Ion therapy guideline (Version 2020)

Radiation Oncology Physicians Branch of Chinese Medical Doctor Association

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1 | INTRODUCTION

Charged particle radiotherapy can be traced back to 1954 when Lawrence Berkeley National Laboratory launched proton therapy. After experimentation with different kinds of particles, including neutrons, mesons, helium ions, and neon ions, the National Institute of Radiological Sciences in Japan started using carbon ions for cancer treatment. Proton therapy has the physical advantage of the Bragg peak, which can well realize the high-dose distribution in the tumor target volume and the low-dose distribution in surrounding normal tissue, so proton therapy has found wide applications in the field of ion radiotherapy. Nevertheless, the physical dose distribution and biological characteristics of carbon ions are significantly superior to those of other particles. Compared with the conventional photon radiotherapy, carbon ion radiotherapy stands out with its favorable radiophysical and biological advantages. In the current clinical practice, heavy ion radiotherapy mainly refers to the carbon ion radiotherapy.

So far, although some textbooks and publications have provided references for standardized applications of ion radiotherapy, there has not yet been any consensus to guide clinical practices. With the rapid development of ion radiotherapy in China, and the increase of proton and heavy ion therapy centers, ion radiotherapy, which serves as a promising radiotherapy technology, has been applicable to more and more indications. Nevertheless, there has not yet been a guideline to guide ion therapy clinical practices based on national circumstances and the current situation of ion radiotherapy. The Chinese Medical Doctor Association Radiation Oncology Physicians Branch has organized domestic relevant experts to formulate the guidelines for ion therapy with reference to the latest research evidence, which should guide the clinical practice, and promote the popularization and application of ion therapy technology in China, so as to benefit the majority of cancer patients.

2 | PHYSICAL PROPERTIES AND BIOLOGICAL CHARACTERISTICS OF ION THERAPY

2.1 | Physical properties

From the physical point of view, photons (X-, γ-rays) have no charge and no mass, but ions, such as protons and heavy ions, are charged and have a certain mass. The energy release of photon therapy is the largest near the tissue surface, and the energy gradually decreases with the depth of the tissue structure. However, ion therapy will show a low-dose plateau area in the initial irradiated tissue, and the maximum energy; that is, Bragg peak, will be deposited when reaching a certain depth of tissue. According to the location and size of the tumor, the spread out Bragg peak can be modulated to accurately cover the tumor target volume, so as to achieve a higher dose of radiation to the tumor, while the surrounding normal tissue is better protected. Due to the...
linear energy transfer difference between proton and carbon ions, they have their own physical characteristics.

The physical characteristics of protons are as follows: (i) nearly three-dimensional dose distribution can be formed in longitudinal and transverse directions; (ii) the penumbra edge is very sharp due to the proton energy deposition track being an approximate straight line; and (iii) the proton beam hardly deposits any dose outside the far edge of the Bragg peak by limiting the range.3

The physical characteristics of carbon ions are as follows: (i) compared with the conventional photon line, carbon ions have the reverse dose distribution characteristics; (ii) the multiple scattering effect of the carbon ion beam in the incident tissue is small, and the transverse scattering of the beam is also small; (iii) the beam distribution is flexible, because the charged particles can deflect under the action of magnetic field, so flexible and diverse beam distribution systems can be adopted according to the actual situation; and (iv) when the medium- and high-energy carbon ion beam penetrates the target material, it can produce radioisotopes by colliding with the target nucleus, and it decays and releases positrons in a short time, and positron emission tomography (PET) is used to monitor the positron position.4

2.2 | Biological characteristics

Protons belong to the low linear energy transfer beam that maintains a low relative biological effect (RBE) in radiobiology, although they have physical properties of the Bragg peak. The RBE of protons is 1.1-fold compared with photon rays.

Carbon ion therapy is a kind of high linear energy transfer beam, which can cause high ionization density and a severe DNA damage rate by radiation damage, mainly DNA double strand damage, resulting in high cell mortality. Carbon ions have the following biological effects: (i) higher RBE, which is generally 2–5-fold compared with photon rays; (ii) lower oxygen enhancement ratio, which can effectively treat hypoxic tumors that are resistant to photon rays; and (iii) less dependence on the cell cycle, as it has a higher radiosensitivity to S-phase cells resistant to photon rays. Therefore, the modes of cell death caused by carbon ion radiation are more diverse, including apoptosis, necrosis, autophagy, premature senility, accelerated differentiation, delayed proliferation, and death of offspring cells and bystander cell death, and so on. In view of the aforementioned physical and biological characteristics, carbon ion therapy can use fewer fractions and shorter time to treat cancer.5

3 | INDICATIONS OF ION THERAPY

Proton therapy has a wide range of indications, covering almost all types cancers using photon radiotherapy, which has certain advantages in reducing the toxicity and side-effects of normal tissue, and is more suitable for children with cancer. Because of its special physical and biological advantages, carbon ion therapy has prominent superiorities in insensitive tumors with photon radiotherapy, hypoxic tumors, re-radiation of recurrent tumors, and some tumors in special sites.

