L (5.2 –4.9 $\times 10^9$/L), 16×10^9/L (247–231 $\times 10^9$/L) respectively. However, the NLR and the PLR increased by 1.2 (2.9–4.1) and 108 (147–239) respectively.

3.2.2. Changes between pre and post-SBRT within 3 months

There was no difference in the trends of change between pre and post-SBRT levels when compared to those seen within 3 or 6 months. The median values of Hb, ALC, ANC and TPC declined post-SBRT as compared to the pre-SBRT level by 4 g/L (129 – 125 g/L), 0.6×10^9/L (1.7–1.1 $\times 10^9$/L), 0.4×10^9/L (5.3–4.9 $\times 10^9$/L), 17×10^9/L (249–232 $\times 10^9$/L) respectively. The changing trends observed for NLR and PLR were also similar to that seen within 6 months except that the magnitude of change was smaller. Both NLR and PLR increased by 0.2 (3.9 –4.1) and 72 (146–218) respectively.

3.3. Survival post SBRT

The median follow-up of all surviving patients was 45.5 months (confidence interval (CI) 41.7–49.2 months) and the median OS was 56.4 months (CI: 49.2 – 64.2 months). The 5 year OS, LFS and DMFS were 46.6, 88.7 and 76.4 respectively as shown in Table 4. We tested known prognostic factors for their significance in our cohort of patients for OS, LFS and DMFS.

3.4. Prognostic factors for various survival end points

A variety of factors were tested as categorical and/continuous variables for their prognostic significance for OS, LFS and DMFS.

3.4.1. Overall survival

The factors that had a p value of $\leq$0.1 on univariate analysis for OS (shown in Table 5) were included for analysis in the multivariate model after accounting for correlation amongst the variables. The factors that were detrimental for OS on multivariate analysis were: pre-SBRT Hb <120 g/L (p = 0.03, HR:1.51), increase in ANC post-SBRT (p = 0.04, HR:1.49) and SUVmax of the primary >4 (p < 0.01, HR:2.16).

3.5. Local recurrence-free survival

The factors that were detrimental for LFS on multivariate analysis were: Hb <120 g/L (p = 0.03; HR:2.66) and a SUVmax of the

Table 4
Patient outcomes after SBRT treatment.

Variable		All patients (n = 464)
Median Follow up in months		45.5 months (41.7–49.2)
Alive/Dead		267/197
Local Failure		37
Distant Failure		72
Any Failure		108
Overall Survival	3 years	65.8%
	5 years	45.3%
	Median	56.4 months (49.2–63.6)
Local recurrence free survival	2 years	94.6%
	5 years	88.2%
Distant metastasis free survival	2 years	88.3%
	5 years	76.3%

Table 3
Hematological parameters recorded within 3 and 6 months prior to and post-SBRT.

Pre SBRT[a] CBC[b]	Within 6 months (n = 464)				Within 3 months (n = 327)			
	Mean	SD	Median	Range	Mean	SD	Median	Range
Hemoglobin (g/L)	128	17	129	(51–178)	127	17	129	(51–173)
ALC[c] ($\times 10^9$/L)	1.7	6	1.7	(0.1–34)	2.4	7.5	1.7	(0.1–34)
ANC[d] ($\times 10^9$/L)	5.4	2.2	5.2	(0.9–16.3)	5.5	2.2	5.3	(0.9–15.2)
TPC[e] ($\times 10^9$/L)	254	82	247	(48–732)	256	79	249	(48–548)
NLR[f]	3.8	3.1	2.9	(0.4–39.8)	3.8	3.3	3.9	(0.4–39.8)
PLR[g]	173	109	147	(11.6–668)	173	112	146	(11.6–668)
Post SBRT CBC	Within 6 months (n = 304)				Within 3 months (n = 225)			
Hemoglobin in g/L	125	17.1	126	(60–173)	124	17	125	(60–164)
ALC[c] ($\times 10^9$/L)	1.7	7.2	1.1	(0.1–37)	1.8	8.4	1.1	(0.1–32)
ANC[d] ($\times 10^9$/L)	5.6	2.9	4.9	(1.3–22.4)	5.6	3.	4.9	(1.3–22.4)
TPC[e] ($\times 10^9$/L)	237	83	231	(17–642)	240	84	232	(17–642)
NLR[f]	6.5	9.4	4.1	(0.5–94)	7	10.7	4.1	(0.5–94)
PLR[g]	248	201	239	(13–805)	261	263	218	(13–805)

