Damage Assessment of Rat Lung Tissue After Irradiation at Different Positions of Proton Spread-out Bragg Peak

Xiaoxin ZUO Jian ZHU*

Cancer Hospital of Shandong First Medical University

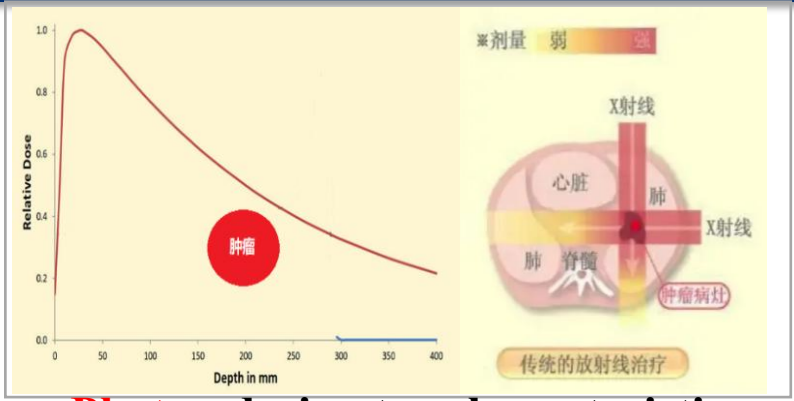
zhujian@sdfmu.edu.cn

The 5th Annual Conference of the Asia-Oceania Particle Therapy Co-Operative Group
Advancing Particle Therapy with Greater Precision and Image-Guidance
7-9 November 2025 in Hong Kong

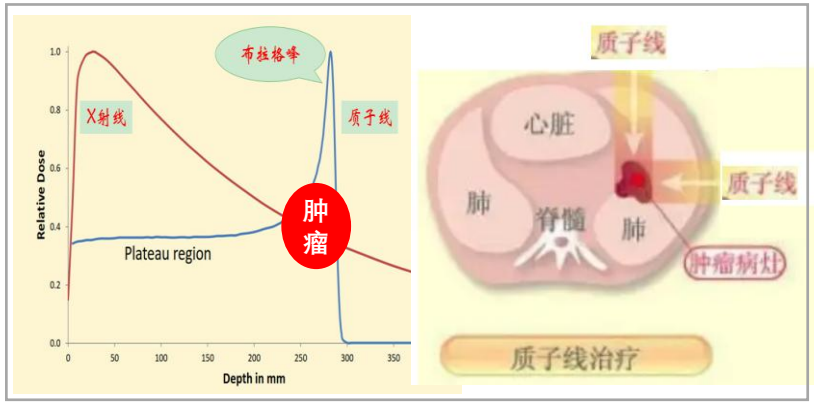
CONTENTS

CONTENTS

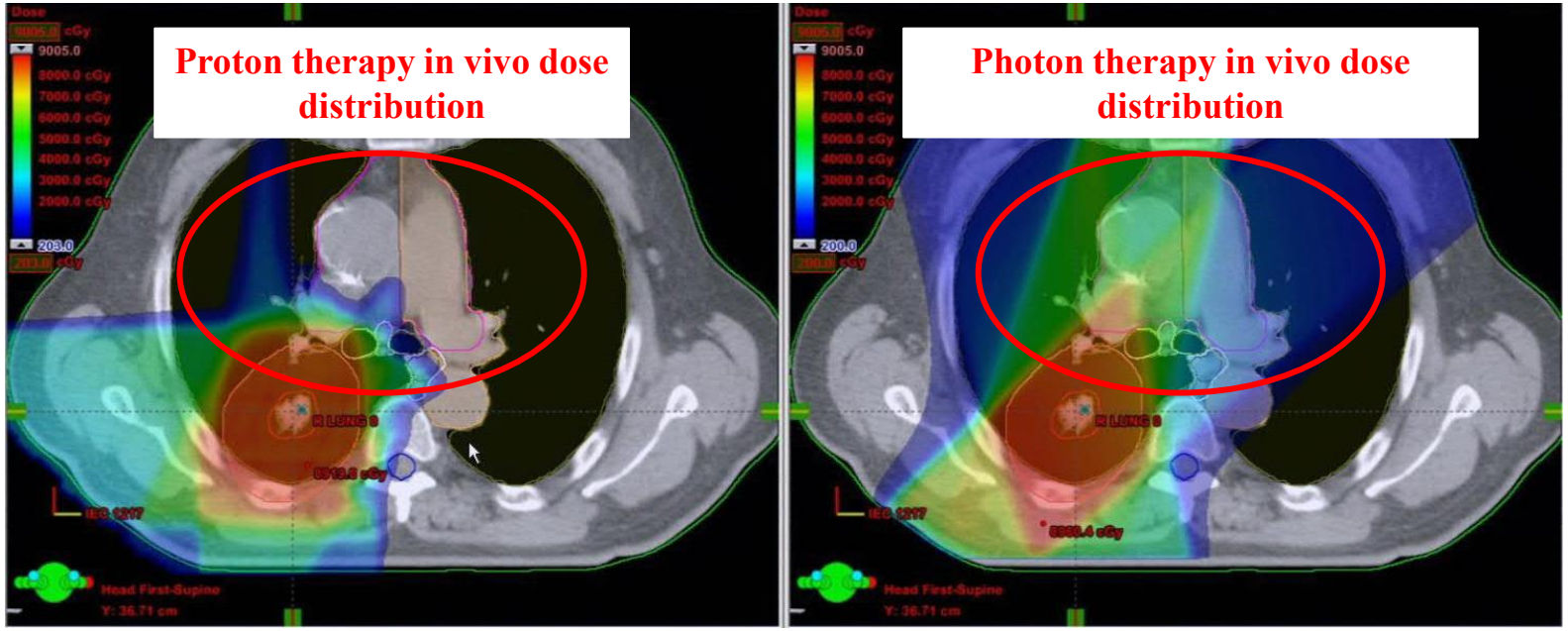
Background: Advantages of proton radiotherapy



Photon dosimetry characteristics



Proton dosimetry characteristics



Physical advantages of proton radiation dose distribution:

1. The dose is released only at the tumor site

2. The proton beam covers the tumor, and the anterior and posterior organs are almost unirradiated

Biological advantage of proton radiation dose distribution:

10% higher bioavailability than photon

Background: Relative biological effects (RBE) of proton radiotherapy

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 53, No. 2, pp. 407–421, 2002

0360-3016/02/$–see front matter

PII S0360-3016(02)02754-2

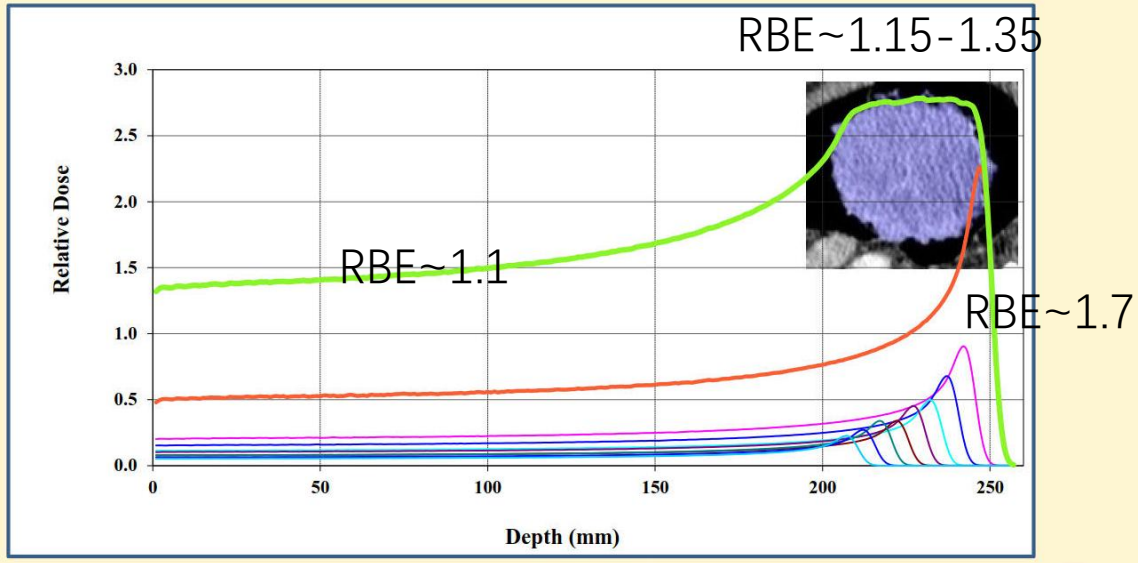
BIOLOGY CONTRIBUTION

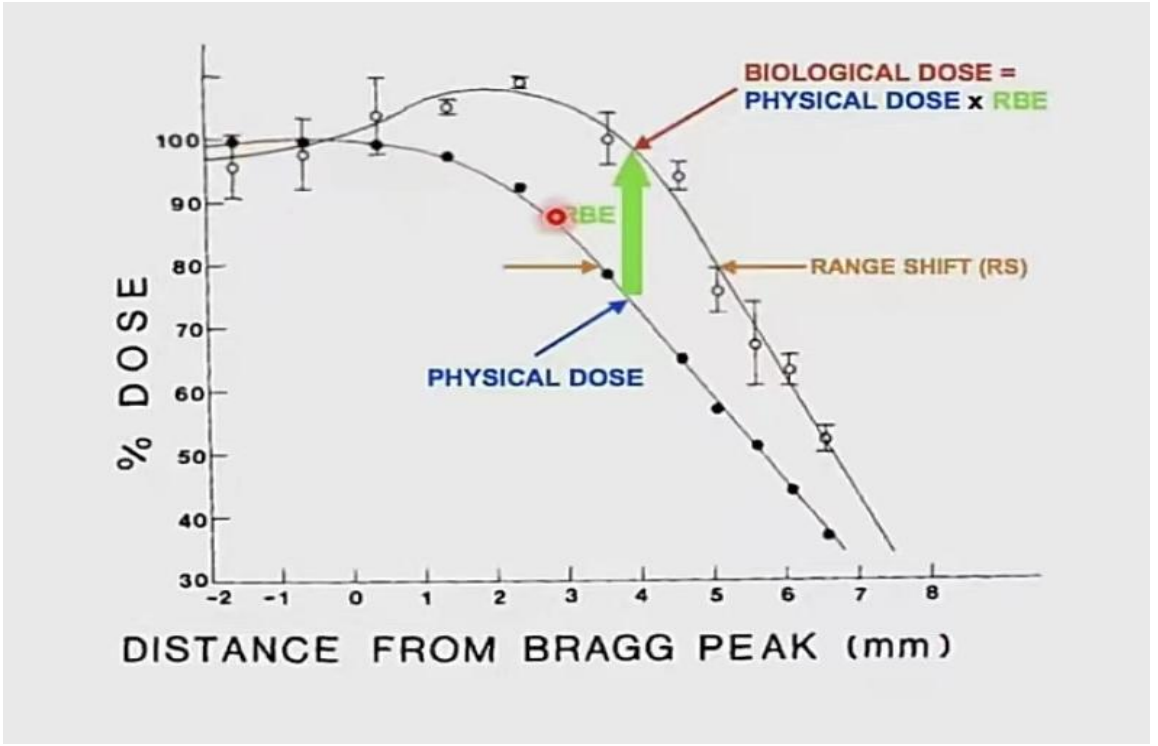
RELATIVE BIOLOGICAL EFFECTIVENESS (RBE) VALUES FOR PROTON BEAM THERAPY

HARALD PAGANETTI, PH.D.,*† ANDRZEJ NIEMIERKO, PH.D.,*† MAREK ANCUKIEWICZ, PH.D.,*† LEO E. GERWECK, PH.D.,*† MICHAEL GOITEIN, PH.D.,*† JAY S. LOEFFLER, M.D.,*† AND HERMAN D. SUIT, M.D., D.PHIL.*†

*Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA; †Harvard Medical School, Boston, MA

When the beams are summed the create a uniform dose distribution across the tumor depth: the "Spread Out Bragg Peak" or SOBP





Biological dose = RBE × physical dose

$$RBE = \frac{D_{ref}}{D_{test}}$$

D_{ref}: The dose of X-rays required to produce specific biological effects

D_{test}: The dose of the measured radiation required to achieve the same biological effect

Background: Proton RBE assay experiment

Int. J. Radiation Oncology Biol. Phys., Vol. 53, No. 2, pp. 407–421, 2002

0360-3016/02/$–see front matter
PII S0360-3016(02)02754-2

BIOLOGY CONTRIBUTION

RELATIVE BIOLOGICAL EFFECTIVENESS (RBE) VALUES FOR PROTON BEAM THERAPY

HARALD PAGANETTI, PH.D.,*† ANDRZEJ NIEMIERKO, PH.D.,*† MAREK ANCUKIEWICZ, PH.D.,*† LEO E. GERWECK, PH.D.,*† MICHAEL GOITEIN, PH.D.,*† JAY S. LOEFFLER, M.D.,*† AND HERMAN D. SUIT, M.D., D.PHIL.*†

*Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA; †Harvard Medical School, Boston, MA

Table A2. RBE values *in vivo* obtained in clinical beams

Biological system	Endpoint	Beam (MeV)	SOBP (cm)	γ-Dose/Fract (Gy)	RBE plateau	RBE SOBP prox	RBE SOBP mid	RBE SOBP distal	RBE distal fall-off	Reference	Ref.
Normal mouse lung	LD_{50} / 180 d	160	10	12.6			0.73			^{60}Co	(37)
				13.0			1.08				
				15.2			1.04				
Mouse lens	MCD_{50}/7 mo			9.9			1.02				
Intest. crypt reg. in mice	Inactivation	200	7	13.6	1.14; 1.18	1.23	1.15	1.26		^{60}Co	(32)
				14.4	1.1; 1.16	1.18	1.12	1.23			
				15.1	1.07; 1.14	1.14	1.09	1.21			
Mouse legs	Acute skin reaction	—	—	21.9			0.89			290 kVp	(71)
		250	6				0.74				
Mouse legs	Acute skin reaction	250	6	10.9			0.75			300 kVp	(72)

in vitro RBE determination experiment			
cell	biological endpoint	SOBP (cm)	conclusion
1 v79 cells	cell clone survival	7	RBE increases from 1.24 at the SOBP entrance region to 1.32 at the distal end of the SOBP
2 melanoma cells	cell clone survival	12	the distal RBE of the SOBP is 1.19
3 pulmonary fibroblast	cell clone survival		platform region, the RBE at the distal end of the SOBP increased by 18.3%
3 glioma cells	cell clone survival		compared with the SOBP platform region, the RBE at the distal end of the SOBP increased by 17.9%.
4 U2OS cells	cell clone survival	10	SOBP distal RBE is 4 three hours after irradiation and 6 twenty-four hours after irradiation.

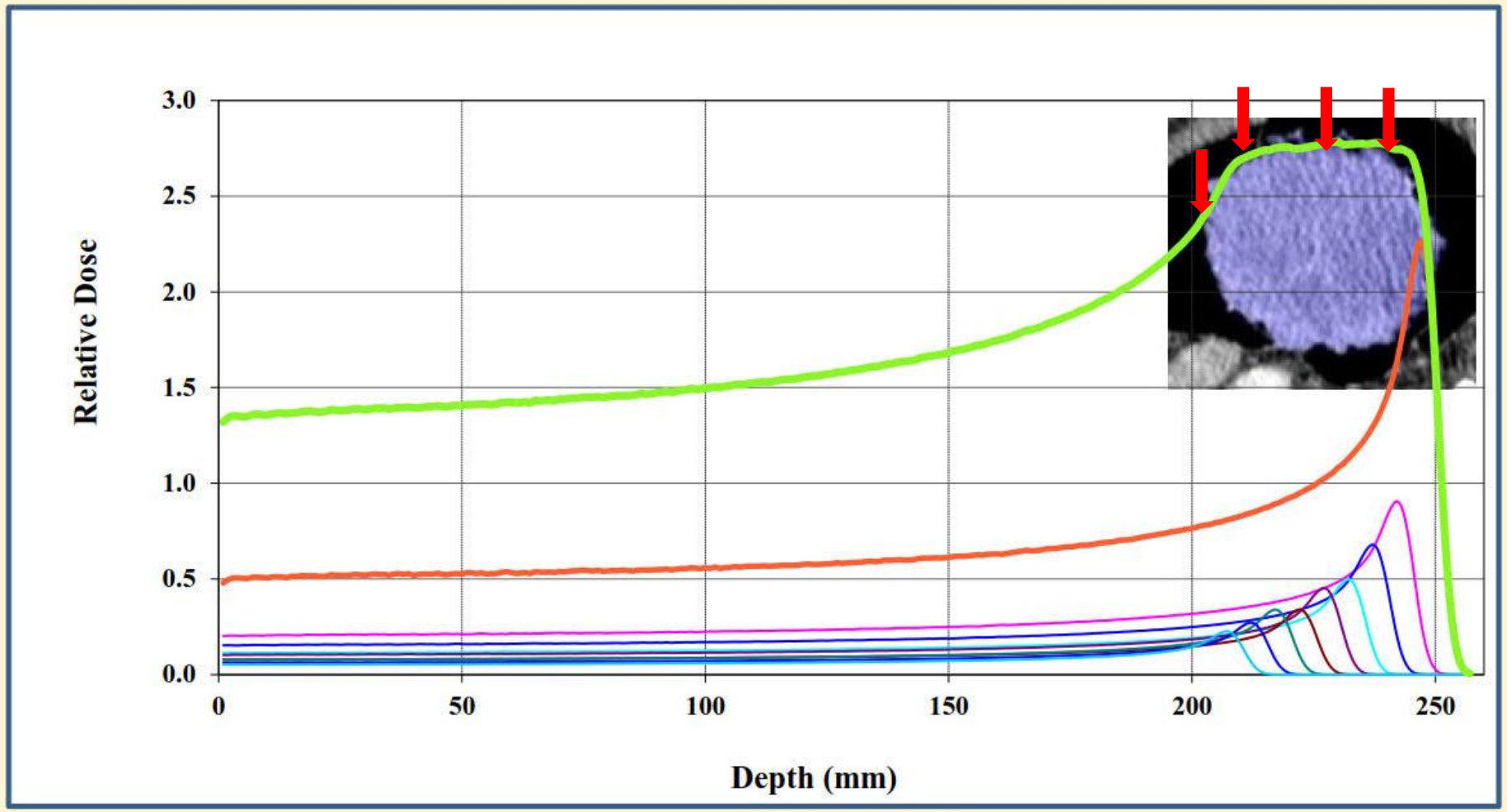
1.Slabbert JP, Jones DTL, Schreuder N, et al. Variations in biological effectiveness with depth in a 200 MeV proton beam. NAC Annual Report 1994:103–106.

2.Courdi A, Brassart N, Herault J, et al. The depth-dependent radiation response of human melanoma cells exposed to 65 MeV protons. Br J Radiol 1994;67:800 – 804.

3.Chaudhary P, Marshall TI, Perozziello FM, et al. Relative biological effectiveness variation along monoenergetic and modulated Bragg peaks of a 62-MeV therapeutic proton beam: a preclinical assessment. Int J Radiat Oncol Biol Phys. 2014;90(1):27-35. doi:10.1016/j.ijrobp.2014.05.0103.

4.Cuaron JJ, Chang C, Lovelock M, et al. Exponential Increase in Relative Biological Effectiveness Along Distal Edge of a Proton Bragg Peak as Measured by Deoxyribonucleic Acid Double-Strand Breaks. Int J Radiat Oncol Biol Phys. 2016;95(1):62-69. doi:10.1016/j.ijrobp.2016.02.018

Scientific question: Are there differences in damage caused at different positions in SOBP in lung tissue?



CONTENTS

Experimental Materials and methods: Experimental verification of the accuracy of proton beam irradiation in small animals

1. Irradiation plan verification

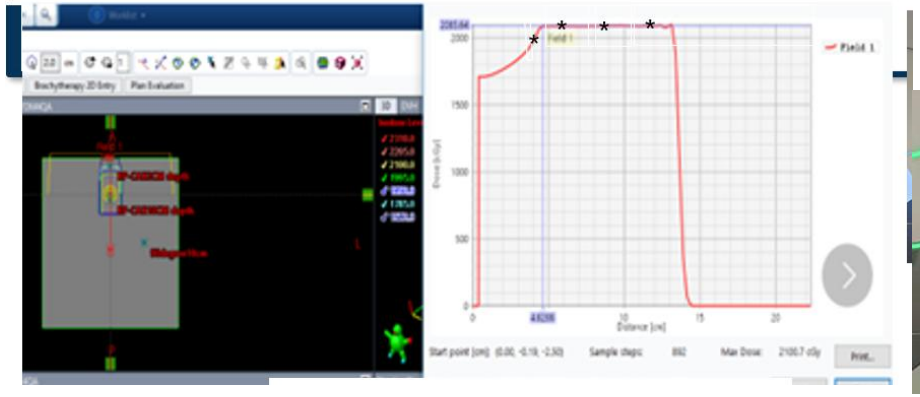
PPC05 Ionization chamber → Absolute dose

Films → Flatness and symmetry

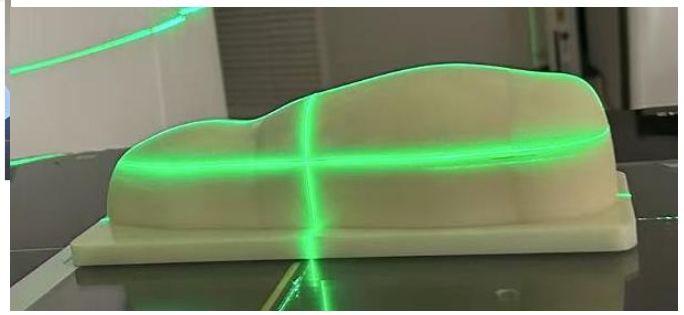
Zebra Ionization chamber → Range

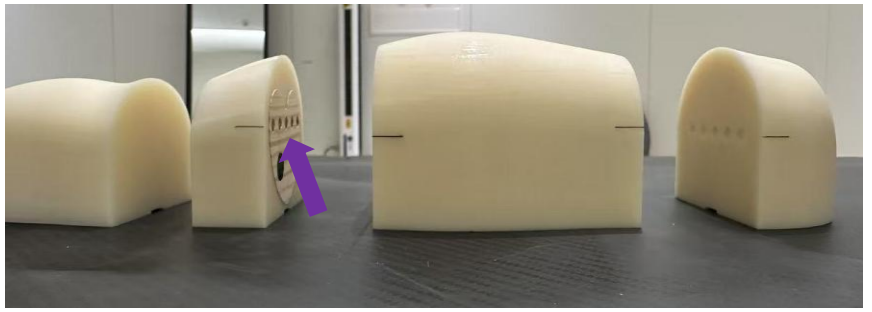
2.Verify dose deposition in lung tissue during proton irradiation using a thermoluminescence dosimeter