3.1 | Brain tumor

1. Tumors of the skull base and upper cervical spine (chordoma and chondrosarcoma);6
2. Meningioma;7
3. High-grade glioma.8

3.2 | Head and neck tumor

1. Mucosal malignant melanoma;9
2. Adenoid cystic carcinoma;10
3. Ocular tumors (choroidal malignant melanoma).11
4. Intra-orbital tumor;12
5. Nasopharyngeal carcinoma, including initial radical radiotherapy and re-radiotherapy after recurrence;13
6. Other tumors: salivary gland tumor, ear tumor, nasal and paranasal sinus cancer, oral cancer, and so on.14

3.3 | Lung cancer

1. Early peripheral non-small cell lung carcinoma (NSCLC);15–16
2. Early central NSCLC;17–18
3. Oligogenic metastasis or recurrence of NSCLC.19
4. Locally advanced NSCLC.20

3.4 | Tumor of the digestive system

1. Hepatocellular carcinoma;21
2. Hepatobiliary cell carcinoma;22
3. Hepatic metastases (hepatic oligometastasis of colorectal cancer);23
4. Pancreatic cancer;24–25
5. Postoperative recurrence of rectal cancer;26
6. Carbon ion therapy for esophageal cancer is still at the preliminary study phase, and proton radical radiotherapy and concurrent chemoradiotherapy can be used.27–28

3.5 | Urinary system tumor

1. Prostate cancer;29
2. Kidney cancer.30

3.6 | Bone and soft tissue tumors

1. Sacrococcygeal chordoma;31
2. Soft tissue sarcoma of trunk and limbs;32
3. Osteosarcoma.33
3.7 | Breast cancer

Carbon ion therapy for breast cancer is still at the preliminary study stage. However, all breast cancer patients with radiotherapy indications can choose proton therapy, which has potential advantages in reducing radiotherapy-related adverse reactions.34

3.8 | Gynecological tumors

1. Cervical cancer: including radical proton therapy and carbon ion therapy for recurrent tumors after radiotherapy;35–36
2. Endometrial cancer;37
3. Gynecological malignant melanoma.38

3.9 | Childhood cancer

Proton therapy has the advantage of reducing toxicity and side-effects. Compared with photon radiotherapy, proton therapy is more suitable for childhood cancers. Indications including central nervous system tumors (medulloblastoma, ependymoma, glioma, atypical teratomas/striated muscle tumor, craniopharyngioma, germ cell tumors) and non-central nervous system tumors (chordoma, chondrosarcoma, rhabdomyosarcoma, Ewing’s sarcoma, osteosarcoma, retinoblastoma, lymphoma, neuroblastoma and renal tumor).39 It is recommended to carry out clinical research on carbon ion therapy for childhood tumors.

4 | CONTRAINDICATIONS

Contraindications to ion therapy are relatively few. The assessment of systemic diseases, tumor status, and history of radiotherapy is, however, necessary before treatment. Patients with the following conditions are not candidates for ion therapy.

4.1 | Systemic diseases

1. Severe heart/lung/liver/kidney/hematological system/nervous system diseases or complications;
2. Uncontrolled systemic infection or sepsis;
3. Routine examination is not up to the basic requirements for radiotherapy;
4. Advanced cancers with severe anemia, emaciation, electrolyte disorders, coma, or cachexia;
5. Patients with severe mental disorders who are unable to cooperate with treatment.

4.2 | Tumor status

1. Extensive metastases;
2. The absolute contraindications, including cancer with massive pleural effusion or ascites, perforation or with the risk of perforations, and bleeding;
3. The relative contraindications, including cancers in hollow organs or rapid progression;
4. With metal prostheses at the irradiated site that seriously affect the calculation of ion dose.

4.3 | History of radiotherapy

1. The same site has received radiotherapy during a short time, or the site has received two or more treatments of radiotherapy;
2. Serious radiation injury, such as unhealed skin ulcer, pulmonary fibrosis, tissue necrosis, or severe luminal narrowing caused by radiation, has occurred at the radiotherapy site.

5 | IMPLEMENTATION OF ION RADIOTHERAPY

The physical characteristics, biological advantages, and beam delivery system of the ion beam should be fully utilized to successfully implement ion radiotherapy.

According to different beam delivery systems, there are two main ion therapy techniques, one is passive scattering and another is the pencil beam scanning technique, the latter has better conformability. Many ion treatment planning systems are currently available in clinical research or practice, such as Raystation, HIPAN, Xio-N, CiPlan, and Syngo. In the design of treatment planning, single-field optimization or intensity-modulated (multi-field simultaneous optimization) method can be selected for plan optimization. The former has better robustness, and the latter has better conformability. Repeated scanning (rescanning) techniques can further increase the accuracy of dose delivery to moving targets.50 The clinical dose is defined as the RBE weighted dose, expressed in Gy (RBE).41 Dose–volume histograms are also suitable for the assessment of ion radiotherapy plans, and the criteria for dose distribution are generally 95% of the prescribed dose line covering 99% of the clinical target volume (CTV) and 90% of the prescribed dose line covering 90% of the planning target volume.42