[a] Stereotactic Body Radiation Therapy.
[b] Complete Blood Count.
[c] Absolute Lymphocyte Count.
[d] Absolute Neutrophil Count.
[e] Total Platelet Count.
[f] Neutrophil to Lymphocyte Ratio.
[g] Platelet to Lymphocyte Ratio.

Table 5
Univariate and Multivariate analysis of prognostic variables for various survival outcomes.

Variables with p value ≤1.0 on Univariate Analysis			Variables included in Multivariate Analysis				
Variable	Categories	p value	Detrimental Category	p value	Hazard Ratio	Lower bound CI	Upper bound CI
Overall Survival							
Age (yrs)	≤70 Vs >70	0.05	>70	0.12	1.41	0.91	2.19
Gender	M Vs F	0.03	M	0.05	1.14	0.99	2.21
Age adjusted CCI[a] group	<5 Vs ≥5	0.05	Not included in the final MV model as it showed significant correlation with the variable Age (−0.46)				
Performance Status	0–1 Vs 2–4	<0.01	2–4	0.08	1.45	0.96	2.21
T stage	T1 Vs T2	0.06	T2	0.46	1.20	0.74	1.93
T size (cm)	≤2 Vs >2	<0.01	Not included in the final MV model as it showed significant correlation with the variable SUV (−0.38) & T stage (−0.27)				
SUVmax[b]	≤4 Vs >4	**<0.01**	**>4**	**<0.01**	**2.01**	**1.35**	**3.01**
Pre-SBRT HB[c] (g/L)	<120 Vs ≥120	**0.01**	**<120**	**0.03**	**1.51**	**1.03**	**2.21**
ALC[d]	Normal Vs Abnormal	0.09	Not included in the final MV model as it showed significant correlation with the variable Post-SBRT PLR (−0.46)				
Increase in ANC[e] post-SBRT[f]	Yes Vs No	**<0.01**	**Yes**	**0.04**	**1.49**	**1.01**	**2.21**
NLR[g]	≤6 Vs >6	0.02	>6	0.43	1.26	0.71	2.22
Post-SBRT HB in g/L	<120 Vs ≥120	<0.01	Not included in the final MV model as it showed significant correlation with the variable Pre-SBRT HB (−0.40) & Gender (−0.44)				
Post-SBRT PLR	≤250 Vs >250	<0.01	>250	0.08	1.42	0.95	2.12
Local recurrence free survival							
Age (yrs)	≤70 Vs >70	<0.01	Not included in the final MV model as it showed significant correlation with the variable Post-SBRT HB (0.34)				
T Stage	T1 Vs T2	0.06	T2	0.90	1.07	0.36	3.24
T Size (cm)	≤2 Vs >2	0.08	Not included in the final MV model as it showed significant correlation with the variable SUV (0.26) & T stage (−0.39)				
SUVmax[b]	≤4 Vs >4	**0.02**	**>4**	**0.04**	**3.00**	**1.05**	**8.61**
BED Gy_{10}	≤125 Vs >125	0.02	≤125	0.65	1.23	0.50	3.10
HB[c] (g/L)	<120 Vs ≥120	**0.03**	**<120**	**0.03**	**2.66**	**1.10**	**6.43**
Post-SBRT HB[c] (g/L)	<100 Vs ≥100	0.09	Not included in the final MV model as it showed significant correlation with the variable Pre-SBRT HB (0.39)				
Post-SBRT[f] PLR[h]	≤250 Vs >250	0.02	>250	0.07	2.35	0.94	5.89
Decrease in ALC[d]	Yes Vs No	0.03	Yes	0.08	5.95	0.79	14.7
Distant Metastasis Free Survival							
Age (yrs)	≤85 Vs >85	0.07	>85	0.13	4.66	0.63	34.47
Gender	M Vs F	**0.01**	**M**	**0.02**	**2.11**	**1.15**	**3.87**
T Stage	T1 Vs T2	0.09	T2	0.34	1.44	0.68	3.09
SUVmax[b]	≤4 Vs >4	**0.01**	**>4**	**0.02**	**2.25**	**1.15**	**4.40**
HB[c] (g/L)	<120 Vs ≥120	**0.04**	**<120**	**0.02**	**2.08**	**1.13**	**3.81**
ALC[d]	Normal Vs Abnormal	0.10	Not included in the final MV model as it showed significant correlation with the variable Post-SBRT PLR (−0.46)				
NLR[g]	≤6 Vs >6	0.03	>6	0.40	1.38	0.65	2.95
PLR[h]	≤250 Vs >250	0.01	Not included in the final MV model as it showed significant correlation with the variable Pre-SBRT NLR (0.65) & Post SBRT PLR (0.44)				
Post-SBRT[f] HB[c] (g/L)	<120 Vs ≥120	0.07	Not included in the final MV model as it showed significant correlation with the variable Pre-SBRT HB (−0.62)				
Post-SBRT[f] TPC[i]	Normal Vs Abnormal	**0.04**	**Abnormal**	**0.05**	**4.32**	**1.03**	**18.22**
Post-SBRT[f] PLR[h]	≤250 Vs >250	<0.01	>250	0.09	1.71	0.92	3.18

