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ORIGINAL ARTICLE

Impact of unfavorable factors on outcomes among inoperable stage II-IV Nonsmall cell lung cancer patients treated with proton therapy

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ABSTRACT

Purpose: To investigate the impact of unfavorable risk factors among patients with locally advanced nonsmall cell lung cancer (LA-NSCLC) treated with proton therapy (PT).

Material and Methods: From May 2008 through July 2015, 90 consecutive patients with unresectable stage II-IV (oligometastatic) NSCLC were treated with PT. Unfavorable factors including age $\geq$80 years, stage IV, weight loss >10% in 3 months, performance status (PS) $\geq$2, FEV1 < 1.0 or O_2 dependency, prior lung cancer, prior lung surgery, prior 2nd cancer in the past 3 years, and prior chest irradiation were evaluated. All patients received standard fractionation of 1.8–2 Gy(RBE) (median dose, 70 Gy[RBE]). Overall survival (OS) and progression-free survival (PFS) were calculated with the Kaplan-Meier method. The impact of unfavorable factors was analyzed in Cox regression models.

Results: Twenty-six percent were favorable-risk, while 42%, 22%, and 10% had 1-, 2-, or $\geq$3 unfavorable factors. The 2-year OS was 52% and 45% ($p = .8522$), and 2-year PFS was 21% and 44% ($p = .0207$), for favorable and unfavorable risk patients, respectively. Among patients with stage III-IV, only PS $\geq$2 adversely impacted OS ($p = .0015$).

Conclusion: Most patients treated with PT for LA-NSCLC have unfavorable risk factors. These patients had similar outcomes to favorable-risk patients. Enrollment in future clinical trials may improve if eligibility is less restrictive.

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Introduction

Proton therapy (PT) provides an alternative pathway to intensifying the radiation dose to the target while limiting the dose to organs at risk [1,2]. Consequently, PT may serve as a potentially less toxic and more effective treatment as compared to conventional photon therapies. Encouraged by early results [3–5], investigators have rolled out several proton cooperative group trials and institution-initiated trials over the last five years. However, such trials have been slow to accrue with some of the institutional trials terminating prematurely [5]. Causes for poor accrual are attributed to private insurance carriers refusing to cover PT treatment and restrictive study eligibility criteria that omit patients with 'unfavorable' factors [5–8]. In fact, of late, the oncology community has been vocal in support of loosening patient eligibility criteria in future cooperative studies for all stages of lung malignancy and clinical oncology in general [9,10].

'Unfavorable' factors that have served as exclusion criteria in most clinical trials of patients with LA-NSCLC have included advanced age, pre-existing pulmonary, cardiac, or other significant co-morbidities, and a history of cancer or chest irradiation. Cardenal et al. [11] identified these 'unfavorable' risk patients as a large subset for whom no clear treatment guidelines exist and would therefore benefit greatly from clinical trials. In the few small prospective studies of conventional photon therapy with systemic therapy for this subset, poor outcomes have been reported [12–15].

In an effort to better understand the impact of 'unfavorable' risk factors on the efficacy of proton therapy, and to provide background for future research questions, we investigated the outcomes of patients with LA-NSCLC who were enrolled on either a prospective outcomes tracking protocol or a clinical trial at our proton therapy institute.

Methods and material

Study design and patient population

We retrospectively analyzed the medical records of 141 patients with biopsy-proven NSCLC enrolled on institutional review board-approved outcomes-tracking protocols or clinical trials and treated with PT with curative intent between May 2008 and July 2015 at a single institution. Fifty patients were excluded because of stage I disease ($n = 36$), treatment with a combination of protons and photons

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($n = 3$), hypofractionated regimens ($n = 11$), or reirradiation of an in-field local relapse ($n = 1$). Patients were included in the present analysis if they had biopsy proven inoperable stage II-IIIB or limited stage IV NSCLC with oligometastasis (a total of 3 or less distant metastasis) that were also treated definitively with proton therapy ($n = 90$).