Screen out dosage tablets with dispersibility <3% using the Probeam accelerator and repeat 3 times. → Calibrate from 0 Gy to 22 Gy and determine the calibration factor. → Place the dosimeter into the rat model and position it according to the actual irradiation plan. → Read the measurement after 24 hours of stabilization → Compare with the planned system readings



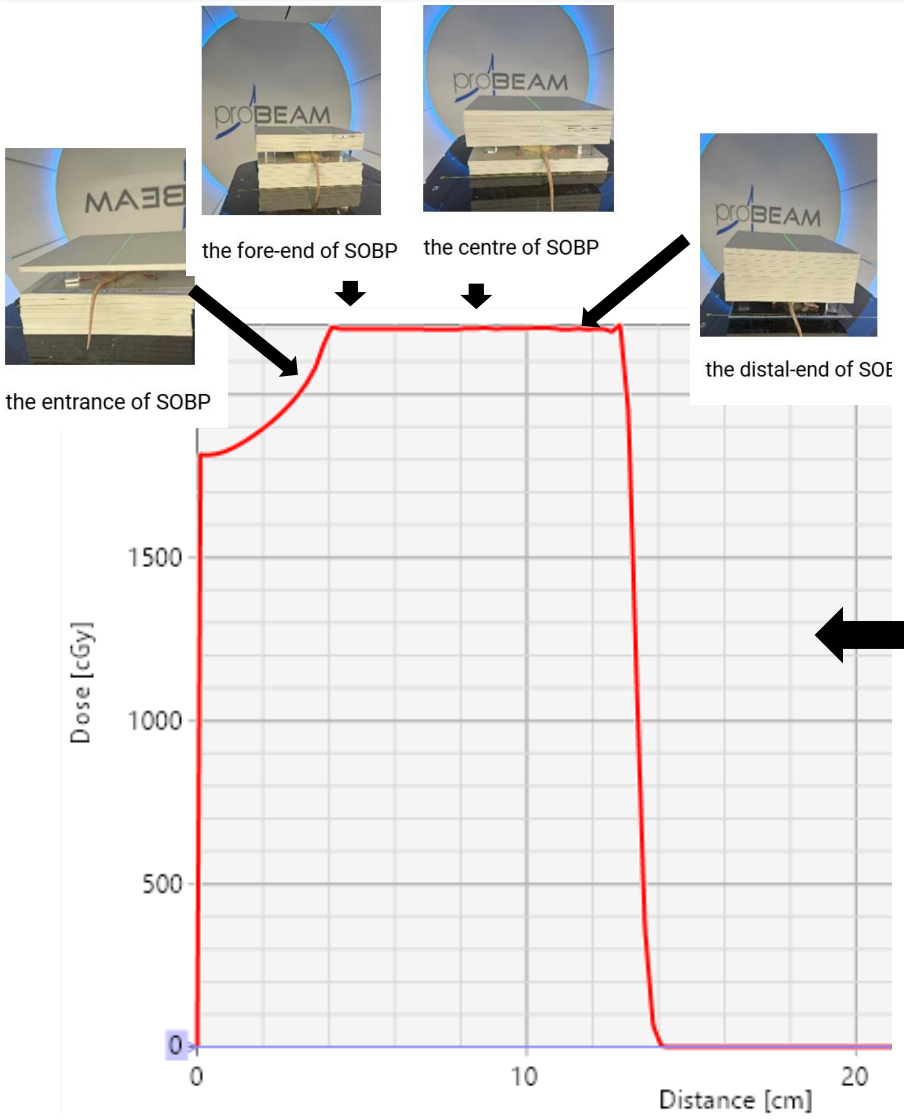
SOBP of water-equivalent depth





Rat model

Experimental Materials and methods : Animal experiments to observe photon and proton damage

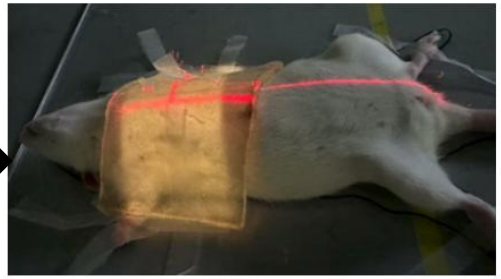


Female SD rats, 6 / group

Proton: Irradiation at different positions of SOBP

Photon

Assessment of inflammatory responses at different positions of the proton SOBP and photon under the same dose irradiation



photon

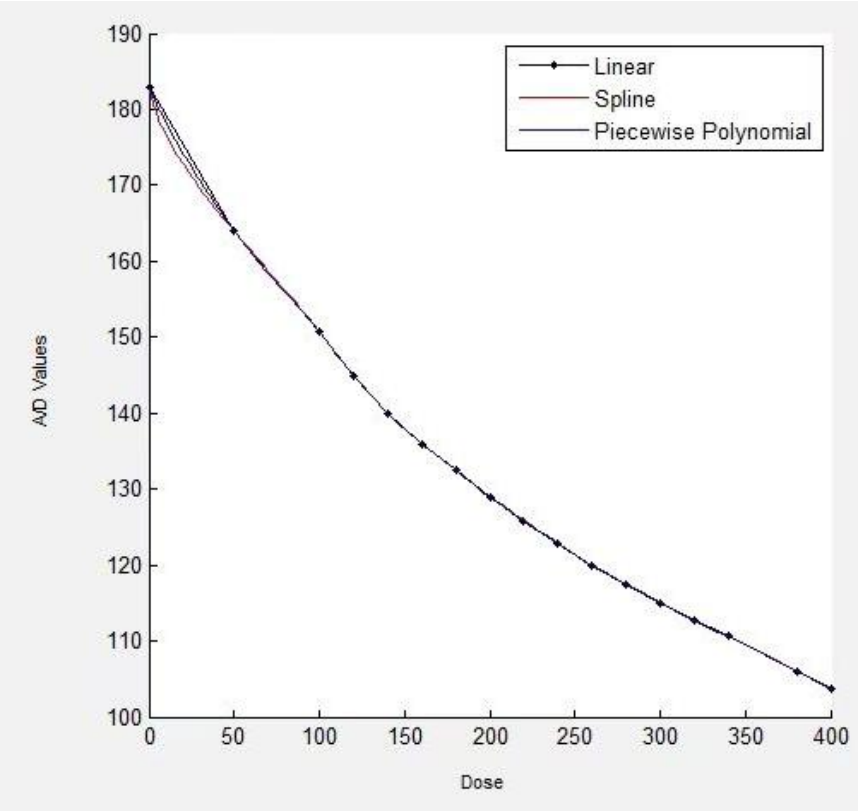
CONTENTS

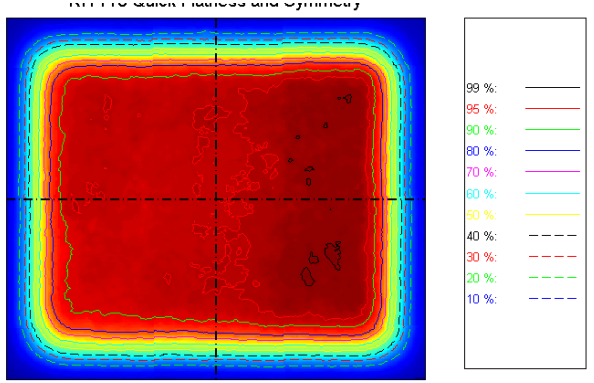
Result 1: The dose can be accurately deposited into the lung tissue

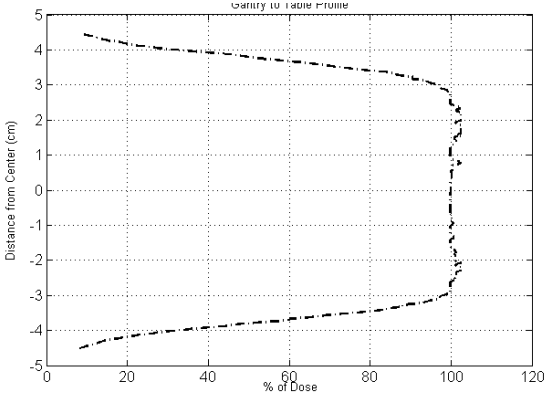
1. PPC05 ionization chamber measurement results: deviation between planned and measured doses <3%.

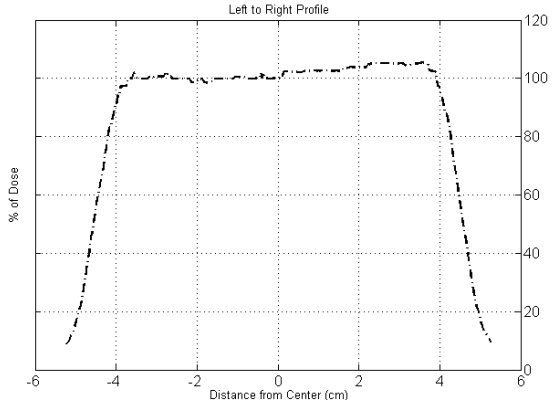
planned system measurement value(Gy)	measured value(Gy)	error
2.02	2.068、2.066、2.047	2.2%、2.3%、1.3%

2. Film measurement results: deviations in flatness and symmetry were approximately 3%.









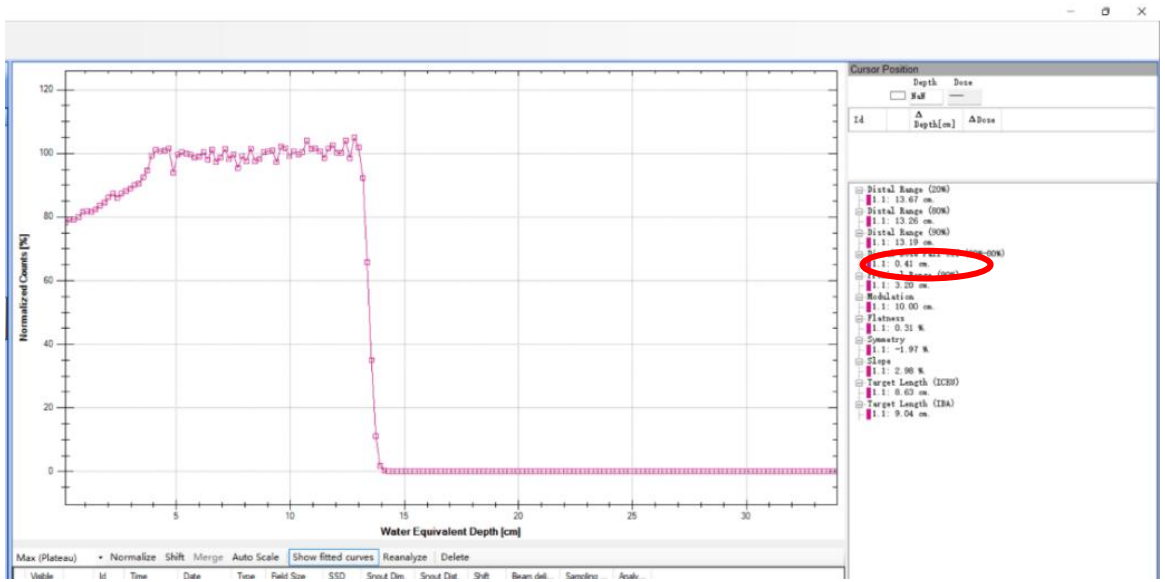
Facility:
File Name: D:\proton\N film\xN UP6001.tif
Cal. File: C:\Users\user\Desktop\zxx bd proton.cal
File Date: 22-一月-2025 11:28:42