The bold text indicates variables with prognostic significance on multivariate analysis.
[a] Charlson Comorbidity Index.
[b] Maximum Standardized Uptake Value.
[c] Hemoglobin level.
[d] Absolute Lymphocyte count.
[e] Absolute Neutrophil Count.
[f] Stereotactic Body Radiation Therapy.
[g] Neutrophil to Lymphocyte Ratio.
[h] Platelet to Lymphocyte Ratio.
[i] Total Platelet Count.

primary >4 (p = 0.04; HR:3.00). No other hematological, patient, tumor or treatment related factors were found to be statistically significant.

3.6. Distant metastasis-free survival

The factors that were detrimental for DMFS on multivariate analysis were: Male gender (p = 0.02, HR 2.11), Hb <120 g/L (p = 0.02, HR:2.08), Abnormal TPC post-SBRT (p = 0.04, HR: 4.32) and a SUVmax of the primary >4 (p = 0.02, HR:2.25). No other hematological, patient, tumor or treatment related factors were found to be statistically significant.

4. Discussion

Our study is the first of its kind to evaluate the hematologic prognostic factors both before and after SBRT in medically inoperable patients with stage I NSCLC. Most studies to date have evaluated the hematologic parameters reported within 3 months from radiation therapy for solid tumors. Since cancer can take a long time to develop from pre-cancerous lesions, the hematologic changes associated with a paraneoplastic effect may also manifest well before the diagnosis and an interval change in the values of hematological parameters could be used as a prognostic/predictive marker. Hence, our study evaluated the hematologic parameters within 3 as well as 6 months of SBRT starting.

The pre-SBRT CBC was within normal range for most of the patients as evidenced by the median values in Table 3. The Pittsburgh Lung Screening Study along with the study by Takashi Arai et al. had shown that the median tumor doubling time was between 166 and 365 days. Even the rapid growers were classified as those that doubles in <183 days [21,22]. The negligible difference in the mean and median values of pre-SBRT hematological parameters between 3 and 6 months could be because of this slow doubling time. Another study done by Ross et al. demonstrated the stability of mean values of the hematologic parameters for healthy subjects within an interval of nine months [23]. Even though a direct comparison between healthy adults and patients with NSCLC may not be ideal, there is lack of any other evidence in literature that evaluated the same. These findings suggest that blood drawn 6 months prior to the treatment for NSCLC can also be used for prognostication for a variety of survival end points and any change from the baseline may be associated with disease progression or resolution of the disease post treatment.