5.1 | Positioning

Computed tomography (CT) images of the patients are the basis for treatment planning design. Given that the dose distribution of ionizing rays is greatly affected by tissue densities, it is important to accurately fix patients according to the treatment requirements. According to the characteristics of the beam delivery system at each treatment unit, the angle of the treatment port and the tumor site determine the incident angle of the ion beam, and then design simulation positioning using individualized fixtures.43

The supine or prone position is usually used for trunk tumors (depending on the location of the tumors), with both hands placed above the top of the head or on both sides of the body, and the lateral or oblique position is avoided as much as possible; Ocular tumors usually require a special beam and treatment room, and a special treatment
chair has been designed to use the sitting position for treatment. The design of the therapeutic bed should fully consider the characteristics of ion radiotherapy equipment beam delivery system, allowing the table plane to rotate around its longitudinal axis. It is recommended to equip a rotating treatment cabin, six-dimensional treatment bed, or robotic arm bed.

The motion management techniques could control the motion of tumors and reduce the irradiated volume of normal tissues. Respiratory gating is recommended for the treatment of thoracic or abdominal tumors. At present, a respiratory control system composed of a position sensor, infrared light marker, and pressure change monitoring is mostly used to monitor and control respiration.

5.2 | Definition and delineation of target volume

The target definition of ion therapy is carried out according to the principle of the Radiation Therapy Oncology Group target delineation, the same as photon radiotherapy. The target volume needs to be comprehensively considered in combination with the medical history of the patient. The image fusion technique using enhanced CT, magnetic resonance imaging, or PET/CT is usually adopted to delineate the target volume. However, the treatment dose is calculated according to the simulation plain CT scan images. Gross tumor volume (GTV) is defined as the primary tumor and metastatic lymph nodes; CTV includes GTV, subclinical lesions, and involved lymph node areas. When delineating CTV, it can be expanded on the basis of GTV and adjusted according to the anatomical barrier. Aside from expanding on the basis of CTV, the margin of planning target volume will depend on setup uncertainty. Ion therapy differs from photon radiotherapy in that planning target volume needs to consider the influence of beam range uncertainty. Depending on the depth of the tumor, a boundary of 0.3–0.5 cm is generally added to the lateral side of the radiation field, and a boundary of 0.7–1.0 cm is added along the incident direction. If using a pattern of carbon ion combined with photon or proton to treat cancer, the target volume is delineated the same as photon radiotherapy. In general, photon or proton is used to radiate CTV, and carbon ion radiates GTV for a boost.

5.3 | Dose constraints for organs at risk

There is no uniform standard for the limit of organs at risk (OARs) in ion therapy. At present, it mainly refers to the data of photon radiotherapy. For hypofractionated radiotherapy, the early and late toxicity of each OAR should be fully considered, and the dose should be strictly limited with reference to stereotactic body radiation therapy. Referring to the OARs dose limitation of proton and carbon ion therapy in Japan and Shanghai, China, the recommended dose of OARs is shown in Table 1.

5.4 | Position verification

All kinds of ion therapy devices should be equipped with an image-guided treatment system. Cone beam CT or digital radiography imaging is usually used for position verification, and it is associated with the treatment control system to realize online position correction. It is required to correct the position of the treatment bed until the position difference between the verified image and reference image in all directions is <3 mm before ion treatment.

In addition, radioactive isotopes are produced when proton or carbon ions collide with the nucleus of the target substance, and positron is emitted in a short period of time. PET can be used to monitor the position of the positron, so as to verify the actual dose distribution of ions. It is suggested that the ion therapy center can carry out the relevant research to verify the actual dose distribution using PET in ion therapy.

6 | TREATMENT DELIVERY TECHNIQUES

According to different scanning modes, treatment delivery techniques of ion therapy are divided into uniform scanning and pencil beam scanning. Different ion therapy devices have different scanning modes. The appropriate scanning mode is selected for treatment according to the lesion site and tumor characteristics. Pencil beam scanning technology is preferred in terms of target volume conformity and dose accuracy, enabling intensity-modulated proton therapy and intensity-modulated carbon ion therapy (IMCT). To many treatment centers without pencil beam scanning technique, uniform scanning mode is recommended. Respiratory motion management techniques are recommended during treatment.

7 | RECOMMENDED DOSE OF ION THERAPY FOR VARIOUS CANCERS

The indications for proton therapy are basically the same as those for photon therapy. The treatment plan basically references the dose fractionation patterns of photon therapy. The proton therapy for pediatric tumors mainly refers to the treatment recommendations in the International Consensus on Proton Therapy for Pediatric Tumors.

There is no standard guideline for carbon ion therapy, and a variety of therapy modes are in the clinical research stages. At present, the main clinical experience comes from Japan. The Shanghai Proton and Heavy Ion Hospital in China has also explored the Shanghai clinical experience for some common cancers. The dose fractionation patterns of carbon ion therapy for tumors in various sites listed as follows refer to National Institute of Radiological Sciences in Japan (Table 2) and Shanghai Proton and Heavy Ion Hospital in China (Table 3).

