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Clinical Outcomes Following Proton and Photon SBRT for Early-Stage Lung Cancer

Bong Kyung Bae, Kyungmi Yang, Jae Myung Noh, Hongryull Pyo, Yong Chan Ahn*

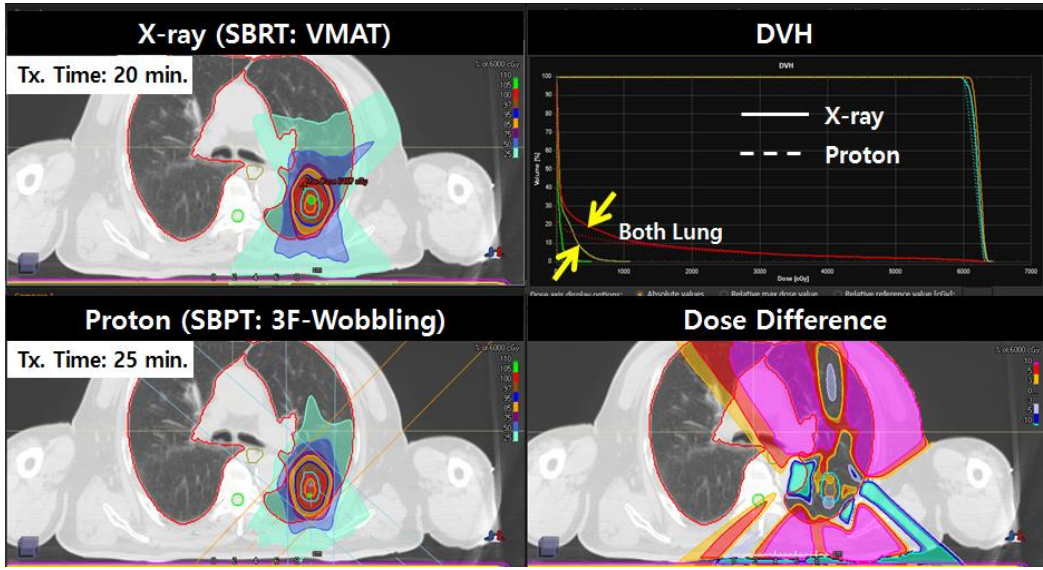
Department of Radiation Oncology, Samsung Medical Center, Seoul, Korea

Background

- Stereotactic body radiation therapy (SBRT) for early-stage lung cancer
  - Standard of care for patients who are medically unfit for surgery

- Proton-SBRT
  - Can reduce low dose irradiated area
  - However, benefit is clinically insignificant for small target such as early-stage lung cancer

- Potentially beneficial situations
  - Centrally located tumor / Adjacent to chest wall / Large tumor / Poor baseline lung function



Purpose

- **Paucity of clinical data comparing two treatment modalities**
- **Present the clinical outcomes following proton or photon SBRT**

Methods

- Patients
  - cT1-2N0M0 by 8th AJCC TNM staging for NSCLC
  - Proton or photon SBRT with 60 Gy in 4 fractions (BED_{10} = 150 Gy)
  - 202 patients (photon - 168 patients / proton – 34 patients)

- SBRT
  - ITV: GTV of treated phases
  - CTV: ITV + 0-5mm
  - PTV: CTV + 5mm

Methods

- Assessments
  - Clinical outcomes
    - Local control, Progression free survival, Cause specific survival, Overall survival
  - Toxicity
    - Radiation pneumonitis, Musculoskeletal, Skin
  - Propensity score matching
    - 2:1 matching
    - T stage, COPD, ILD, baseline FEV1, baseline DLCO