Even though there was a decline in the absolute values for all hematological parameters post-SBRT, both NLR and PLR increased highlighting the differential reduction in the various parameters. A few studies have suggested that such a decline post SBRT for lung cancer could be due to irradiation of the bone marrow in the thoracic vertebral bodies [24,25] or due to exposure of large pools of blood in the heart or great vessels to low dose radiation [26]. Higher NLR and PLR have been associated with poor outcomes as seen in various studies [16,27,28]. Interestingly, our study did not show association of pre-SBRT NLR or PLR with any survival end points on multivariate model which has been seen in another study as well [29]. A meta-analysis evaluating the role of PLR showed that the strongest association between PLR and survival was seen in the metastatic or mixed groups of patients rather than those with loco-regional disease which also may have contributed to the reason for our results [30]. These parameters analyzed with various bio-markers and other known prognostic factors may help in dividing patients into favorable and unfavorable categories and be used for stratification in randomized studies. Recognizing such prognostic factors can also help develop various predictive models using higher order analytics like machine learning algorithms. The decision of escalation and de-escalation of subsequent therapies may be offered based on these categories.

The HB <120 g/L significantly adversely affected the OS, DMFS and the LFS. Many studies have shown that lower hemoglobin levels are a poor prognostic factor for OS in a variety of malignancies similar to our patient population [31–34]. The hypothesis for lower HB levels is that tumor cells secrete factors such as TNF-α and IL-6 which suppress erythropoiesis [35]. Hypoxia due to anemia causes increase tumor angiogenesis and metastasis and could be the reason for poor DMFS [36]. Treatment with SBRT causes direct tumor cell kill, and also destroys the tumor vascular beds, leading to tumor cell death indirectly. It is also associated with release of large quantities of tumor antigens which stimulate anti-tumor immunity that aid in suppressing recurrence and metastases. It is currently believed that reoxygenation, repair, repopulation, and redistribution, which play an integral role in conventional fractionated radiotherapy, hold relatively little importance in SBRT [37]. Yet, for the first time our study showed that even when all patients were uniformly treated with SBRT doses $\geq$100 Gy_{10}, HB <120 g/L was associated with poor LFS and may point towards unknown mechanisms of action of SBRT. Further studies should be directed towards validating these results prospectively.

The SUV max in a FDG PET-CT scan acts as a surrogate for tumor biology where higher values are associated with rapidly proliferating, aggressive tumors. The higher pre-treatment SUVmax values have been shown to correlate with poor LFS, DMFS and OS for NSCLC and many other solid tumors irrespective of the treatment used [38–40]. Our study results further help in establishing similar correlation and encourages its inclusion in a predictive model that aims at personalizing therapy.

The blood reports were collated from the records of the Cancer Centre and the community labs and therefore the reason for getting the blood drawn was not recorded. Intercurrent illnesses can dramatically change the peripheral blood count and confound the results and therefore need to be validated prospectively. There were missing CBC reports for many patients post-SBRT even within the 6 month period and these missing values may potentially introduce bias. The strength of our study lies in the large number of consecutive biopsy proven stage I NSCLC patients uniformly treated with SBRT at a single institute and the long follow-up. Even though ours is a simple study it has limitations associated with the retrospective nature of the study.

5. Conclusion

The median values of hematological parameters remain stable even at 6 months as compared to 3 months prior to SBRT starting and may be used interchangeably in absence of any intercurrent illness known to affect the hematological parameters. Stage I NSCLC patients even when treated with SBRT doses of BED >100 Gy_{10} have a significantly higher local recurrence, distant metastases and poor overall survival if their pre-treatment Hb is <120 g/L and the primary tumor has a pre-treatment SUVmax >4. Hematologic parameters should be grouped with other patient and tumor characteristics to develop prognostic tools such as nomograms in patients with stage I NSCLC for individualizing and guiding therapy.

Acknowledgment

Dr. Rima S. Pathak was funded by The Ethel Ward Cushing Legacy Endowment Fund for a stereotactic ablative radiation therapy fellowship during which this work was produced. There was no direct funding for this study.