8 | COMPLICATIONS OF ION RADIOTHERAPY

Complications of ion therapy are basically consistent with the conventional photon radiotherapy. In general, the incidence of serious adverse events caused by ion therapy is lower than that of photon radiotherapy because of the physical advantages of ion therapy. As the normal tissue dose limit of carbon ion therapy has not been clarified, it is
### TABLE 1  Dose constraints for organs at risk in ion therapy

| Organs at risk                                      | Proton therapy\(^{48}\) | Carbon ion therapy\(^{49}\) |
|----------------------------------------------------|--------------------------|-----------------------------|
| Brain or head and neck tumors                      |                          |                             |
| Visual pathway (optic chiasma and optic nerve were evaluated respectively) | \(D_1 <54 \text{ GyE}\) | \(D_{20} <30 \text{ GyE}\) |
| Brainstem                                          | \(D_1 \leq 54 \text{ GyE}\) | \(D_{\text{max}} < 45 \text{ GyE}\) |
| \(V_{50 \text{GyE}} <1\% PRV\)                     | \(D_1 \leq 38.5 \text{ GyE}\) |                             |
| Temporal lobes                                      | \(V_{60 \text{GyE}} \leq 1\%\) | \(V_{50 \text{GyE}} < 7.66 \text{ cc}\) |
| \(V_{50 \text{GyE}} < 4.66 \text{ cc}\)           | \(D_{\text{max}} < 30 \text{ GyE}\) | \(V_{50 \text{GyE}} < 4.66 \text{ cc}\) |
| Spinal cord                                         | \(V_{50 \text{GyE}} <1\% PRV\) | \(D_{\text{max}} < 30 \text{ GyE}\) |
| \(D_{\text{max}} < 45 \text{ GyE}\)               | \(D_1 \leq 31.5 \text{ GyE}\) | \(D_1 \leq 38.5 \text{ GyE}\) |
| Eyes                                               | \(D_{\text{mean}} < 35 \text{ GyE}\) | \(D_{\text{mean}} < 30 \text{ GyE}\) |
| Lens                                               | \(D_{\text{mean}} < 6 \text{ GyE}\) | \(D_1 < 6 \text{ GyE}\) |
| \(D_1 < 8 \text{ GyE}\)                           | \(D_1 < 8 \text{ GyE}\) |                             |
| Cochlea                                            | \(V_{55 \text{GyE}} < 5\%\) | \(D_{\text{mean}} < 30 \text{ GyE}\) |
| \(D_{\text{mean}} < 36 \text{ GyE}\)             | \(D_{\text{mean}} < 36 \text{ GyE}\) |                             |
| Parotid gland                                       | \(D_{\text{mean}} < 25 \text{ GyE}\) (bilateral) | \(D_{\text{mean}} < 21 \text{ GyE}\) (Bilateral) |
| \(D_{\text{mean}} < 20 \text{ GyE}\) (unilateral) | \(D_{\text{mean}} < 18 \text{ GyE}\) (Unilateral) |                             |
| Temporomandibular joint                            | \(D_{\text{mean}} < 35 \text{ GyE}\) | \(D_{\text{mean}} < 30 \text{ GyE}\) |
| Thoracic tumors                                     |                          |                             |
| Spinal cord                                         | \(V_{50 \text{GyE}} < 1\% PRV\) | \(D_{\text{max}} < 45 \text{ GyE}\) |
| Heart and pericardium                               | \(D_{\text{mean}} < 26 \text{ GyE}\) | \(D_{\text{max}} < 72 \text{ GyE}\) |
| \(V_{50 \text{GyE}} < 40\%\)                      | \(D_{\text{max}} < 40 \text{ GyE}(5 \text{ GyE/fx})\) | \(D_{\text{max}} < 40 \text{ GyE}\) (5 GyE/fx) |
| \(V_{50 \text{GyE}} < 50\%\)                      | \(D_{\text{max}} < 40 \text{ GyE}\) (5 GyE/fx) |                             |
| Esophagus                                          | \(D_{\text{mean}} < 34 \text{ GyE}, V_{50 \text{GyE}} < 50\%\) | \(D_{\text{max}} < 60 \text{ GyE}\) |