Clinical & treatment characteristics

Variables	Entire Cohort (N = 202)				Matched Cohort (N = 74)		
	Overall (n = 202)	Photon SBRT (n = 168)	Proton SBRT (n = 34)	p value	Photon SBRT (n = 46)	Proton SBRT (n = 28)	p value
Age (years, median, IQR)	75 (70–79)	76 (70–79)	72.5 (68–76)	0.288	75 (70–78)	73 (68–76)	0.411
Sex				0.963			0.667
Male	161 (79.7%)	134 (79.8%)	27 (79.4%)		38 (82.6%)	22 (78.6%)	
Female	41 (20.3%)	34 (20.2%)	7 (20.6%)		8 (17.4%)	6 (21.4%)	
ECOG PS				0.151			0.113
0–1	167 (82.7%)	136 (81.0%)	31 (91.2%)		35 (76.1%)	26 (92.9%)	
2-	35 (17.3%)	32 (19.0%)	3 (8.8%)		11 (23.9%)	2 (7.1%)	
Pathology				0.241			0.589
Adenocarcinoma	77 (38.1%)	66 (39.3%)	11 (32.4%)		16 (34.8%)	10 (35.7%)	
Squamous cell carcinoma	47 (23.3%)	38 (22.6%)	9 (26.5%)		12 (26.1%)	8 (28.6%)	
Other	13 (6.4%)	13 (7.7%)	0 (0.0%)		3 (6.5%)	0 (0.0%)	
Unproven	65 (32.2%)	51 (30.4%)	14 (41.2%)		15 (32.6%)	10 (35.7%)	
Location				0.176			0.479
LLL	34 (16.8%)	25 (14.9%)	9 (26.5%)		5 (10.9%)	7 (25.0%)	
LUL	55 (27.2%)	48 (28.6%)	7 (20.6%)		12 (26.1%)	6 (21.4%)	
RLL	41 (20.3%)	31 (18.5%)	10 (29.4%)		11 (23.9%)	8 (28.6%)	
RML	7 (3.5%)	6 (3.6%)	1 (2.9%)		3 (6.5%)	1 (3.6%)	
RUL	65 (32.2%)	58 (34.5%)	7 (20.6%)		15 (32.6%)	6 (21.4%)	
Tumor size (mm, mean ± SD)	21.77 ± 8.52	21.62 ± 8.22	22.50 ± 10.00	0.584	22.00 ± 9.60	23.32 ± 9.96	0.573
T stage				0.178			0.667
T1	170 (84.2%)	144 (85.7%)	26 (76.5%)		38 (82.6%)	22 (78.6%)	
T2	32 (15.8%)	24 (14.3%)	8 (23.5%)		8 (17.4%)	6 (21.4%)	
COPD	85 (42.1%)	61 (36.3%)	24 (70.6%)	**<0.001**	25 (54.3%)	18 (64.3%)	**0.401**
COPD GOLD grade				**0.001**			**0.645**
Grade 1	22 (10.8%)	18 (10.7%)	4 (11.8%)		6 (13.0%)	3 (10.7%)	
Grade 2	46 (22.7%)	33 (19.6%)	13 (38.2%)		13 (28.3%)	12 (42.9%)	
Grade 3	16 (7.9%)	9 (5.4%)	7 (20.6%)		6 (13.0%)	3 (10.7%)	
Grade 4	1 (0.5%)	1 (0.6%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
ILD	25 (12.4%)	18 (10.7%)	7 (20.6%)	0.149	9 (19.6%)	6 (21.4%)	0.847
ILD GAP stage				0.065			0.845
Stage 1	6 (3.0%)	6 (3.6%)	0 (0.0%)		1 (2.2%)	0 (0.0%)	
Stage 2	17 (8.4%)	11 (6.5%)	6 (17.7%)		7 (15.2%)	5 (17.9%)	
Stage 3	2 (1.0%)	1 (0.6%)	1 (2.9%)		1 (2.2%)	1 (3.6%)	