Left to Right Profile
Central Axis Value: 719.9629 cGy
FWHM = 9.0716 cm
Flatness(TG45) = 3.3765 %
Symmetry(TG45) =-4.994 %
Left Penumbra(20-80 %) = 8.1139 mm
Right Penumbra(20-80 %) = 7.4083 mm

Table to Gantry Profile
Central Axis Value: 719.9629 cGy
FWHM = 7.5634 cm
Flatness(TG45) = 3.0243 %
Symmetry(TG45) =0.8238 %
Left Penumbra(20-80 %) = 7.7611 mm
Right Penumbra(20-80 %) = 8.1139 mm

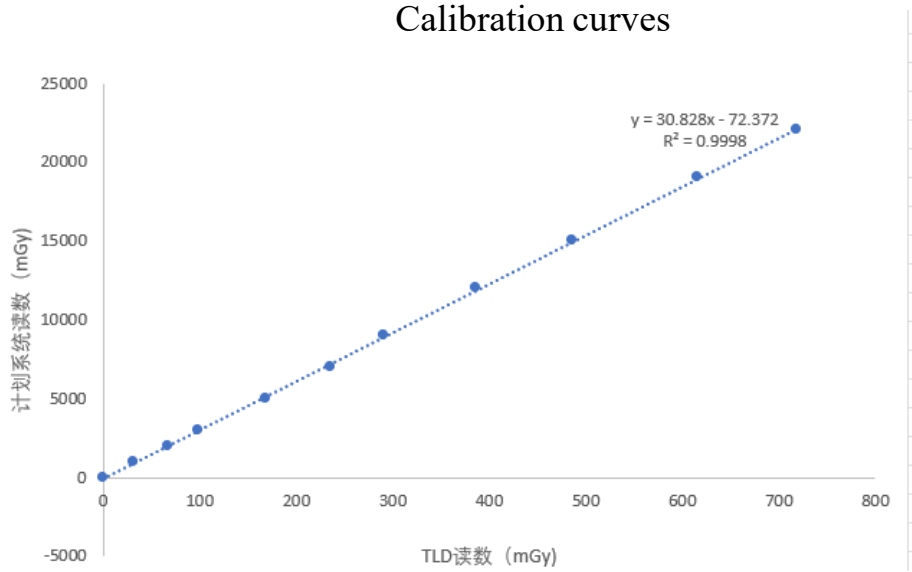
Result 1: The dose can be accurately deposited into the lung tissue

3. Zebra ionization chamber measurement results: range deviation at the SOBP entrance and distal end was 2–3 mm.



	planning system(cm)	ionization chamber measurement(cm)	difference(cm)
distal range	12.966	13.19	0.2
proximal range	2.843	3.2	0.35

4. Rat model measurement results: deviation from the planning system <3%.

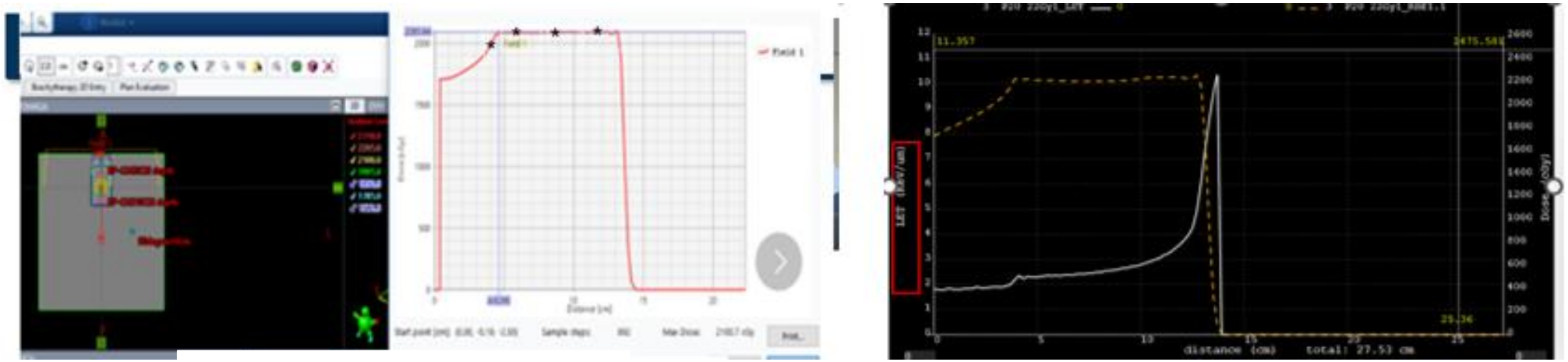


given dose(Gy)	measured value(Gy)	*calibration factor(cm)	planned measurement(cm)	error
16	506.6	15545.09	15991.6	2.70%
	516	15834.876		0.98%
	512.8	15736.2264		1.60%
20	631.9	19407.84	19991	2.90%
	642.7	19740.78		1.20%
	637.8	19589.73		2%

The dose we expect to achieve can be accurately achieved in rats

Result 2: LET corresponding to SOBP

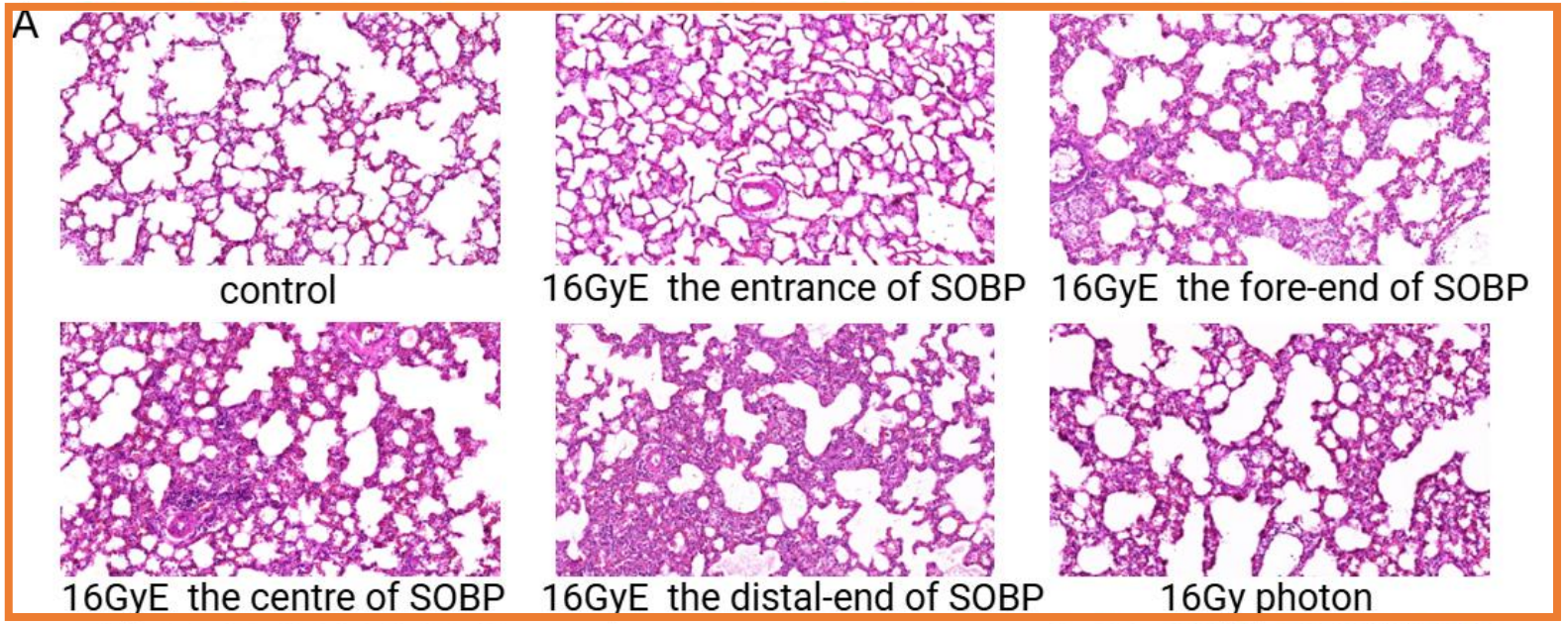
Using the Moriak Proton 1.0 software （Hefei Huiguang Healing Technology Co., Ltd） to analyze the irradiation plan, we found that with the increase of irradiation depth, the LET also increased, with a more significant rise at the distal end of the SOBP.



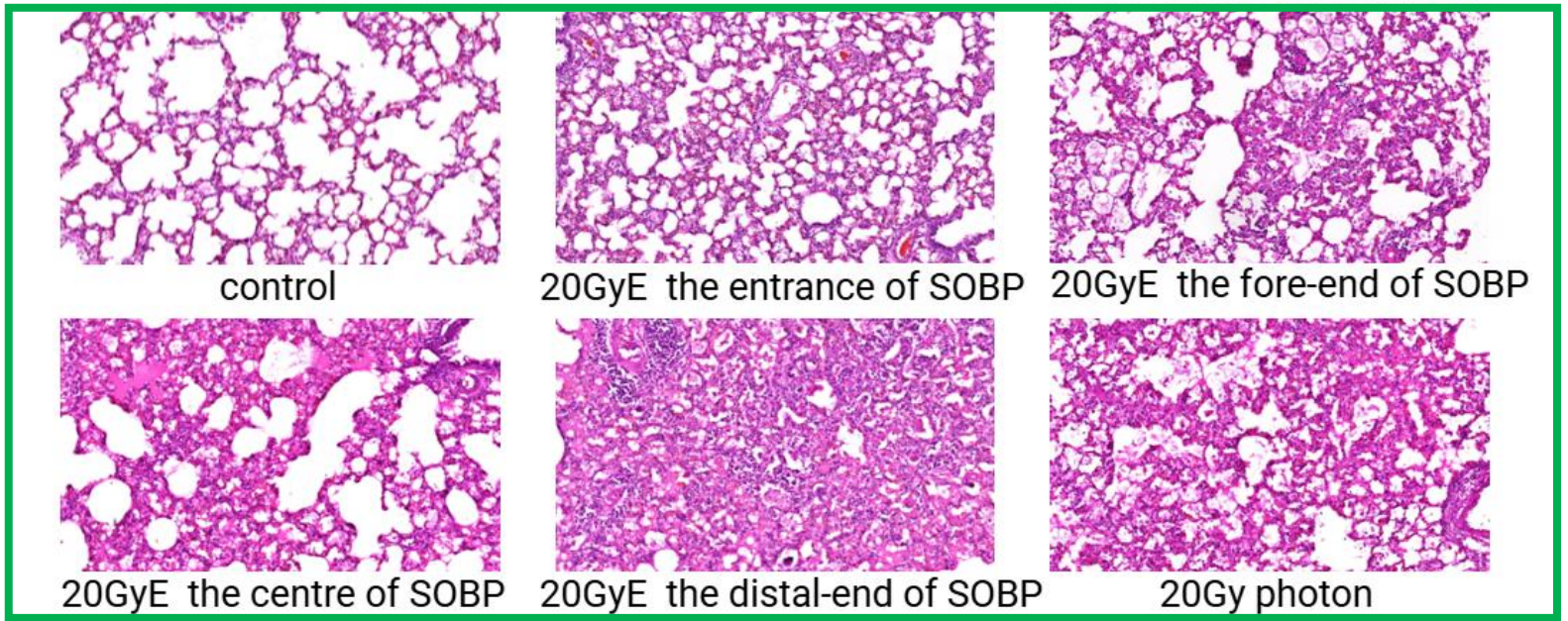
SOBP of water-equivalent depth

Central position of lung tissue [mm]	Dose-averaged LET [keV/μm]
25	1.304
55	2.235
85	2.577
115	4.215