| \(D_{\text{mean}} < 36 \text{ GyE}\)             | \(D_{\text{max}} < 40 \text{ GyE}\) (5 GyE/fx) | \(D_{\text{max}} < 40 \text{ GyE}\) (5 GyE/fx) |
| Lung                                               | \(V_{20 \text{GyE}} < 30\%\) | \(D_{\text{mean}} < 14 \text{ GyE}\) and \(V_{20 \text{GyE}} < 20\%\) (single lung) |
| \(D_{\text{mean}} < 20 \text{ GyE}\)             | \(V_{20 \text{GyE}} < 30\%\) (single lung) | \(V_{20 \text{GyE}} < 30\%\) (single lung) |
| \(V_{20 \text{GyE}} < 40\%\)                      | \(V_{5 \text{GyE}} < 40\%\) (single lung) | \(V_{5 \text{GyE}} < 40\%\) (single lung) |
| Trachea (point dose)                                | \(D_{\text{max}} < 63 \text{ GyE}\) | \(D_{\text{max}} < 63 \text{ GyE}\) |
| Abdominal tumors\(^{50-51}\) (The following OARs’ dose constraints are based on conventional fraction in proton therapy or 3–5 GyE per fraction in 12–16 fractions in carbon ion therapy) | \(D_{\text{mean}} \leq 30 \text{ GyE}\) | \(V_{50 \text{GyE}} \leq 30\%\) |
| Liver                                              | \(V_{50 \text{GyE}} \leq 30\%\) | Non-cirrhotic liver, normal liver MLD \(< 30 \text{ GyE}\); Cirrhosis (Child–Pugh A), normal liver MLD \(< 23 \text{ GyE}\) |
| Kidney                                             | \(D_{\text{mean}} \leq 18 \text{ GyE}\) | \(D_{\text{mean}} \leq 14 \text{ GyE}\) and \(V_{18 \text{GyE}} < 80\%\); Single kidney, \(V_{18 \text{GyE}} < 80\%\); double kidney, one \(> 20 \text{ GyE}\), another \(V_{18 \text{GyE}} < 10\%\) |
| \(V_{12 \text{GyE}} < 55\%\)                      | \(V_{5 \text{GyE}} < 0.03 \text{ mL}\) | \(V_{5 \text{GyE}} < 0.03 \text{ mL}\) |
| \(V_{20 \text{GyE}} < 33\%\)                      | \(V_{5 \text{GyE}} < 0.03 \text{ mL}\) | \(V_{5 \text{GyE}} < 0.03 \text{ mL}\) |
| Stomach                                            | \(D_{\text{max}} \leq 54 \text{ GyE}\) | \(V_{50 \text{GyE}} < 5 \text{ mL}\) |
| \(V_{50 \text{GyE}} \leq 2\%\)                     | \(V_{50 \text{GyE}} < 5 \text{ mL}\) | \(V_{50 \text{GyE}} < 5 \text{ mL}\) |
| \(V_{45 \text{GyE}} \leq 25\%\)                   | \(V_{45 \text{GyE}} < 30 \text{ mL}\) | \(V_{45 \text{GyE}} < 30 \text{ mL}\) |
| Duodenum                                           | \(D_{\text{max}} \leq 55 \text{ GyE}\) | \(V_{50 \text{GyE}} < 0.03 \text{ mL}\) |
| \(V_{45 \text{GyE}} \leq 25\%\)                   | \(V_{50 \text{GyE}} < 0.03 \text{ mL}\) | \(V_{50 \text{GyE}} < 0.03 \text{ mL}\) |
| \(V_{45 \text{GyE}} \leq 25\%\)                   | \(V_{50 \text{GyE}} < 0.03 \text{ mL}\) | \(V_{50 \text{GyE}} < 0.03 \text{ mL}\) |
| Small bowel                                        | \(D_{\text{max}} \leq 60 \text{ GyE}\) | \(V_{50 \text{GyE}} < 10 \text{ mL}\) |
| \(V_{54 \text{GyE}} \leq 2\%\)                     | \(V_{50 \text{GyE}} < 10 \text{ mL}\) | \(V_{50 \text{GyE}} < 10 \text{ mL}\) |
| \(V_{50.4 \text{GyE}} \leq 5\%\)                   | \(V_{50 \text{GyE}} < 30 \text{ mL}\) | \(V_{50 \text{GyE}} < 30 \text{ mL}\) |
| \(V_{45 \text{GyE}} \leq 25\%\)                   | \(V_{50 \text{GyE}} < 1\% PRV\) | \(V_{50 \text{GyE}} < 1\% PRV\) |
| Spinal cord                                         | \(D_{\text{max}} \leq 45 \text{ GyE}\) | \(V_{50 \text{GyE}} < 1\% PRV\) |
| \(V_{50 \text{GyE}} < 1\% PRV\)                   | \(V_{50 \text{GyE}} < 1\% PRV\) | \(V_{50 \text{GyE}} < 1\% PRV\) |