Conflicts of interest notification

The authors do not have any conflicts of interest.

References

[1] Videtic GM, Donington J, Giuliani M, Heinzerling J, Karas TZ, Kelsey CR, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: executive summary of an ASTRO Evidence-based guideline. Pract Radiat Oncol 2017;7:295–301. https://doi.org/10.1016/j.prro.2017.04.014.

[2] Ettinger DS, Wood DE, Akerley W, Bazhenova LA, Borghaei H, Camidge DR, et al. Guidelines Insights: non-small cell lung cancer, Version 4.2016. J Natl Compr Canc Netw 2016;14:255–64.

[3] Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for Stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94–S100. https://doi.org/10.1097/JTO.0b013e318074de34.

[4] Nagata Y, Takayama K, Matsuo Y, Norihisa Y, Mizowaki T, Sakamoto T, et al. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. Int J Radiat Oncol 2005;63:1427–31. https://doi.org/10.1016/j.ijrobp.2005.05.034.

[5] Baumann P, Nyman J, Hoyer M, Wennberg B, Gagliardi G, Lax I, et al. Outcome in a prospective phase II trial of medically inoperable stage i non–small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 2009;27:3290–6. https://doi.org/10.1200/JCO.2008.21.5681.

[6] Baumann P, Nyman J, Lax I, Friesland S, Hoyer M, Rehn Ericsson S, et al. Factors important for efficacy of stereotactic body radiotherapy of medically inoperable stage I lung cancer. A retrospective analysis of patients treated in the Nordic countries. Acta Oncol (Madr) 2006;45:787–95. https://doi.org/10.1080/02841860600904862.

[7] Xie D, Marks R, Zhang M, Jiang G, Jatoi A, Garces YI, et al. Nomograms predict overall survival for patients with small-cell lung cancer incorporating pretreatment peripheral blood markers. J Thorac Oncol 2015;10:1213–20. https://doi.org/10.1097/JTO.0000000000000585.

[8] Suzuki R, Lin SH, Wei X, Allen PK, Welsh JW, Byers LA, et al. Prognostic significance of pretreatment total lymphocyte count and neutrophil-to-lymphocyte ratio in extensive-stage small-cell lung cancer. Radiother Oncol 2018;126:499–505. https://doi.org/10.1016/j.radonc.2017.12.030.

[9] Wang J, Kalhor N, Hu J, Wang B, Chu H, Zhang B, et al. Pretreatment neutrophil to lymphocyte ratio is associated with poor survival in patients with stage I-III non-small cell lung cancer. PLoS One 2016;11:. https://doi.org/10.1371/journal.pone.0163397e0163397.

[10] Dirican N, Dirican A, Anar C, Atalay S, Ozturk O, Bircan A, et al. A new inflammatory prognostic index, based on c-reactive protein, the neutrophil to lymphocyte ratio and serum albumin is useful for predicting prognosis in non-small cell lung cancer cases. Asian Pac J Cancer Prev 2016;17:5101–6. https://doi.org/10.22034/APJCP.2016.17.12.5101.

[11] Jeong E, Hyun SH, Moon SH, Cho YS, Kim B-T, Lee K-H. Relation between tumor FDG uptake and hematologic prognostic indicators in stage I lung cancer patients following curative resection. Medicine (Baltimore) 2017;96:. https://doi.org/10.1097/MD.0000000000005935e5935.

[12] Derman BA, Macklis JN, Azeem MS, Sayidine S, Basu S, Batus M, et al. Relationships between longitudinal neutrophil to lymphocyte ratios, body weight changes, and overall survival in patients with non-small cell lung cancer. BMC Cancer 2017;17:141. https://doi.org/10.1186/s12885-017-3122-y.

[13] Yuan C, Li N, Mao X, Liu Z, Ou W, Wang S. Elevated pretreatment neutrophil/white blood cell ratio and monocyte/lymphocyte ratio predict poor survival in patients with curatively resected non-small cell lung cancer: results from a large cohort. Thorac Cancer 2017;8:350–8. https://doi.org/10.1111/1759-7714.12454.