Patient- and disease-specific characteristics

Patient- and disease-specific characteristics, retrospectively extracted from prospectively collected data forms or from patient medical records, are listed in Table 1. For the purposes of this study, 10 'unfavorable' factors were identified as common exclusion criteria for LA-NSCLC trials and evaluated for each patient. Unfavorable factors included the following: age ≥80 years at diagnosis, prior lung lobectomy surgery, and the eligibility factors listed in the NRG 1308 trial [16]: stage IV (oligometastasis), weight loss exceeding 10% in 3 months, performance status (PS) of 2 or worse, poor baseline lung function defined as forced expiratory volume in 1 second (FEV1) less than 1.0 L or home oxygen dependency (at least nightly), history of lung cancer, prior 2nd nonthoracic cancer in the past 3 years (excluding nonmelanoma skin cancer), prior chest irradiation, and other severe comorbidities listed as ineligibility criteria in most currently accruing cooperative group trials, such as severe cardiac diseases requiring hospitalization within 6 months before the start of PT, severe nonmalignant pulmonary diseases requiring hospitalization within 1 month of the start of PT, or other organ system conditions precluding patients from receiving chemotherapy.

Treatment

Our simulation and treatment planning processes for this cohort of patients have been previously described [17]. Adaptive replanning was allowed during the course of PT to optimize PTV coverage or minimize doses to critical structures because of anatomical changes from tumor response, resolution of atelectasis, development of pleural effusion, or infectious etiologies during the course of therapy. In the case of tumor shrinkage, the GTV/iGTV was recontoured for the purposes of dose and range recalculation, but the ITV and PTV volumes were left unchanged. All patients received verification computed tomography (CT) simulation every 1 to 2 weeks during treatment to assess the need for adaptive planning; this scan was fused to the original treatment plan to assess proton range changes due to anatomical change on CT and to evaluate planned target volume coverage or doses to organs at risk.

All PT plans were delivered using passive-scatter PT. The median PT dose delivered was 70 Gy(RBE) (range, 12–80 Gy[RBE]) using standard fractionations (1.8–2 Gy[RBE]/fraction). Four patients received less than 59 Gy(RBE), due to pulmonary embolism leading to death (12 Gy[RBE]), neutropenic fever and death (26 Gy[RBE]), cardiac arrest and death (40 Gy[RBE]), and planned for 50 Gy(RBE) due to prior chest radiation. Twelve patients received 59–69 Gy(RBE) and 74 patients received 70 Gy(RBE) or higher. Overall, 22 patients (24.4%) underwent adaptive replanning as described in NRG 1308 (NCT01993810) during the course of PT for the following reasons: tumor shrinkage ($n = 10$), pleural effusion ($n = 2$), significant normal tissue toxicities like dermatitis ($n = 1$), esophagitis ($n = 1$), treatment position changes influencing target coverage ($n = 5$), reopened collapsed lung ($n = 1$), lung abscess ($n = 1$), and tumor progression ($n = 1$).

Chemotherapy was individualized based on patients' clinical stages and comorbidities, and in accordance with respective clinical protocols. Concurrent chemotherapy with PT was strongly encouraged but not always required. The most common regimens were carboplatin-based weekly doublet chemotherapy. Induction and adjuvant chemotherapies were allowed and left to the discretion of the treating

Table 1. Patient, cancer, and treatment characteristics for favorable-risk and unfavorable-risk groups.

Characteristics	Favorable pts ($n = 23$)	Unfavorable pts ($n = 67$)	p value
No. of unfavorable factors			
1 factor	–	38 (57%)	–
2 factors	–	20 (30%)	
≥3 factors	–	9 (13%)	
Age, median (range)	62, (40–75) yrs	69 (40–88) yrs	–
No. of patients age ≥65	11 (48%)	49 (73%)	.0395
Sex			
Female	7 (30%)	30 (45%)	.3263
Male	16 (70%)	37 (55%)	
Clinical stages			
IIA	0	7 (10%)	.0028*
IIB	1 (4%)	5 (7%)	
IIIA	8 (35%)	28 (42%)	
IIIB	14 (61%)	15 (22%)	
IV	0	12 (18%)	
Histology			
Squamous cell carcinoma	15 (65%)	32 (48%)	.2261
Adenocarcinoma	7 (30%)	28 (42%)	
Large cell carcinoma	1 (4%)	4 (6%)	
Undifferentiated	0	3 (4%)	
Concurrent chemoradiation therapy	22 (96%)	54 (81%)	.1054
Median radiation therapy dose (range)	70 (26 to 80) Gy(RBE)	70 (12 to 80) Gy(RBE)	–
Adaptive re-planning	4 (17%)	18 (27%)	.4153

