Role of Carbon Ion Therapy for Stage I NSCLC Using a Regimen of Four Fractions over Week

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Stage I NSCLC can be cured with radical surgery; the reported 5-years overall survival rate ranged from 55% up more than 70%. Even with modern techniques there is a low, but nonzero, in-hospital death rate of 0.8%. Lobectomy, performed by thoracotomy or video-assisted thoracoscopic approach is the surgical procedure of choice, being more limited resection less effective in local control rates. Loss of pulmonary parenchyma has a negative impact on respiratory function and can reflect in a decreased quality of life. In the past, patients unable to withstand lobectomy and/or the related surgical stress have been traditionally treated with standard radiotherapy (RT) at doses of about 60 Gray. The outcomes were clearly inferior to those of surgery with reported 5-years overall survival of 23%. Modern high precision photons radiotherapy (Image-Guided RT and others) can be substantially more effective. For example, stereotactic technique (SRT) allow to selectively deliver higher doses to the detectable tumor (plus a margin). Hypofractionated schedules with only few (typically less than 5) treatment sessions are given. A large retrospective analysis has shown that, with a biological equivalent dose greater than 100 Gray, the 3-years overall survival rate was 88% and local control rivalled with the best surgical series. Based on the preliminary results obtained in many phase I and phase II trials, two new trials are about to start (RTOG 0618 and Japan Clinical Oncology Group 0403) in which SRT will not be limited to inoperable patients but will be proposed as an alternative to surgery.

Protontherapy (PT) has been used for small series of inoperable stage I NSCLC with promising results. Carbon ion radiotherapy (CIRT) has been used only in two Japanese centers (Hyogo Ion Beam Medical Centre, HIBMC and Heavy Ion Medical Accelerator in Chiba, HIMAC) and only HIMAC has published its early results. In this limited scenario the role of hadrontherapy is not still clearly defined, with major concerns in terms of cost-effectiveness and results based on evidence.

Thanks to their favorable physical characteristics both carbon ions and protons are able to deliver high doses to target volumes of complex shapes at least as well as other high precision RT techniques. They are furthermore capable to significantly reduce the volume of lung parenchyma receiving middle and low doses, and to reduce almost to zero irradiation of other organs (heart, esophagus, and spinal cord). CIRT has the theoretical advantage over PT of delivering a radiation with an increased radiobiological efficacy (RBE) and thus possibly killing also radioresistant clonogens. The high RBE is selectively limited to the target with normal tissues receiving a low RBE radiation; therefore the possible increase in local control can be achieved without any increase in the risk of toxicity. The only theoretical disadvantage of PT and CIRT is their increased risk of geographic miss. Not only organ motion but also organ deformation can significantly affect the actual delivered dose and must be specifically addressed.

In their current article Miyamoto et al report the excellent results achieved with a four fractions schedule of CIRT for stage I NSCLC patients that were either inoperable or refused surgery. In this and in their previous papers the treatment techniques was described, giving details on the gating procedures used to deal with organ motion and on the special strategies necessary to expand the GTV accounting for the finite range of
penetration of carbon ions. The group from HIMAC has moreover reported data on late pulmonary toxicity after CIRT, assessed both radiologically and with functional spirometric tests. Results of CIRT for lung cancer are to be considered extremely interesting and this treatment modality appears safe and effective. Until now the main limit of PT and CIRT seems to be their scarce availability.

Unfortunately to day it is definitely not possible to compare results obtained with CIRT and with other RT techniques. Different dose and different schedules employed, different follow up available, different strategies for organ motion control would make such a comparison extremely difficult. Anyway the key factor that makes such a comparison impracticable is the difference in selection criteria used. For example patients treated with SRT in Japan tend to show a better outcome, at the same dose levels, compared with those treated in Europe and USA. This has been attributed to a selection bias possibly deriving from a less aggressive approach of Japanese surgeons.

A prospective randomized trial is the only tool that will be able to tell if the potential advantages of PT over SRT and of CIRT over PT are of clinical relevance. The endpoints of this trial should include local control and late toxicity. Preserving respiratory function is of paramount importance and PT and CIRT may be beneficial, on the other hand the reported costal bone fractures after CIRT may be a concern. Such a trial would require the coordinated efforts of radiation oncologists from traditional and hadrontherapy centers. As soon as data from PT and CIRT will be more mature these treatments could be included in trials comparing surgery and radiotherapy.

One of the most common arguments against hadrontherapy is its greater economic costs. CIRT is more expensive than PT which is in turn more expensive than SRT or other RT techniques; but any RT technique is much less expensive than the golden standard of lobectomy. Cost and cost-effectiveness are therefore of minor concern for NSCLC and we believe that the only ethical approach would be to strive for the most effective kind of radiotherapy as it will anyway result in a saving compared to surgery.

Finally, it is worth mentioning that patients surviving a first lung cancer have an increased risk of developing a second NSCLC of about 10%. PT and CIRT could offer the advantage of an easier second radical radiotherapy even though it would be very difficult to measure it in a trial.

In conclusion, CIRT is a promising treatment that needs to be tested against other advanced techniques with a methodologically sound approach. After the pioneering works of HIMAC many new carbon ion facilities are nowadays being built and will hopefully allow carrying out the indispensable phase III trials.

REFERENCES