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Hypofractionation in current clinical practice: a flash forward to the near future of radiation oncology?

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To the Editor: At the XXI AIRO (*Associazione Italiana Radioterapia Oncologica*) National Congress, held in Genoa, Italy, on November 19-22, 2011, "hypofractionation" was one of the most discussed issues. Various lectures regarding reviews from the literature and several experiences from various Italian centers were presented and debated with increasing interest in the radiation oncology community[1]. But what does the term "hypofractionation" mean? Conventional radiotherapy is delivered in fraction sizes of 1.8 to 2.0 Gy for several weeks. This method of fractionation emerged from the observation that late side effects of radiotherapy have been reduced without an apparent compromise in cancer local control. With the term "hypofractionation" radiation oncologists intend the prescription of fewer, larger-dose-per-fraction treatments that are usually performed over a shorter time period than conventional radiation fraction sizes. From the beginning of radiotherapy, hypofractionation has been historically applied for a series of cancer diseases, mainly with a palliative intent to reduce the discomfort of the patient due to the usual long duration of conventional fractionated radiation treatments. It was frequently assumed that hypofractionation is affected by a higher risk of late complications due to irreversible damage in irradiated healthy tissues surrounding the target. Thus, hypofractionation was often limited to patients with a relatively short life expectation. Only over the last few decades has hypofractionation with a curative intent been rapidly and more extensively adopted in the clinical practice of radiation oncology. In recent years: a) for the continuous high technology assessment improvement in treatment units, b) for the fast and intense acquisition of new radiobiological data, radiotherapy has been in the midst of revolutionary changes. More sophisticated stereotactic, intensity-modulated and image-guided techniques of delivering radiation have allowed clinicians to safely prescribe higher doses than in the past, frequently with hypofractionated schedules[2,3]. Emerging clinical evidence is showing that, for several of the most common cancers needing radiotherapy, the total length of treatment can be significantly shortened, maintaining the same efficacy and tolerability of conventional radiotherapy[4-13]. Much radiobiological data would seem to support the clinical hypothesis concerning potential hypofractionation efficacy without increasing toxicity: the paradigm is represented by prostate cancer[14-15]. The alpha/beta ratio, which represents a parameter to estimate also the attitude of radiation response of a tissue, is thought to be low for prostate cancer[14,15]. According to a "linear-quadratic" model, the lower the alpha/beta ratio, the higher the sensitivity of the tumor for dose per fraction. Low dose-rate brachytherapy results, utilized to evaluate the linear component (alpha) of survival curves, and several external beam radiotherapy data were analyzed and elaborated to indirectly estimate the alpha/beta ratio for prostate cancer[16]. The rectal alpha/beta ratio was estimated approximately equal to 3[16]. If the alpha/beta of prostate cancer is less than 3, as was assumed in various studies, it is possible to increase the therapeutic window by applying hypofractionated schedules for prostate cancer[14-16]. Controversies remain on the "linear-quadratic" formula: this is a simple application that does not take into account some fractionation-related parameters such as reoxygenation, redistribution, and repopulation[17]. Nevertheless, a high number of clinical trials of hypofractionation in prostate cancer have been published or are still ongoing[4-9]. Most trials have evaluated modest increases in daily fraction size, whereas some investigators have introduced more aggressive hypofractionated regimens[4-7]. In both cases, preliminary or long-term data seem to confirm hypofractionation as safe and effective in the results of the larger part of the experiences regarding prostate radiotherapy.

Compared to the prostate, fewer radiobiological arguments in favor of hypofractionation have been published for breast cancer[8-11]. However, short schedules could probably be the most commonly adopted fractionations in the near future for most cancer patients submitted to conservative breast surgery. Over the last 20 years, several randomized trials involving more than 7,000 women compared hypofractionated adjuvant radiotherapy to a standard regimen of 50 Gy in 25 fractions: START-A trial, START-B trial, RMH/GOC trial, ONTARIO trial[8-11]. Long-term results of these trials indicated similar rates of local-regional relapse comparing the two radiation treatment arms. Breast cosmesis at a median follow-up of more than 10 years was equivalent in both treatment arms[11]. From these results, it was confirmed that a 13-16 fraction regimen delivered over 5 weeks is as safe and effective as 50 Gy in 25 fractions[8-11].

In the near future, hypofractionation will probably revolutionize the standard treatment of the initial stage of lung cancer. Recent clinical data show that hypofractionated stereotactic radiation therapy (SBRT) for peripheral lesions of inoperable patients with early stage non-small cell lung cancer is able to achieve outcomes comparable to that of surgery[12-13]. For the large doses prescribed, the "linear-quadratic" model is not applicable for stereotactic treatment. However, other clinical and radiobiologic data support the theory that SBRT compares favorably to surgery. For early stages of non-

small cell lung cancer, using biological effective doses greater than 100 Gy, 5-year controls are approximately 85-90%[12-13]. Excellent toxicity profiles were also recorded with hypofractionation by means of SBRT. Despite the wide variability of fractionation reported in published experiences, cancer-specific survival values are significantly higher with SBRT than with traditional radiotherapy with standard fractionation. Doses of 60-70 Gy, usually prescribed in conventional fractionated 3D-conformal radiotherapy, lead to disappointing local control rates of only 30-50% for stage I disease and therefore could not meet the demand to replace surgery. The rationale of extreme hypofractionation, as a surrogate of surgery, is based on the real possibility to deliver, with various precision techniques of radiotherapy, ablative doses in a few fractions. In the range of 8-20 Gy per fraction, the alpha/beta ratio seems to be less determinant in radiation response of the tumor than other prevalent phenomena such as endothelium apoptosis and stoma damage[18]. If this assumption is true, extreme hypofractionation with SBRT and ablative doses should be more effective than conventional fractionation for different types of small primary and metastatic solid tumors in the body. For example, the role of hypofractionated SBRT has proven to be interesting in oligometastatic disease, where preliminary data in the literature showed a higher local control than with conventional radiation therapy, with potential impact on quality of life and initial promising results on survival in selected patients[19-20].

Several debated issues remain for hypofractionation, and the unresolved questions concern mainly optimal patient selection, radiation techniques, and the risk of late toxicity. In spite of this, promising clinical data from an increasing number of recent trials are convincing clinicians to widely accept hypofractionation as an option for several types of cancer patients.

Although with different radiobiological background and with different schedules of hypofractionation (for example, “moderated” in adjuvant breast, “extreme” in early lung, both in prostate), the choice of a short course of fractionation can be advantageous not only for its potential clinical impact. Fewer fractions would enhance patient convenience compared to conventional external beam radiotherapy treatments, which can extend for five to nine weeks. Hypofractionation may also result in increased cost-effectiveness by potentially decreasing the cost of a course of treatment.

In summary, hypofractionation, in its different declinations, could replace definitively conventional fractionation in a large number of cancer patients requiring radiotherapy. In the next few years, it will be even more common to confront short schedules of fractionation in daily clinical activity, as confirmed by several experiences, recently published also in *Tumori*[21-25]. Thus, the new generation of radiation oncologists will probably learn how to better manage hypofractionation treatments.

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