*Stage 3 versus stage 2 versus stage 4.

medical oncologists. Ultimately, 76 (84.4%) patients received concurrent chemotherapy while 6 patients were treated sequentially with chemotherapy followed by PT; 3 refused chemotherapy; 2 were not fit for chemotherapy based on medical comorbidities; and 3 never received chemotherapy for early-stage disease.

Follow-up and observed outcomes

Follow-up care included a medical history and physical examination at 3-month intervals following treatment. Follow-up imaging was performed at 3-month intervals with alternating chest CT or positron emission tomography-CT.

Toxicity

Toxicity was prospectively assessed per Common Terminology Criteria for Adverse Events, version 3.0 (prior to 2010) or 4.0. If toxicity was initially recorded using Version 3.0, it was retrospectively regraded according to Common Terminology Criteria for Adverse Events, version 4.0 using a lung toxicity form (supplement). The acute toxicities were defined as adverse events observed within 6 months of the start of PT and were assessed for all patients. The late toxicities were those observed after 6 months of the start of PT and were assessed for the 78 patients who lived 6 or more months. Specific attention was paid to weight change, chest wall pain, pneumonitis (within 6 months after PT), pulmonary fibrosis or bronchial stenosis (starting 6 months after PT), pleural effusion, bronchial hemorrhage, esophagitis, esophageal stricture or ulceration, and development of home oxygen dependency after PT. All patients had toxicity assessed and recorded before beginning PT, weekly while undergoing PT, and at 3-month intervals after completing PT. All follow-up imaging was assessed by the treating radiation oncologists or a thoracic diagnostic radiologist to determine grade 1 toxicities found only by imaging criteria. Toxicities were censored at the time of any disease recurrence or progression.

Statistics

All statistical computations were performed with SAS and JMP software (SAS Institute, Cary, NC). The Kaplan-Meier product-limit method provided estimates of survival. The impact of unfavorable factors was analyzed in univariate and multivariate Cox regression models.

Results

Unfavorable factors

Among the 90 patients analyzed in the study, only 23 patients (25.5%) were considered 'favorable', while most 67 (74.5%) had at least 1 unfavorable factor, distributed as follows: 1 factor, 38 patients; 2 factors, 20 patients; 3 factors, 8 patients; and 4 factors, 1 patient (Table 1).

Although the median age was similar between the two cohorts (66 vs 70 years), there were significantly more patients with unfavorable characteristics aged 65 or older ($p = .0395$). There was no significant difference in the number of black patients (22% vs 18%), the gender of patients, or the histology of patients between the favorable and unfavorable groups. The stage distribution differed between the cohorts with a significantly higher percentage of patients in the unfavorable group with stage II disease and stage IV disease ($p = .0028$).

The median dose for both groups was 70 Gy(RBE). Three patients—1 favorable but with history of pulmonary fibrosis and 2 unfavorable patients—did not complete their radiotherapy due to nonradiation-related events that resulted in death (neutropenic fever after 26 Gy(RBE), pulmonary embolism after 12 Gy(RBE), and MI after 40 Gy(RBE).

Survival outcomes

The median follow-up was 23.0 months (range, 0.3–107.7 months); the median follow-up among living patients was 54.6 months (27.4–107.7). The 2-year OS rate for this entire cohort was 47% and the disease-free survival rate was 38%. The local control rate at 2 years was 77% and the regional control rate was 83%, although the freedom from metastasis rate was 49%.

Impact of unfavorable factors on survival outcomes

Favorable-risk patients were not significantly different from unfavorable-risk patients in terms of 2-year OS (52% vs. 45%, respectively; $p = .8522$). Unfavorable-risk patients had significantly better progression-free survival (PFS) at 2 years compared to favorable-risk patients (44% vs 21%; $p = .0207$) (Figure 1); however, all stage IIA patients were in the unfavorable risk group. When restricted to stage III patients, the 2-year overall survival rate (50% vs 37%; $p = .7032$) and PFS (17% vs 41%, $p = .0596$) were not significantly different between the favorable risk and unfavorable risk groups.