Result 3: HE representative image

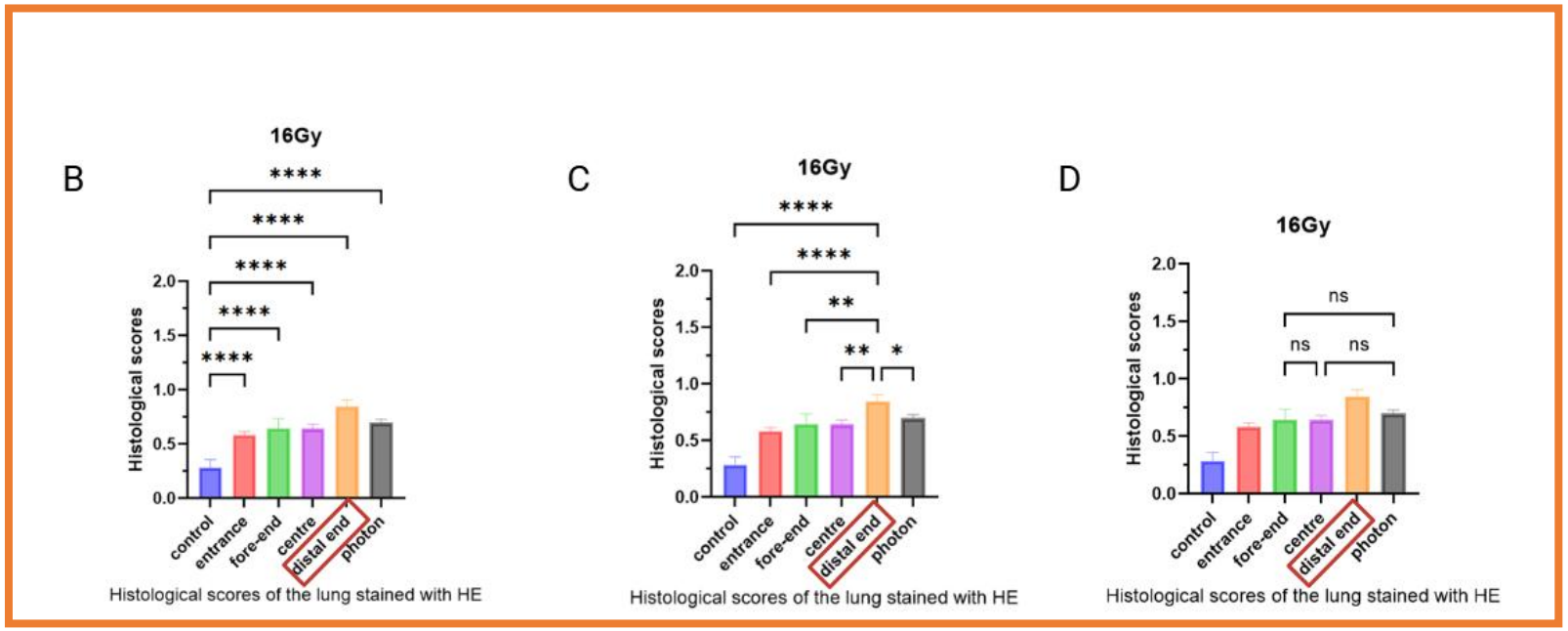


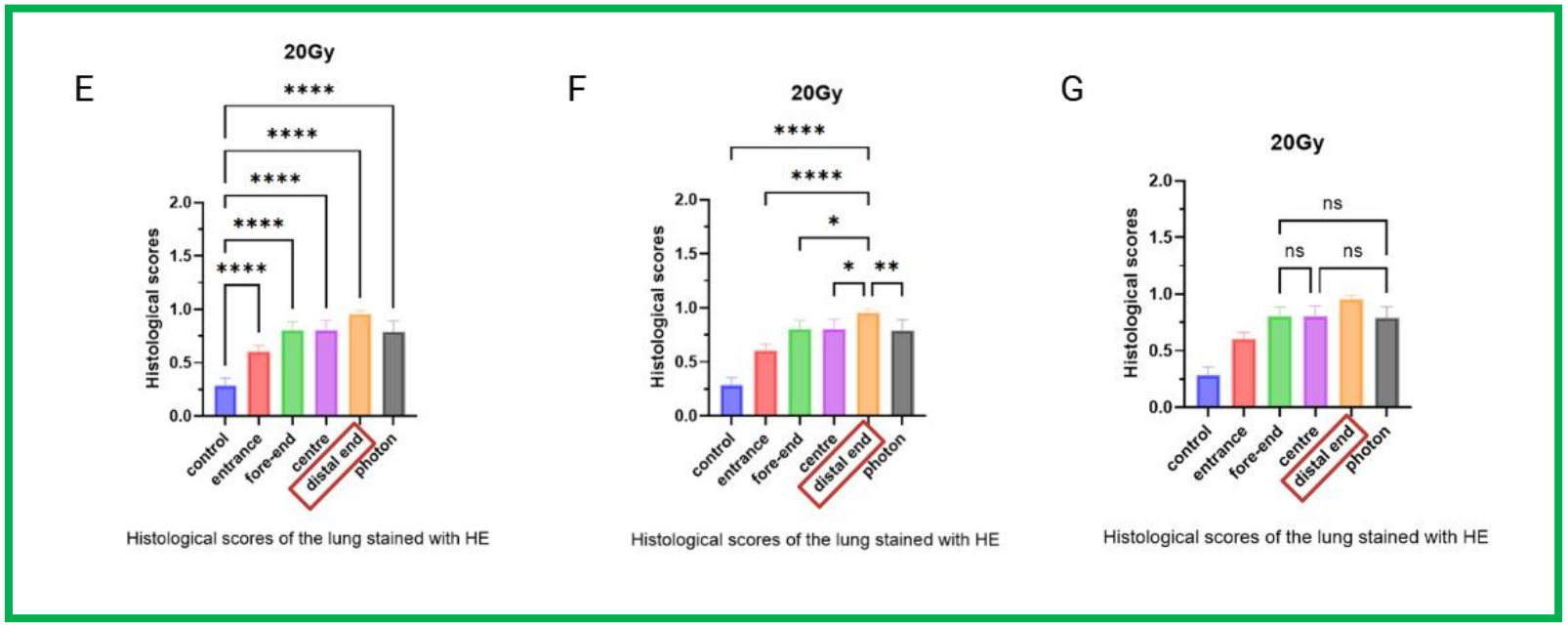
16 Gy



20 Gy

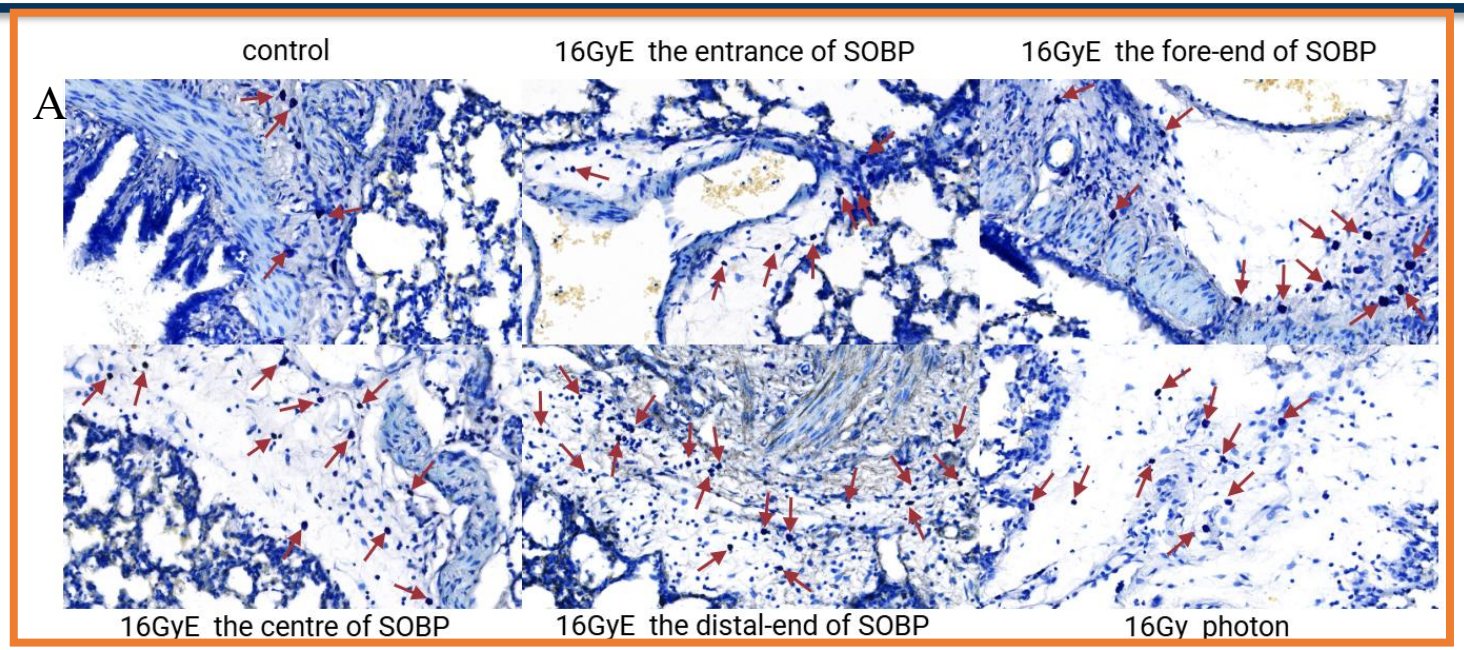
In the lung tissue irradiated with proton and photon beams at 16 and 20 Gy, we observed that, compared with the unirradiated group, both the proton and photon irradiated groups exhibited alveolar damage, widened alveolar septa, and infiltration of inflammatory cells. Edematous fluid and inflammatory cells were also observed within the alveolar cavities.