[14] Wang H, Zhao J, Zhang M, Han L, Wang M, Xingde L. The combination of plasma fibrinogen and neutrophil lymphocyte ratio (F-NLR) is a predictive factor in patients with resectable non small cell lung cancer. J Cell Physiol 2018;233:4216–24. https://doi.org/10.1002/jcp.26239.

[15] Luo H, Ge H, Cui Y, Zhang J, Fan R, Zheng A, et al. Systemic inflammation biomarkers predict survival in patients of early stage non-small cell lung cancer treated with stereotactic ablative radiotherapy – a single center experience. J Cancer 2018;9:182–8. https://doi.org/10.7150/jca.21703.

[16] Giuliani M, Sampson LR, Wong O, Gay J, Le LW, Cho BCJ, et al. Prognostic value of pretreatment circulating neutrophils, monocytes, and lymphocytes on outcomes in lung stereotactic body radiotherapy. Curr Oncol 2016;23:362. https://doi.org/10.3747/co.23.3051.

[17] Lee YH, Choi H-S, Jeong H, Kang KM, Song JH, Lee WS, et al. Neutrophil-lymphocyte ratio and a dosimetric factor for predicting symptomatic radiation pneumonitis in non-small-cell lung cancer patients treated with concurrent chemoradiotherapy. Clin Respir J 2017;12:1264–73. https://doi.org/10.1111/crj.12660.

[18] Senthi S, Lagerwaard FJ, Haasbeek CJA, Slotman BJ, Senan S. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. Lancet Oncol 2012;13:802–9. https://doi.org/10.1016/S1470-2045(12)70242-5.

[19] Lagerwaard FJ, Haasbeek CJA, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. Int J Radiat Oncol 2008;70:685–92. https://doi.org/10.1016/j.ijrobp.2007.10.053.

[20] Clinical Laboratory Tests-reference Values. http://www.royalcollege.ca/portal/pls/portal/!PWEB_PORTAL.wwpob_page.show?_docname=2219901.PDF. n.d.

[21] Wilson DO, Ryan A, Fuhrman C, Schuchert M, Shapiro S, Siegfried JM, et al. Doubling times and CT screen-detected lung cancers in the Pittsburgh lung screening study. Am J Respir Crit Care Med 2012;185:85–9. https://doi.org/10.1164/rccm.201107-1223OC.

[22] Zhao B, James LP, Moskowitz CS, Guo P, Ginsberg MS, Lefkowitz RA, et al. Evaluating variability in tumor measurements from same-day repeat CT scans of patients with non-small cell lung cancer. Radiology 2009;252:263–72. https://doi.org/10.1148/radiol.2522081593.

[23] Ross DW, Ayscue LH, Watson J, Bentley SA. Stability of hematologic parameters in healthy subjects intraindividual versus interindividual variation. Am J Clin Pathol 1988;90:262–7.

[24] Maehata Y, Onishi H, Kuriyama K, Aoki S, Araya M, Saito R, et al. Immune responses following stereotactic body radiotherapy for stage I primary lung cancer. Biomed Res Int 2013;2013:. https://doi.org/10.1155/2013/731346731346.

[25] Barney CL, Scoville N, Allan E, Ayan A, DiCostanzo D, Haglund KE, et al. Radiation dose to the thoracic vertebral bodies is associated with acute hematologic toxicities in patients receiving concurrent chemoradiation for lung cancer: results of a single-center retrospective analysis. Int J Radiat Oncol 2018;100:748–55. https://doi.org/10.1016/J.IJROBP.2017.11.025.

[26] Venkatesulu BP, Mallick S, Lin SH, Krishnan S. A systematic review of the influence of radiation-induced lymphopenia on survival outcomes in solid tumors. Crit Rev Oncol Hematol 2018;123:42–51. https://doi.org/10.1016/J.CRITREVONC.2018.01.003.