Univariate analyses revealed no significant association between any defined unfavorable factor and survival (Table 2). Similarly, multivariate analyses did not show significant impact on survival from any unfavorable factor. In a subgroup analysis excluding stage II patients who typically have better outcomes and were only in the unfavorable group, a PS of 2 or worse was adversely associated with survival ($p = .0094$) (Table 2 and Figure 2). The median OS was 10 months for those with PS of 2 or higher, while other unfavorable-risk patients with a PS of 0-1 had a median OS of 24 months.

Toxicities

Both acute and late toxicities potentially associated with PT or chemotherapy were prospectively recorded during on-treatment and follow-up visits (Table 3). Toxicity assessments on the first treatment day indicate patients' baseline pulmonary issues. Overall, no significant difference in either acute or

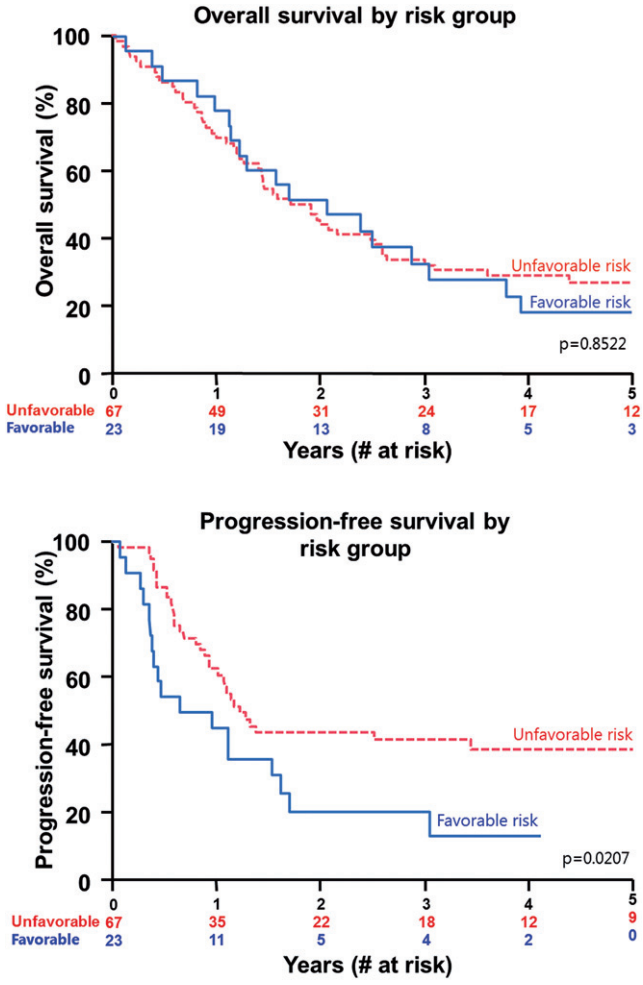

Figure 1.. Kaplan-Meier overall survival (OS; solid line) and progression-free survival (PFS; dashed line) curves for patients with (red line) and without (blue line) unfavorable risk factors who received conventional fractionation.

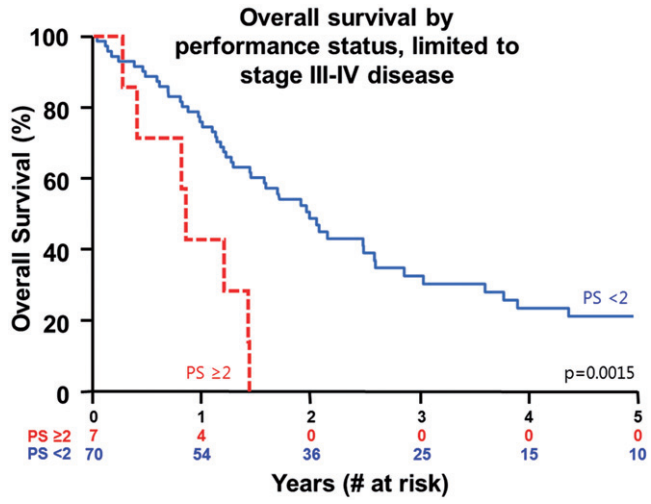

Figure 2.. Kaplan-Meier overall survival (OS) curves for stage III-IV patients with (red, solid line) and without (blue, dashed line) poor performance status (PS ≥2) who received conventional fractionation.