(Continues)
Organs at risk Proton therapy\textsuperscript{48} Carbon ion therapy\textsuperscript{49}

| Organs at risk | Proton therapy | Carbon ion therapy |
|---------------|----------------|--------------------|
| Pelvic tumors\textsuperscript{52–53} | | |
| Large bowel | | |
| Rectum | Low-risk patients: | Intermediate-risk patients: |
| | $V_{50\text{GyE}} < 35\%$ | $V_{50\text{GyE}} < 40\%$ |
| | $V_{50\text{GyE}} < 25\%$ | $V_{50\text{GyE}} < 30\%$ |
| | $V_{70\text{GyE}} < 15\%$ | $V_{70\text{GyE}} < 20\%$ |
| Rectum | $D_{\text{max}} < 83\%$ prescription dose | $D_{\text{max}} < 50\text{ GyE}$ |
| | $D_{\text{mean}} < 50\text{ GyE}$ | $D_{\text{mean}} < 66\text{ GyE}$ |
| | $D_{5} < 60\text{ GyE}$ | $D_{5} < 66\text{ GyE}$ |
| | $D_{10} < 50\text{ GyE}$ | $D_{10} < 50\text{ GyE}$ |
| Bladder | $V_{65\text{GyE}} < 25\%$ | $V_{65\text{GyE}} < 40\%$ |
| | $V_{40\text{GyE}} < 50\%$ | $\text{D}_{\text{mean}} < 18\text{ GyE}$ |
| Femoral heads | $D_{\text{max}} < 50\text{ GyE}$ | $\text{D}_{\text{max}} < 40\%$ |
| | $D_{\text{mean}} < 18\text{ GyE}$ | $\text{D}_{\text{max}} < 50\text{ GyE}$ |

Organs at risk (OARs) dose constraints are equal to intensity-modulated radiation therapy for proton therapy, but for carbon ion therapy, they mainly refer to the clinical experiences from the National Institute of Radiological Science in Japan recommended to monitor and record the adverse events in detail during ion therapy in a timely manner, so as to establish the dose–effect relationship of OARs and collect original data. The long-term toxicity of OARs after high-dose irradiation should be closely observed.

8.1 **Common complications of ion therapy for head and neck cancer**

Compared with photon radiotherapy, ion therapy can reduce the dose to the retina, optic nerve, optic chiasm, cochlea, parotid gland, and brainstem, and reduce the incidence of acute oral mucositis, prolonged xerostomia, and other toxicity and side-effects, significantly reducing the incidence of late radiation-induced brain injury (for example, the incidence of radiation-induced brain injury of skull base malignant tumors is < 3%), and significantly improving the treatment tolerance and quality of life of patients. Prospective studies indicate that the grade 3 mucosal reaction of proton therapy for nasopharyngeal cancer is 11%, which is much lower than the 30–40% of intensity-modulated radiation therapy, and no grade ≥ 4 toxicity.\textsuperscript{56,57}

According to reports of many carbon ion therapy centers, carbon ion therapy has more advantages in reducing adverse events, as the incidence of late adverse events is approximately 1–7%, and most adverse events were mild to moderate. The late severe toxicity of carbon ion therapy in re-irradiation was significantly reduced compared with re-irradiation of photon (the incidence of grade ≥ 3 toxicity was ~ 7%).\textsuperscript{58}

8.2 **Common complications of ion therapy for thoracic tumors**

Ion therapy has a lower incidence of grade ≥ 3 radiation pneumonitis than stereotactic body radiation therapy to early-stage lung cancer. For patients combined with interstitial pneumonitis, the incidence of radiation pneumonitis will increase after ion therapy.

For locally advanced lung cancer, the most common complications of ion therapy are radiation pneumonitis and radiation esophagitis. Prospective studies have found that the incidence of grade 2 radiation pneumonitis with carbon ion therapy is approximately 6%, grade 3 radiation pneumonitis is approximately 2%, and the incidence of grade 3 tracheo-esophageal fistula is approximately 2%.\textsuperscript{59} After carbon ion re-irradiation for locally recurrent NSCLC, only approximately 2.1% of patients experience grade 3 radiation pneumonitis.\textsuperscript{60}

Concurrent chemotherapy has the potential to increase the toxicity of ion therapy. What is worth paying great attention to is that the tumor shrinkage during concurrent chemoradiotherapy will lead to a higher than planned therapeutic dose to the esophagus or spinal cord behind the target volume. Therefore, adaptive radiotherapy techniques are especially warranted.

8.3 **Common complications of ion therapy for abdominal and pelvic tumors**

The most common complication of ion radiotherapy for liver cancer is hepatotoxicity. The incidence is higher in patients who have poor basic liver function, poor liver reserve before treatment or received previous radiotherapy. Therefore, it is essential to assess the liver function of patients before treatment. The injury of the biliary system is secondary, including inflammation of the hepatic duct or biliary stricture (14–28%), but also gastrointestinal toxicity, which may present with hemorrhagic duodenitis, hemorrhagic ulcers in the colon, and esophagitis (1–7%). When liver tumors are close to the chest wall, especially peripheral tumors, rib fractures and chest wall pain syndrome are potential risks of toxicity that may adversely affect the quality of life of cancer patients, with a median time to rib fractures of approximately 2 years.\textsuperscript{61}
**TABLE 2** Dose fractionation patterns of carbon ion therapy in the National Institute of Radiological Sciences, Japan