[27] Templeton AJ, Ace O, McNamara MG, Al-Mubarak M, Vera-Badillo FE, Hermanns T, et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2014;23:1204–12. https://doi.org/10.1158/1055-9965.EPI-14-0146.

[28] Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. JNCI J Natl Cancer Inst 2014;106:dju124. https://doi.org/10.1093/jnci/dju124.

[29] Unal D, Eroglu C, Kurtul N, Oguz A, Tasdemir A. Are neutrophil/lymphocyte and platelet/lymphocyte rates in patients with non-small cell lung cancer associated with treatment response and prognosis? Asian Pacific J Cancer Prev 2013;14:5237–42. https://doi.org/10.7314/APJCP.2013.14.9.5237.

[30] Ding N, Pang Z, Shen H, Ni Y, Du J, Liu Q. The prognostic value of PLR in lung cancer, a meta-analysis based on results from a large consecutive cohort. Sci Rep 2016;6:34823. https://doi.org/10.1038/srep34823.

[31] Aoe K, Hiraki A, Maeda T, Katayama H, Fujiwara K, Tabata M, et al. Serum hemoglobin level determined at the first presentation is a poor prognostic indicator in patients with lung cancer. Intern Med 2005;44:800–4.

[32] Gauthier I, Ding K, Winton T, Shepherd FA, Livingston R, Johnson DH, et al. Impact of hemoglobin levels on outcomes of adjuvant chemotherapy in resected non-small cell lung cancer: the JBR.10 trial experience. Lung Cancer 2007;55:357–63. https://doi.org/10.1016/j.lungcan.2006.10.021.

[33] Van Belle SJ-P. What is the value of hemoglobin as a prognostic and predictive factor in cancer? Eur J Cancer Suppl 2004;2:11–9. https://doi.org/10.1016/S1359-6349(03)00103-4.

[34] Shaverdian N, Veruttipong D, Wang J, Kupelian P, Steinberg M, Lee P. Pretreatment anemia portends poor survival and nonlocal disease progression in patients with stage I non-small cell lung cancer treated with stereotactic body radiation therapy. J Thorac Oncol 2016;11:1319–25. https://doi.org/10.1016/j.jtho.2016.04.030.

[35] Madu AJ, Ughasoro MD. Anaemia of chronic disease: an in-depth review. Med Princ Pract 2017;26:1–9. https://doi.org/10.1159/000452104.

[36] Muz B, de la Puente P, Azab F, Azab AK. The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. Hypoxia (Auckland, NZ) 2015;3:83–92. https://doi.org/10.2147/HP.S93413.

[37] Kim M-S, Kim W, Park IH, Kim HJ, Lee E, Jung J-H, et al. Radiobiological mechanisms of stereotactic body radiation therapy and stereotactic radiation surgery. Radiat Oncol J 2015;33:265–75. https://doi.org/10.3857/roj.2015.33.4.265.

[38] Berghmans T, Paesmans M, Sculier J-P. Prognostic factors in stage III non-small cell lung cancer: a review of conventional, metabolic and new biological variables. Ther Adv Med Oncol 2011;3:127–38. https://doi.org/10.1177/1758834011401951.

[39] Paesmans M, Berghmans T, Dusart M, Garcia C, Hossein-Foucher C, Lafitte J-J, et al. Primary tumor standardized uptake value measured on fluorodeoxyglucose positron emission tomography is of prognostic value for survival in non-small cell lung cancer: update of a systematic review and meta-analysis by the european lung cancer working party for the international association for the study of lung cancer staging project. J Thorac Oncol 2010;5:612–9. https://doi.org/10.1097/JTO.0b013e3181d0a4f5.

[40] Nair VJ, MacRae R, Sirisegaram A, Pantarotto JR. Pretreatment [18F]-fluoro-2-deoxy-glucose positron emission tomography maximum standardized uptake value as predictor of distant metastasis in early-stage non-small cell lung cancer treated with definitive radiation therapy: rethinking the role of positron emission tomography in personalizing treatment based on risk status. Int J Radiat Oncol Biol Phys 2014;88:312–8. https://doi.org/10.1016/j.ijrobp.2013.10.029.