Table 2. Univariate analysis of unfavorable risk factors on overall survival for (A) all patients and (B) only stage III-IV patients treated with conventional fractionation.

	Five-year overall survival		
Unfavorable risk factors	Yes, % pts	No, % pts	*p* value
All patients			
Performance status ≥2	18%	26%	.1898
Age ≥80 years	30%	25%	.8167
Comorbidities	10%	27%	.1954
Prior 2nd nonthoracic cancer	22%	26%	.8275
Prior lung surgery	42%	23%	.3026
Poor pulmonary function test or needs O_2	44%	21%	.1429
Prior lung cancer	31%	24%	.5232
Prior thoracic radiation therapy	25%	25%	.6068
Oligometastasis (stage IV)	38%	23%	.1640
Weight loss >10% in 3 months	18%	26%	.4949
Stage III-IV patients only			
Performance status ≥2	0%	24%	.0015
Age ≥80 years	33%	21%	.9049
Comorbidities	11%	23%	.4088
Prior 2nd nonthoracic cancer	33%	21%	.3897
Prior lung surgery	33%	20%	.4500
Poor pulmonary function test or needs O_2	33%	20%	.7701
Prior lung cancer	24%	21%	.6412
Prior thoracic radiation therapy	0%	23%	.9098
Oligometastasis (stage IV)	38%	19%	.0825
Weight loss >10% in 3 months	20%	22%	.6895

late toxicities was observed between the two risk groups. Both groups reported a high rate of grade 2 acute esophagitis (70% and 48%) with subtle differences attributed to lower use of concurrent chemoradiation and more stage II patients in the unfavorable cohort, but only 4% and 3% developed grade 3 esophagitis in the favorable and unfavorable groups, respectively. Late esophageal toxicities more than 6 months after treatment were similar between the two groups with 1 grade 3 or higher event in both groups. Symptomatic (grade 2 or higher) radiation pneumonitis within 6 months of treatment occurred in 14% of unfavorable-risk patients and 13% of favorable-risk patients, including 4 patients with grade 3 toxicity, 3 of whom had a prior history of lung surgery. Maximum late pulmonary toxicity reflects that only a couple of patients developed the majority of the grade 3 or higher pulmonary toxicities. In fact, only 1 favorable patient developed a grade 3 or higher late pulmonary complication, while 6 complained of a grade 2 or higher late complication under the setting of 3 having complained at baseline. Among the unfavorable patients, 6 complained of a late grade 3 toxicity (4 complained at baseline) and 24 complained of grade 2 toxicity (14 complained at baseline).

Discussion

The aim of this study was to investigate the impact of unfavorable risk factors on survival outcomes after PT in order to understand how revising trial eligibility may impact outcomes. To our best knowledge, this is the first report focusing on unfavorable-risk patients who underwent PT.

The present study found that the patient population receiving curative PT was much older than the patients in published major studies with photons [18–20]. First, there was no age limitation for participation in the outcomes tracking protocols at our institution. Furthermore, current Medicare insurance policies allow for PT to be more easily approved than other insurance carriers; therefore, most patients we treated were over 65 years old. In comparison,

Table 3. Acute and late toxicities distributed by grade before and after treatment among patients with and without unfavorable risk factors.