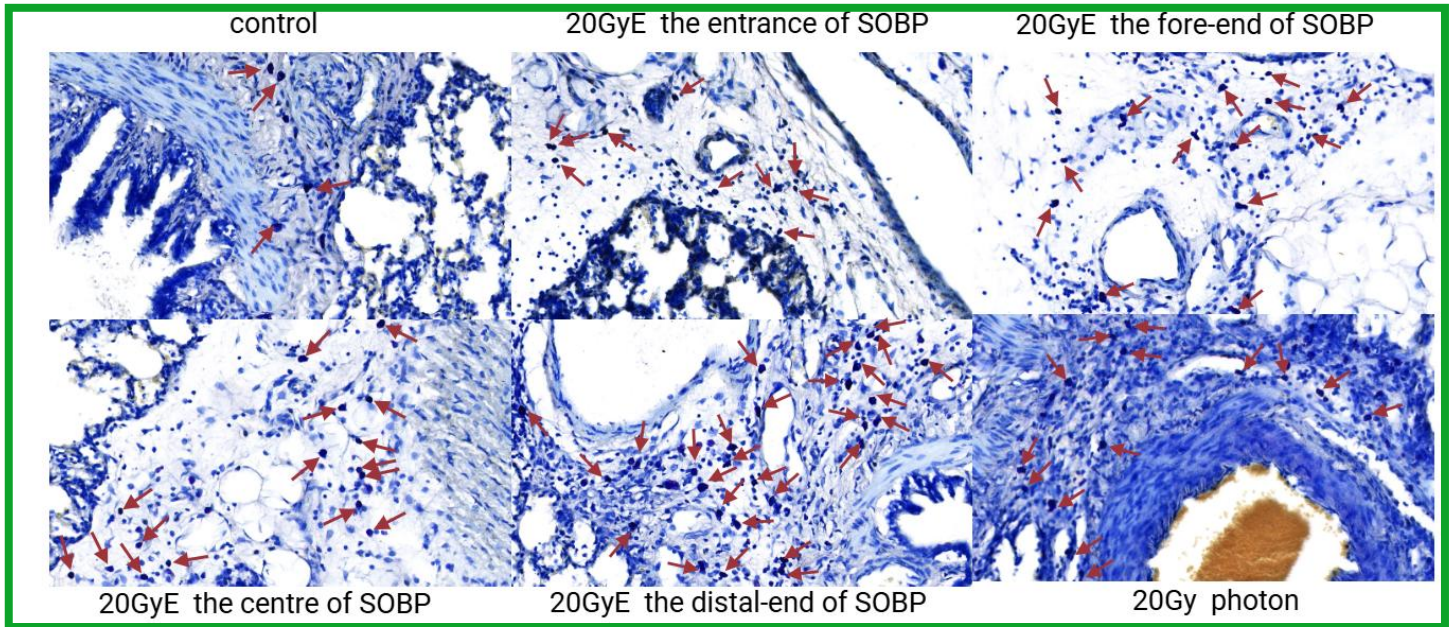


Under the same dose of irradiation, the damage to lung tissue at the distal end of the proton SOBP is more severe.

Result 4: Mast cells

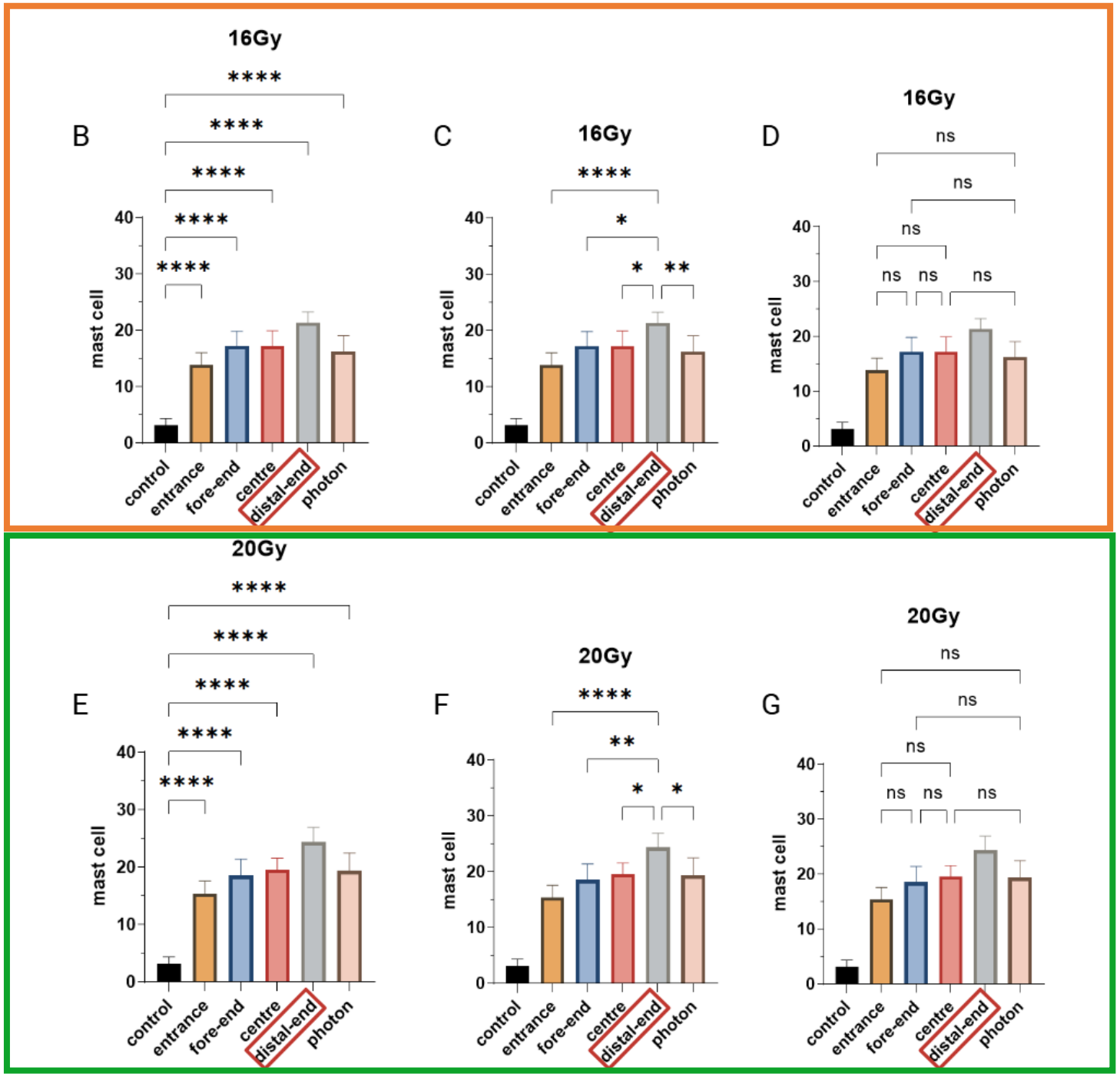


16 Gy



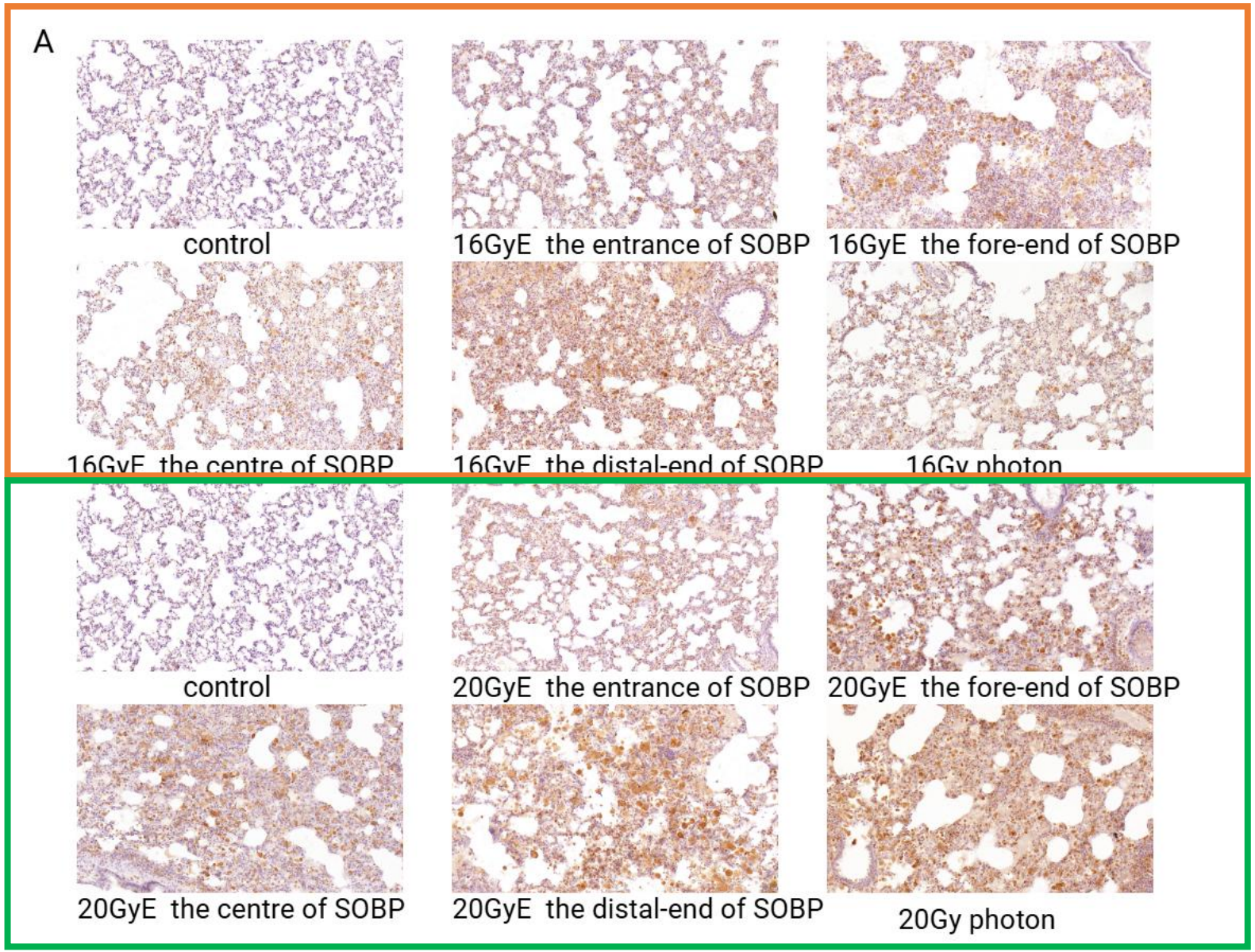
20 Gy

Compared with the unirradiated group, the perivascular and mucosal regions of the trachea in both the proton and photon groups showed an increased number of mast cells.



Compared with irradiation of photons and other parts of the SOBP, the distal lung tissue of the SOBP shows a greater increase in mast cells.