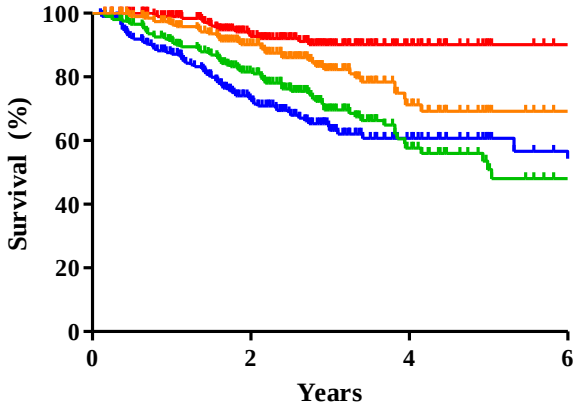
Variables	Entire Cohort (N = 202)				Matched Cohort (N = 74)		
	Overall (n = 202)	Photon SBRT (n = 168)	Proton SBRT (n = 34)	p value	Photon SBRT (n = 46)	Proton SBRT (n = 28)	p value
Baseline FEV1 (% predicted, mean ± SD)	77.85 ± 24.74	80.19 ± 25.24	67.38 ± 19.44	**0.006**	71.46 ± 22.71	71.25 ± 16.45	**0.967**
Baseline DLCO (% predicted, mean ± SD)	68.98 ± 22.82	72.42 ± 21.87	54.52 ± 21.29	**<0.001**	60.28 ± 17.51	57.68 ± 21.40	**0.571**
Operability				**<0.001**			**0.001**
Operable	47 (23.3%)	47 (28.0%)	0 (0.0%)		13 (28.3%)	0 (0.0%)	
Inoperable	155 (76.7%)	121 (72.0%)	34 (100.0%)		33 (71.7%)	28 (100.0%)	
SBRT technique							
3D-CRT	130 (64.4%)	130 (77.4%)	0 (0.0%)		29 (63.0%)	0 (0.0%)	
IMRT	38 (18.8%)	38 (22.6%)	0 (0.0%)		17 (37.0%)	0 (0.0%)	
Passive scattering	4 (2.0%)	0 (0.0%)	4 (11.8%)		0 (0.0%)	4 (14.3%)	
IMPT	30 (14.8%)	0 (0.0%)	30 (88.2%)		0 (0.0%)	24 (85.7%)	
Respiratory motion control				<0.001			<0.001
Free breathing	187 (92.6%)	167 (99.4%)	20 (58.8%)		46 (100.0%)	16 (57.1%)	
Gating	1 (0.5%)	0 (0.0%)	1 (2.9%)		0 (0.0%)	1 (3.6%)	
DIBH	14 (6.9%)	1 (0.6%)	13 (38.2%)		0 (0.0%)	11 (39.3%)	
Dosimetric parameters							
ITV (cc, mean ± SD)	14.44 ± 18.73	13.39 ± 15.07	19.44 ± 30.55	0.274	12.48 ± 13.63	19.68 ± 32.38	0.189
PTV (cc, mean ± SD)	38.57 ± 34.74	36.00 ± 29.07	51.28 ± 53.62	0.115	34.38 ± 27.77	52.61 ± 55.59	0.064
Lung V_{40Gy} (%, mean ± SD)	4.07 ± 2.66	4.06 ± 2.72	4.12 ± 2.38	0.907	4.16 ± 3.68	4.49 ± 2.40	0.674
Lung V_{20Gy} (%, mean ± SD)	8.74 ± 4.33	8.90 ± 4.45	7.93 ± 3.61	0.233	9.28 ± 5.51	8.51 ± 3.45	0.513
Lung V_{10Gy} (%, mean ± SD)	13.78 ± 5.52	14.28 ± 5.52	11.33 ± 4.90	**0.004**	14.72 ± 6.09	12.07 ± 4.68	**0.053**
Lung V_{5Gy} (%, mean ± SD)	20.40 ± 7.90	21.69 ± 7.61	14.04 ± 6.09	**<0.001**	22.02 ± 7.79	14.90 ± 5.86	**<0.001**

- Patients with poor baseline lung function were more allocated to proton SBRT

- Low dose irradiated volume was significantly smaller for proton SBRT, both entire cohort and matched cohort

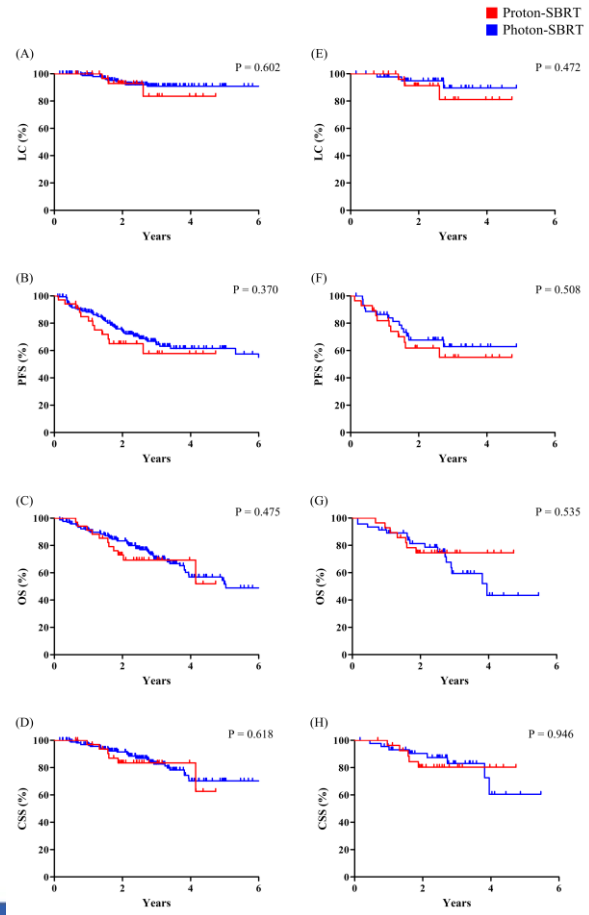
Survivals

- Overall entire cohort
  - Favorable clinical outcomes



Survivals	2-year	5-year
LC	92.7%	90.1%
PFS	72.8%	60.7%
OS	81.5%	50.8%
CSS	90.1%	69.2%