	Favorable risk									Unfavorable risk								
	Baseline			Acute ($n = 23$)			Late($n = 20$)			Baseline			Acute ($n = 67$)			Late ($n = 58$)		
Toxicity *Grade*	2	3	4/5	2	3	4/5	2	3	4/5	2	3	4/5	2	3	4/5	2	3	4/5
Chest pain	2	0	0	5	0	0	4	0	0	2	0	0	15	0	0	9	0	0
Cough	0	0	0	4	0	0	1	0	0	2	0	0	11	0	0	8	0	0
Dyspnea	1	0	0	3	0	0	3	0	0	5	3	0	13	4	0	9	2	1
Hypoxia	0	0	0	0	0	1	1	1	0	6	2	0	10	2	0	12	1	1
Pneumonitis	0	0	0	2	1	0	–	–	–	0	0	0	7	3	0	–	–	–
Esophagitis	0	0	0	16	1	0	–	–	–	0	0	0	32	2	0	–	–	–
Pleural effusion	0	0	0	–	–	–	1	0	0	0	0	0	–	–	–	5	2	1
Bronchial stricture	0	0	0	–	–	–	3	1	0	0	0	0	–	–	–	3	1	1
Esophageal stricture	0	0	0	–	–	–	2	1	0	0	0	0	–	–	–	6	1	0
Esophageal ulcer	0	0	0	–	–	–	2	0	0	0	0	0	–	–	–	1	1	0
Worst pulmonary toxicity	3	0	0	10	1	1	6	1	0	14	4	0	32	8	0	24	6	1
Worst esophageal toxicity	0	0	0	16	1	0	3	1	0	0	0	0	32	2	0	6	1	0

Acute toxicity was defined as an adverse event within 6 months since the start of proton therapy. Late toxicity occurred after 6 months from completing proton therapy.

although many clinical trials did not specify an age limit, strict inclusion criteria often excludes the elderly because of complicated pulmonary history or other comorbidities [21].

The present study included patients with oligometastases. Although oligometastasis is not a localized disease, mounting evidence has shown an improvement in survival by treating both primary and metastatic sites with curative intent, as reflected in the current National Comprehensive Cancer Network guideline update (version 3.2017). In one recent phase II study, patients with 3 or fewer extrathoracic metastases were randomized to aggressive local consolidative therapies to all involved sites or maintenance therapy. At least 74% of these patients had stage III intrathoracic disease. Patients who received local consolidative therapies achieved a PFS time of 11.9 months with curative therapies [22], which resembles the survival outcomes of stage III patients without metastases [18]. The definition of oligometastasis for NSCLC is debatable. In the recent literature [22–25], 5 or fewer metastases were commonly defined as oligometastatic disease, but patients with 4 to 5 metastases were severely underrepresented. Therefore, in the present study, patients with only 3 or fewer metastases were included in the analysis and considered as having an unfavorable risk factor.

OS from conventional fractionation was not significantly different between favorable-risk and unfavorable-risk patients (2-year overall survival, 52% and 43%). These rates are similar to those reported in the RTOG 0617 study of 58% for patients treated to 60 Gy and 43% for those treated to 74 Gy [18]. The RTOG 0617 study, however, further excluded patients with supraclavicular lymph node involvement and bilateral hilar involvement, who are included in the present study. There were noticeably more patients (25.7%) in the unfavorable-risk group who died with intercurrent disease than in the favorable-risk group (18.1%). However, the unfavorable-risk group included 8 patients (11.4%) with stage IIA and 4 patients (6%) with stage IIB disease, which have historically shown much better survival outcomes. The favorable group included only 1 stage IIB patient (4.8%). In a subgroup analysis excluding these stage II patients, OS was again found to be similar with or without unfavorable risk factors.

In the present study, among all 10 unfavorable risk factors, none impacted OS, including age. Although elderly patients are considered more vulnerable to toxicities from concurrent chemoradiation due to comorbidities and, therefore, are often excluded from major studies, a Japanese phase III trial randomizing patients with stage III unresectable NSCLC who are 71 years old or older to concurrent chemoradiation or radiotherapy alone found that the median OS time of 22.4 months was associated with concurrent chemoradiation [26]. A great majority of these patients had a PS of 0 to 1 (96.5%) and experienced minimal weight loss (84%). This study showed that older age alone would not necessarily be an independent adverse factor to survival.