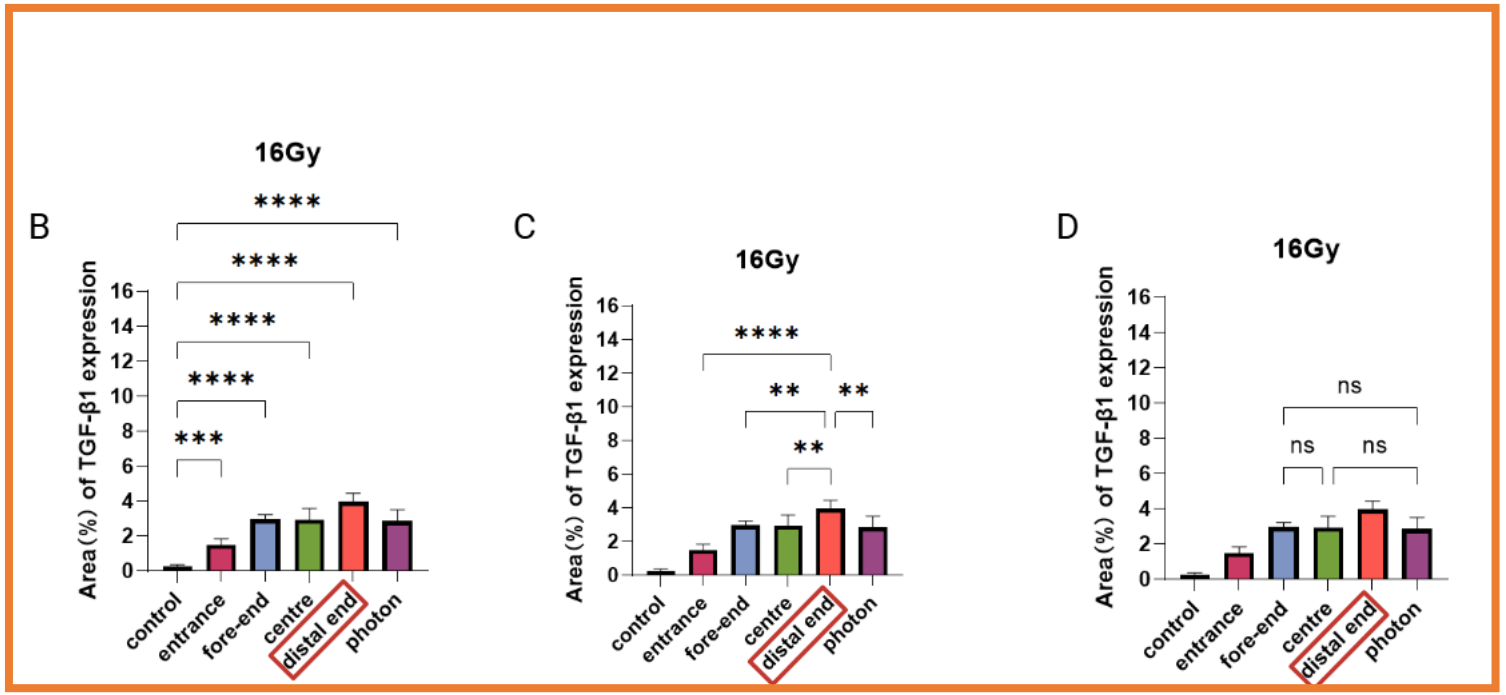
Result 5: Expression of inflammatory factor TGF-β1

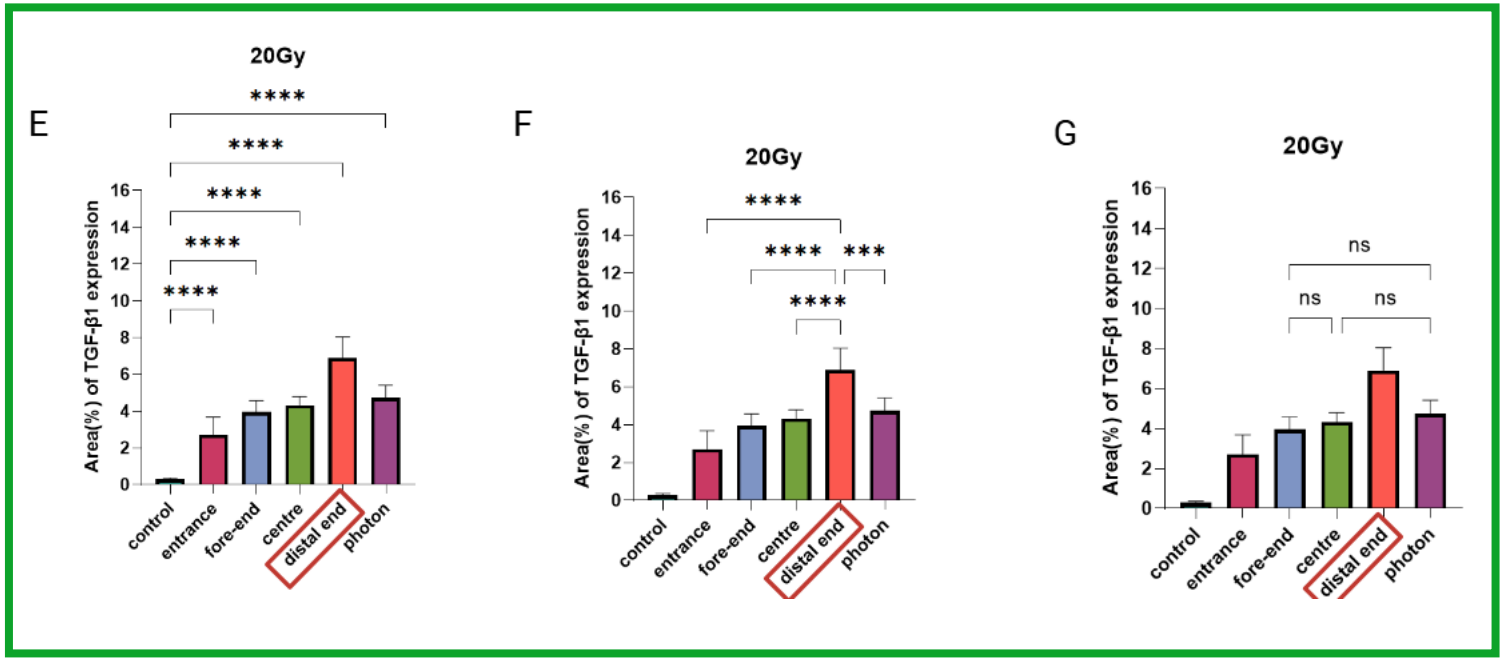


16 Gy

20 Gy

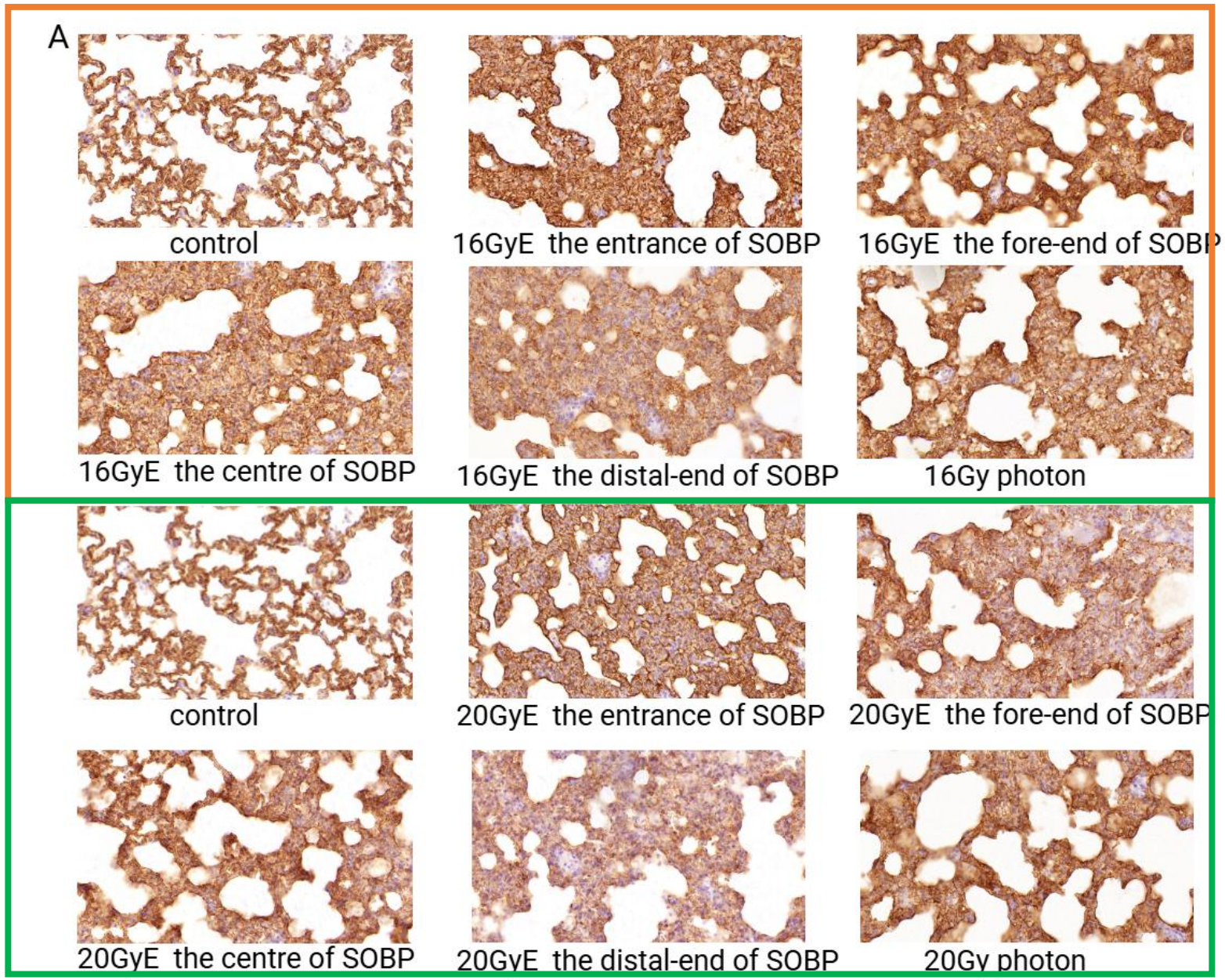
In the unirradiated control lung tissue, the lung tissue structure was observed to be orderly, and TGF-β1 was almost not expressed. However, Its expression was elevated in both the proton and photon groups.





The expression of TGF-β1 at the distal end of the proton SOBP was significantly increased.