| Site                      | Tumor types                                      | Total dose (GyE) | No. fractions | Dose per-fraction (GyE) | Treatment time (weeks) |
|---------------------------|--------------------------------------------------|------------------|---------------|-------------------------|------------------------|
| Head and neck tumors      | Adenocarcinoma, ACC, MMM                         | 57.6             | 16            | 3.6                     | 4                      |
|                           | Sarcoma                                          | 70.4             | 16            | 4.4                     | 4                      |
| Skull base tumors         | Chordoma, chondrosarcoma                         | 60.8             | 16            | 3.8                     | 4                      |
| Ocular neoplasm           | Malignant melanoma of choroid                    | 70.0             | 5             | 14.0                    | 1                      |
|                           | ACC/adenocarcinoma Meibomian gland               | 52.8             | 12            | 4.4                     | 3                      |
| Lung cancer               | Peripheral (T1–2N0M0)                            | 50.0             | 1             | 50.0                    | 1 day                  |
|                           | Mediastinal lymph node                           | 60.0             | 4             | 15.0                    | 4 days                 |
|                           | Early central lung cancer (T1–2N0M0)             | 48.0             | 12            | 4.0                     | 3                      |
| Liver cancer              | HCC                                              | 48.0             | 2             | 24.0                    | 2 days                 |
| Bone and soft tissue tumors | Rectal cancer with liver metastases              | 58.0             | 1             | 58.0                    | 1 day                  |
|                           | Osteosarcoma                                     | 70.4             | 16            | 4.4                     | 4                      |
|                           | Chordoma, chondrosarcoma                         | 67.2             | 16            | 4.2                     | 4                      |
|                           | Spine, paraspinal                                | 64.0             | 16            | 4.0                     | 4                      |
| Prostate cancer           | Low/intermediate/high risk                       | 57.6             | 16            | 3.6                     | 4                      |
|                           | Locally unresectable                             | 51.6             | 12            | 4.3                     | 3                      |
| Pancreatic cancer         | Locally unresectable                             | 55.2             | 12            | 4.6                     | 3                      |
|                           | Preoperative carbon ion therapy + gemcitabine chemotherapy | 36.8         | 8             | 4.6                     | 2                      |
| Rectal cancer             | Postoperative recurrence cases without history of radiotherapy | 73.6         | 16            | 4.6                     | 4                      |
|                           | Reirradiation for recurrent pelvic tumor         | 70.4             | 16            | 4.4                     | 4                      |
| Cervical cancer           | Whole pelvis                                     | 36               | 12            | 3                       | 4                      |
|                           | Primary tumor + positive lymph node              | 15               | 5             | 3                       | 4                      |
|                           | Primary lesion                                    | 16–19.2          | 4             | 4–4.8                   | 4                      |

The above dose fractionation patterns refer to the treatment recommendations in "Carbon-Ion Radiotherapy: Principles, Practices, and Treatment Planning" edited by Tsujii et al.49

ACC, adenoid cystic carcinoma; HCC, hepatocellular carcinoma; MMM, mucosal malignant melanoma.

Gastrointestinal toxicity is the main adverse reaction related to proton therapy for pancreatic cancer, which might be manifested as nausea, vomiting, abdominal pain, and so on, and gastrointestinal bleeding and perforation might occur in severe cases. The incidence of adverse reactions above grade 3 was 3–12%. Radiation-induced ulcerative lesions of the gastrointestinal tract are the pathological cause of gastrointestinal related symptoms, with up to 51% of antral lesions and 39% of ulcers at the level of the duodenum.62

The most common complications of ion therapy for prostate cancer are radiation enteritis and cystitis.64 Overall, ion therapy has certain advantages in decreasing toxicity compared with traditional radiotherapy, but further study is still required.