- Comparison between treatment modalities (Proton vs. Photon)
  - No significant difference in clinical outcomes



Survivals		Entire Cohort (N=202)			Matched Cohort (N=74)		
		Photon SBRT (*n*=168)	Proton SBRT (*n*=34)	*p* value	Photon SBRT (*n*=46)	Proton SBRT (*n*=28)	*p* value
LC	2-year	92.8%	92.8%	0.602	94.9%	91.3%	0.472
	5-year	90.8%	83.6%		89.6%	81.1%	
PFS	2-year	74.4%	65.0%	0.370	67.7%	61.9%	0.508
	5-year	61.6%	57.8%		62.9%	55.0%	
OS	2-year	83.3%	73.1%	0.475	81.3%	74.5%	0.535
	5-year	51.7%	51.9%		43.4%	74.5%	
CSS	2-year	91.5%	83.5%	0.618	90.4%	80.4%	0.946
	5-year	70.3%	62.6%		60.5%	80.4%	

Toxic events

- Comparable toxic events

- However, though statistically insignificant, proportion of radiation pneumonitis was reversed in the matched cohort, favoring proton SBRT

	Entire Cohort (N=202)							Matched Cohort (N=74)						
	Photon SBRT (*n*=168)			Proton SBRT (*n*=34)			*p* value	Photon SBRT (*n*=46)			Proton SBRT (*n*=28)			*p* value
	≥ G2	≥ G3	G4	≥ G2	≥ G3	G4		≥ G2	≥ G3	G4	≥ G2	≥ G3	G4	
Radiation pneumonitis	33 (19.6%)	20 (11.9%)	0 (0.0%)	9 (26.4%)	6 (17.6%)	0 (0.0%)	0.371*	14 (30.4%)	11 (23.9%)	0 (0.0%)	6 (21.4%)	3 (10.7%)	0 (0.0%)	0.398*
Musculoskeletal	23 (13.7%)	6 (3.6%)	0 (0.0%)	2 (5.9%)	0 (0.0%)	0 (0.0%)	0.264**	7 (15.2%)	1 (2.2%)	0 (0.0%)	2 (7.1%)	0 (0.0%)	0 (0.0%)	0.285**
Skin	7 (4.2%)	4 (2.4%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.604**	3 (6.6%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.468**

Toxic events

- Binary logistic regression analysis of G3 radiation pneumonitis
  - Significant risk factors in UVA
    - Poor performance status, inoperable status, poor baseline FEV1, poor baseline DLCO
  - Significant risk factors in MVA
    - Poor performance status, poor baseline DLCO

Variables	Univariable		Multivariable	
	OR (95 % CI)	*p*-value	OR (95 % CI)	*p*-value
Sex (Male)	7.606 (1.002-57.709)	0.054		
Age (> 70)	1.400 (0.498-3.934)	0.523		
ECOG PS (2 or higher)	**3.054 (1.231-7.580)**	**0.016**	**3.162 (1.215-8.226)**	**0.018**
Smoking History (Yes)	2.349 (0.669-8.252)	0.183		
COPD (Yes)	1.444 (0.633-3.297)	0.383		
ILD (Yes)	2.479 (0.886-6.937)	0.084		
T stage (T2)	1.731 (0.635-4.718)	0.284		
Operability (Inoperable)	**8.846 (1.165-67.144)**	**0.035**	**7.204 (0.929-55.863)**	**0.059**
Baseline FEV1 (<40%)	**3.818 (1.062-13.731)**	**0.040**		
Baseline DLCO (<40%)	**4.980 (1.636-15.162)**	**0.005**	**3.995 (1.259-12.675)**	**0.019**
Respiratory motion control (No)	0.611 (0.162-2.310)	0.468		
Treatment modality (Photon)	0.631 (0.233-1.710)	0.365		

Conclusion

- **Proton SBRT significantly reduces low dose irradiated volume**
- **Proton and photon SBRT resulted in comparable oncologic outcomes with similar toxicity profiles**
  - Though insignificant, the proportion of radiation pneumonitis was reversed after matching, favoring proton SBRT
- **Proton SBRT could be considered for patients at high-risk of radiation pneumonitis**
  - Patients with poor performance status or poor baseline DLCO