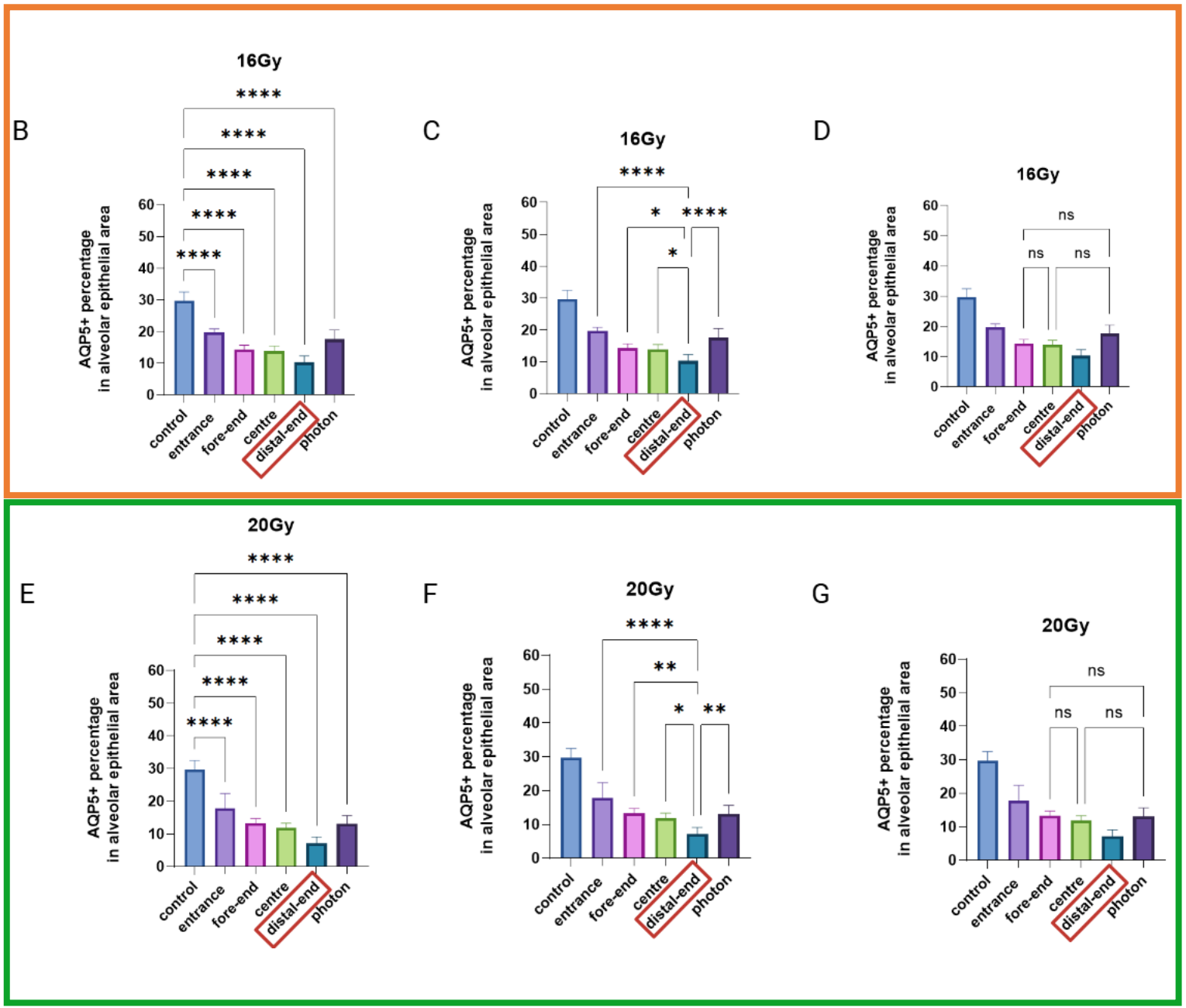
Result 6: Proportion of AQ5-labeled ATI



16 Gy

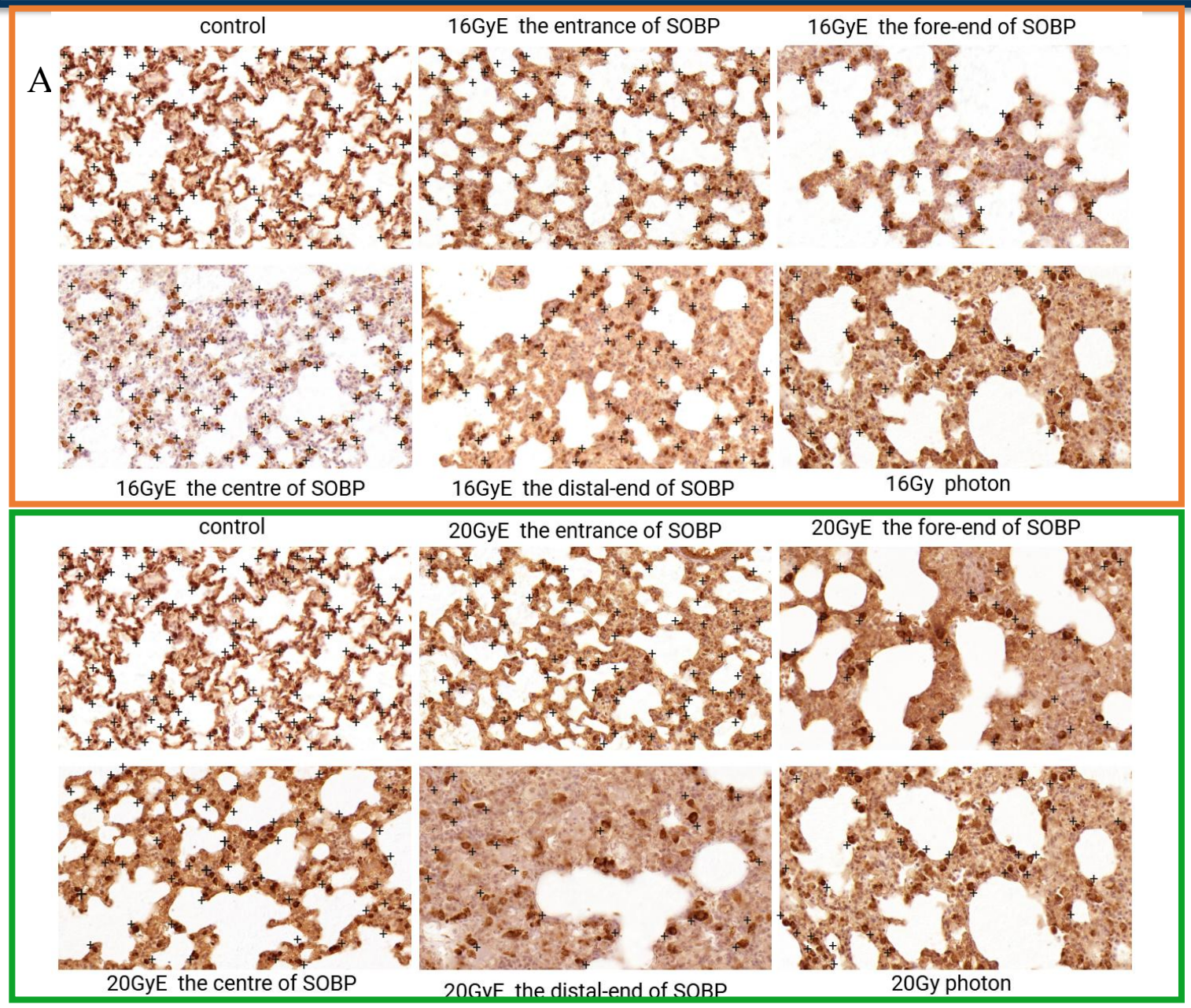
20 Gy

In the unirradiated lung tissue, AQP5 was continuously distributed along the alveolar walls, indicating intact type I alveolar epithelium. In contrast, the number of type I alveolar cells was reduced in the lung tissue following proton and photon irradiation.



The proportion of type I alveolar epithelial cells in the alveolar epithelium decreases more at the distal end of the proton SOBP.

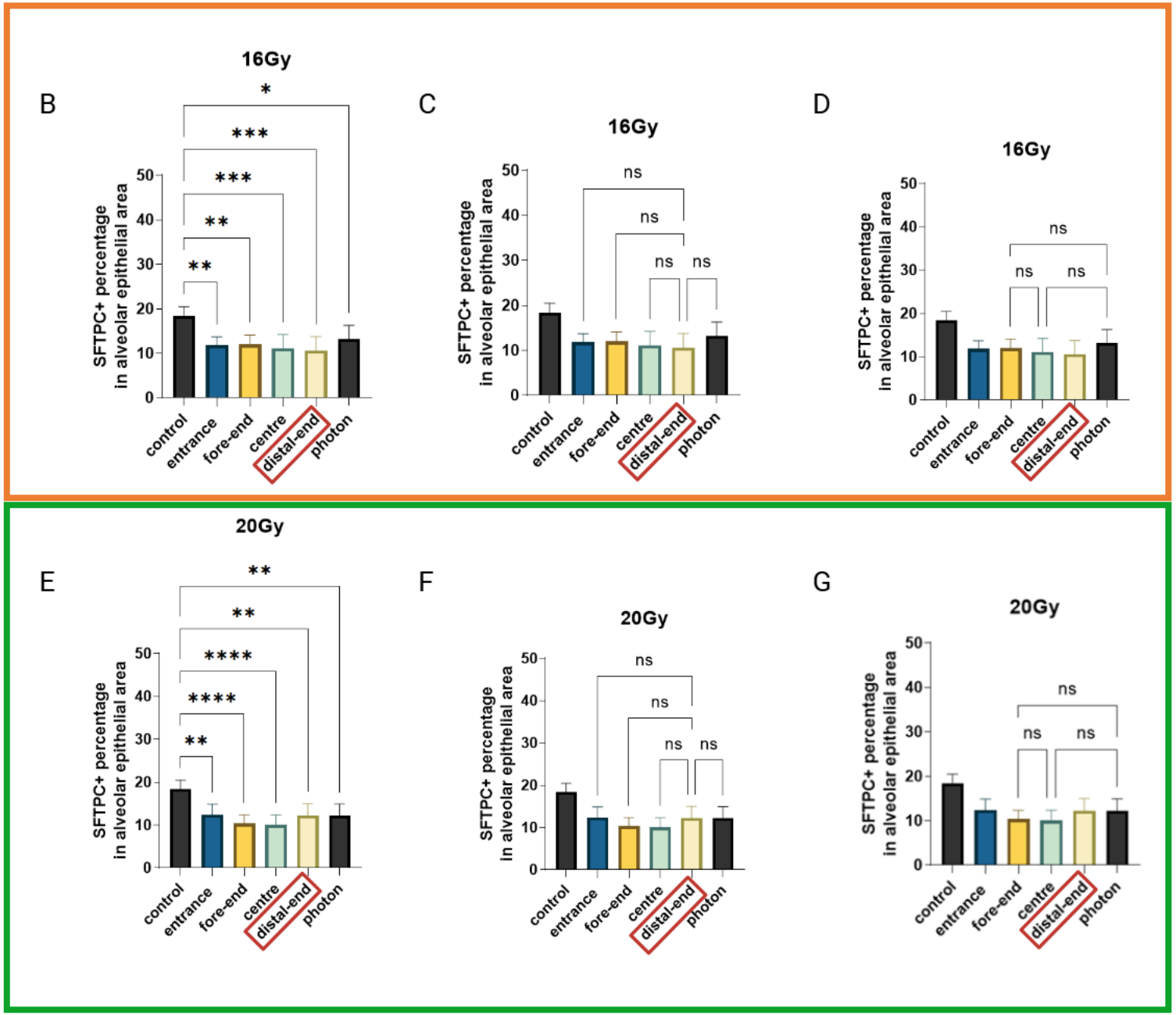
Result 7: Proportion of SFTPC-labeled ATII



16 Gy

20 Gy

In the unirradiated group, $SFTPC^+$ alveolar type II (AT2) cells were evenly distributed along the alveolar walls. In contrast, numerous morphologically abnormal $SFTPC^+$ AT2 cells appeared in the lung tissue following proton and photon irradiation.



However, the changes in the proportion of type II alveolar epithelial cells in the alveolar epithelium were not significant under different irradiation conditions, suggesting that ATII may be involved in the repair of alveolar structures.

CONTENTS

Conclusion:

1. This study confirms at both the tissue and microscopic levels that, for lung tissue, the distal end of the proton SOBP causes more severe tissue damage compared to the entrance, fore-end, and centre regions of the SOBP, manifested as aggravated pathological damage and enhanced inflammatory response.
2. Proton irradiation in regions with high energy deposition and high LET can induce stronger local immune and inflammatory responses.
3. When type I alveolar epithelial cells (AT1 cells) are injured, type II alveolar epithelial cells (AT2 cells) contribute to the regeneration of alveolar structures through proliferation and differentiation.

THANKS

zuoxiaoxin0202@163.com

zhujian@sdfmu.edu.cn