8.4 Complications of ion therapy for bone and soft tissue tumors

Ion therapy, like photon radiotherapy, also has the following radiotherapy complications: delayed postoperative incision healing; abnormal growth, and development of bone and soft tissue; limb length inequality (those with a gap of 2–6 cm use modified shoes, otherwise surgical correction is required); osteoporosis of the affected bone; increased risk of fracture; dysfunction caused by joint fibrosis; soft tissue edema; radiotherapy recall reaction caused by chemotherapeutic drugs; skin discoloration and/or telangiectasia; secondary second malignant tumors, and...
| Site                                      | Tumors types                                      | Total dose (GyE) | No. fractions | Dose per-fraction (GyE) | Treatment time (weeks) |
|------------------------------------------|--------------------------------------------------|------------------|---------------|-------------------------|------------------------|
| Head and neck tumors                     | ACC                                              | P: 56            | P: 28         | P: 2.0                  | 6.6                    |
|                                          |                                                 | C: 17.5          | C: 5          | C: 3.5                  |                        |
|                                          |                                                 | C: 70            | 20            | 3.5                     | 4                      |
|                                          | MMM                                             | C: 70            | 20            | 3.5                     | 4                      |
|                                          | Uveal malignant melanoma                        | C: 45            | 5             | 9                       | 1                      |
|                                          | Soft tissue sarcoma                              | C: 70            | 20            | 3.5                     | 4                      |
|                                          | Recurrent NPC                                    | C: 63            | 21            | 3.0                     | 4.2                    |
|                                          | Newly diagnosed nasopharyngeal carcinoma         | P or X: 56       | P or X: 28    | P: 2.0                  | 6.6                    |
|                                          |                                                 | C: 17.5          | C: 5          | C: 3.5                  |                        |
|                                          | Head and neck squamous carcinoma                 | P or X: 56       | P or X: 28    | P: 2.0                  | 6.6                    |
|                                          |                                                 | C: 17.5          | C: 5          | C: 3.5                  |                        |
|                                          | Postoperative radiotherapy for head and neck cancer | P: 56–66       | 28–33         | 2.0                     | 5.6-6.6                |
|                                          |                                                 | C: 60–63         | 20–21         | 3.0-3.5                 | 4-4.2                  |
| Intracranial neoplasms                   | High-grade glioma                                | P: 60            | 30            | 2.0                     | 6                      |
|                                          | Glioblastoma (in clinical trials)                | P: 60            | P: 28         | P: 2.0                  | 7                      |
|                                          |                                                 | C: 15            | C: 3          | C: 5.0                  |                        |
|                                          | Low-grade glioma                                 | P: 54            | 27            | 2.0                     | 5.4                    |
|                                          | Meningioma                                       | P: 50–60         | 25–30         | 1.8-2.0                 | 5-6                    |
|                                          | Pituitary tumor                                  | P: 54–60         | 27–30         | 2.0                     | 5.4-6                  |
| Skull base tumors                        | Chordoma, chondrosarcoma                         | P: 70            | 35            | 2.0                     | 7                      |
|                                          |                                                 | C: 70            | 20            | 3.5                     | 4                      |
| Lung cancer                              | Early peripheral (T1–2N0M0)                       | C: 60–68         | 8             | 7.5–8.5                 | <2                    |
|                                          | Early intermediate (T1–2N0M0)                     | C: 60–70         | 10            | 6.0–7.0                 | 2                      |
|                                          | Early central (T1–2N0M0)                         | C: 75–80         | 20            | 3.5–4.0                 | 4                      |
|                                          | Locally advanced (T1–4N1–3M0)                    | C: 79.2–80       | 20–22         | 3.6–4.0                 | 4-4.2                  |
| Liver cancer                             | HCC                                             | C: 65            | 10            | 6.5                     | 2                      |
|                                          | Rectal cancer with liver metastases              | C: 65            | 10            | 6.5                     | 2                      |
| Bone and soft tissue tumors              | Postoperative adjuvant radiotherapy              | P: 50            | P: 25         | P: 2.0                  | 6                      |
|                                          |                                                 | C: 20            | C: 5          | C: 4.0                  |                        |
|                                          | Chordoma, chondrosarcoma                         | C: 70.4          | 16            | 4.4                     | 3.1                    |
|                                          | Spine, paraspinal                                | C: 72            | 18            | 4.0                     | 3.6                    |
| Urinary system tumors                    | Prostate cancer cT1–3N0M0                         | C: 65.6          | 16            | 4.1                     | 3.2                    |
|                                          | Prostate cancer cT1-3N1-2M0                       | P: 46            | P: 23         | P: 2.0                  | 7                      |
|                                          |                                                 | C: 32            | C: 8          | C: 4.0                  |                        |
| Pancreatic cancer                        | Locally unresectable                             | C: 67.5          | 15            | 4.5                     | 3                      |
| Rectal cancer                            | Postoperative recurrence without history of radiotherapy | C: 67.5       | 15            | 4.5                     | 3                      |
|                                          | Reirradiation for pelvic tumor                   | C: 67.5          | 15            | 4.5                     | 3                      |
| Cervical cancer                          | Whole pelvis                                     | P: 46            | P: 23         | P: 2.0                  | 7                      |
|                                          | Primary tumor + positive lymph node              | C: 15            | C: 5          | C: 3.0                  |                        |
|                                          | Tumor lesions                                    | C: 20–22         | C: 5          | C: 4–4.4                |                        |

The above dose fractionation patterns refer to clinical practice in Shanghai Proton and Heavy Ion Hospital, China. ACC, adenoid cystic carcinoma; C, carbon ion therapy; HCC, hepatocellular carcinoma; MMM, mucosal malignant melanoma; NPC, nasopharyngeal cancer; P, proton therapy; X, X-ray radiotherapy.
so on; and there is still a lack of data for direct comparison with photon radiotherapy.\textsuperscript{65}

9 | EFFICACY EVALUATION AND FOLLOW UP AFTER TREATMENT

The efficacy evaluation method after ion therapy is basically the same as that of photon radiotherapy. For all cases, baseline and efficacy evaluation after radiotherapy are carried out according to the Response Evaluation Criteria in Solid Tumors (RECIST). The patients are followed up every 3–4 months in the first 2 years, and then every 6 months. Each follow-up visit should include at least collection of the medical history, physical examination, relevant imaging examinations at the tumor site (CT, magnetic resonance imaging, bone scan or PET/CT, etc., carried out as required), laboratory tests, and tumor biomarkers. It is suggested that all cases of ion therapy should be included in the clinical trials, especially clinical research comparing carbon ions with protons or photons. The short-term efficacy and long-term survival results of ion therapy should be recorded in detail, and close attention should be paid to treatment-related acute and late toxicities, so as to provide more experience and research data for ion therapy.

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