In the present study, compromised lung conditions from previous chest irradiation, lung malignancy, surgery, and nonmalignant pathology were not found to be associated with poor survival outcome. Previous major trials excluded these patients partially from a concern for exacerbated pulmonary toxicity from radiotherapy. For example, investigators of the Radiation Therapy Oncology Group trial 0617 reported an 8.6% rate of grade 2 to 4 acute pneumonitis and a 10% rate of late pneumonitis in the standard-dose arm (60 Gy); the dose-escalated arm (74 Gy) resulted in a 10.7% rate of acute pneumonitis and 3.2% rate of late pneumonitis [18]. Considering that the dose-volume constraint for the lung was not mandated, this result is not surprising. In comparison, multiple dosimetric studies consistently show better reduction of radiation dose to lung tissue using PT [1]. In the present study, the rate of grade 2 or higher radiation pneumonitis was 15% for unfavorable-risk patients with compromised baseline lung conditions. Importantly, 3 of the 4 cases of grade 3 pneumonitis occurred among patients with prior lung surgery, 1 of whom also received prior chest irradiation for another malignancy. Therefore, prior lung cancer surgery may increase the risk of pneumonitis, although it does not significantly compromise survival.

Poor PS was not associated with OS, but in a subgroup analysis of patients with stage III-IV disease (oligometastasis), PS was adversely associated with poor survival outcome. This finding was consistent with other published reports on unfavorable-risk patients treated with photon therapy [11]. The present study showed that the median survival time

for patients with PS 2 or higher is 11 months compared to 23 months for other unfavorable-risk patients with PS 1 or lower. Hence, patient's PS may remain an important predictor of PT outcome and is probably an important inclusion/exclusion criteria for clinical trials.

A recent open-label single-arm phase II proton trial for stage III NSCLC reported similar survival outcomes and toxicity profiles compared to our present study [27]. Although not specifically designed for unfavorable risk patients, this trial included elderly patients (age >70) and those with less ideal PS (Karnofsky score 70–80). All enrolled patients completed concurrent chemoradiation. A median OS of 26.5 months with a recurrence pattern dominated by distant failure appeared similar to our findings in the present study. Despite a dose escalation to 74 Gy(RBE), a total 10% of their patients experienced grade 3 esophagitis and 12% had late grade 3 pneumonitis. In comparison, toxicities were quite tolerable for most unfavorable-risk patients in the present study.

The randomized phase II trial from M D Anderson Cancer Center (Houston, TX) comparing IMRT to proton therapy demonstrated similar median survival rates of 29.5 months for IMRT and 26 months for proton therapy [28]. While this study did not show an improvement in disease control and pneumonitis rates, the study suffered from a high proportion of patients who were randomized to one arm or another and who did not receive their appropriate treatment due to insurance barriers and patient preferences. Additionally, proton planning improved greatly during the second half of the trial enrollment with improvements in local control and pneumonitis rates; however, due to the Bayesian study design, patients were not equally randomized at that time. Thus, we will need to rely on the outcomes of NRG 1308 to most clearly define whether a benefit exists in managing locally advanced NSCL patients with proton therapy.

The present study has several limitations. Although data were collected prospectively, it is a retrospective analysis. The favorable-risk group was likely underpowered to fully analyze the survival difference between the two risk groups. In addition, a guideline for patient selection for PT was only recently published and yet to be fully utilized by the medical community or insurance carriers [5]. Therefore, selection bias was inherent in the present study. Nevertheless, the prevalence of unfavorable-risk patients referred for PT is unlikely to change. To the best of our knowledge, this is the first study to report the PT outcomes in this group of patients and results compared favorably to previous photon therapy-based studies [12–15]. A multi-institutional cohort study would give further strength to the survival analysis, but a randomized trial that includes these unfavorable-risk patients would be the best study design to test the hypothesis that most unfavorable risk factors, other than PS, do not reduce patients' survival and toxicities are acceptable. Finally, this study was conducted prior to the establishment of immunotherapy as standard-of-care consolidation among patients with stage III NSCLC. Thus, we must wait for the results of NRG 1308, which allows consolidation immunotherapy, to understand whether the same benefit exist for patients receiving proton therapy [29].

Conclusion

Most patients treated with PT for LA-NSCLC have unfavorable risk factors, presenting a major challenge to current PT trials that exclude these patients. The present study showed that these patients had similar OS to favorable-risk patients with comparable toxicities. Enrollment in future clinical trials may improve if eligibility is less restrictive.

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