

## EDITORIAL

# The promise of adaptive radiotherapy for pelvic tumors: “too high cost for too little result” or “a low cost for a significant result”?

The sound and thorough review by Thornqvist et al. [1] on the clinical experience with adaptive radiotherapy (ART) in the treatment of pelvic tumors arrives in a “hot” and quite timely moment. This approach was originally suggested almost two decades ago [2] as a sort of “visionary” way to drastically minimize the risk of missing the tumor and, more importantly, to reduce the volume of irradiated normal tissues when applying (large) margins to gross tumor volume (GTV)/clinical target volume (CTV). The use of safe recipes for margins had already been well assessed at that time [3,4] due to the recognition of the relevant impact of systematic and random set-up errors during fractionated radiotherapy and to the possibility to model their effects on the dose distribution in a “rigid body” approximation. The “margin dogma” surely had a positive impact in reducing local relapses due to geographical misses but with an implicit price to be paid in terms of irradiated normal tissues. Being based on the priority of minimizing the risk of missing the target even in the most “critical patients” (from the point of view of set-up error), population-based margins are intrinsically “redundant”, or, in other words, if we knew the extent of systematic (and secondarily random) errors on an individual basis, we could apply much smaller (individualized) margins, with consequently, far greater sparing of the normal tissue surrounding GTV/CTV. With this in mind, the ART concept may be considered as the first attempt at moving treatment personalization forward to include the individual variability of set-up in the optimization and delivery process; not by chance, the first applications came mostly in the paradigmatic and appropriate case of prostate cancer.

As often happens in the case of “visionary” ideas, the ART approach in its original formulation by Yan, remained a niche for few patients in few academic centers for many years, mainly owing to the difficulty of its practical implementation due to both the scarcity of automatic tools and the need for extensive skilled manpower. The perception that this approach represented “too high cost for too little results” remained prevalent for a long period; ART was simply considered to be unfeasible for the great majority of centers, even in well equipped academic institutions.

However, after the pioneering period, the term ART began to assume a number of variations that are still in rapid evolution. Nowadays, it is clear that ART for pelvic tumors is a term with many different meanings.

## ART – one word, different worlds

In general, we may categorize the available ART approaches for pelvic tumors into three large categories: (1) Off-line

adaptation through individual margin assessment and re-planning (and/or re-fit of MLC leaves); (2) On-line plan adaptation, mostly based on daily plan selection; and (3) Off-line adaptation following tumor regression.

Several points related to the development of proper strategies in each of the three categories and their perspectives deserve discussion. The first family (1) mainly includes experiences following Yan’s original approach, trying to adapt the margins (accompanied by re-planning) to the individual patient’s characteristics after an adequate sampling of set-up error measurements taken during the initial phase of the treatment; it dealt mostly with prostate cancer and, more marginally, with its extension to deformable targets, as in the case of bladder cancer. Very interestingly, although this approach was the first to be implemented in the 1990s, as may be seen in Table 2 of the Thornqvist et al. review [1], only eight series have been published (five for prostate and three for bladder cancer) with the majority of the data referring to patients treated in the 1990s and in the early 2000s. On the contrary, the second category (2), mainly represented by on-line plan selection approaches for cervix and bladder cancer seems to be currently quite “vital”, as confirmed by the publication of significant new experiences during the time of preparation of the review [5–7]. The third category is the largest: the potential of adapting the brachytherapy boost to tumor regression drove several centers toward the implementation of adaptive brachytherapy for gynecological cancers [8].

Interestingly, a similar approach was recently adopted at our institute for boosting the residual rectal cancer tumor during neo-adjuvant radio-chemotherapy with external beams [9].

It is clear that the cost-benefit balance for each category depends on the objectives and the instruments available. What kinds of ART approaches are expected to continue and how will they evolve? In what situation could they become the “standard” and what possible benefit could be expected in the near future? It is difficult to provide appropriate answers to these questions; here, we just wish to discuss a few key points with the aim of contributing to the discussion toward a better definition of priorities and visions regarding the future of ART for pelvic malignancies.

## On-line IGRT killed off-line ART for prostate cancer – any room for a new life?

Despite the increased availability of in-room imaging and fast contouring and optimization tools, off-line ART with re-planning seems to be in use in very few institutions. One of the possible explanations is, in our opinion, the rapidly spreading use of daily set-up correction consequent to the large

availability of in-room imaging systems for image guidance. At least in the case of prostate cancer, in which the application of rigid translations/rotations to correct the daily set-up is associated with relatively small residual errors (the prostate in fact represents a good approximation of a “rigid body”), off-line ART re-planning is less attractive (i.e. more time consuming) with respect to the fast correction of the set-up at each fraction. Adaptive re-planning and margin customization could find new life in counteracting intra-fraction motion [10] for those patients showing significant shifts during a session. However, this approach could be rendered unnecessary by efficient on-line tracking/monitoring of prostate position, an issue which is more important for stereotactic applications. Off-line re-planning after the quantification of the residual error after daily correction could potentially have interesting applications in the treatment of pelvic nodes concomitantly to the prostate, with the aim of customizing the (residual) margin around pelvic lymph nodes [11–13].

### **A smart future for on-line plan selection approaches for deformable targets?**

There is an impression that the on-line plan selection from a library of pre-optimized treatment plans may represent a very robust and efficient ART approach in external radiotherapy for targets showing potentially large inter-fraction variation because of their deformability. This is primarily the case for bladder and cervical cancer. An important issue remains that of the development of tools for speeding up both the contouring and the planning phases. In particular, promising developments in the implementation of accurate biomechanical models for bladder distension could help in automatizing the contouring phase [14]; coupled to this development, the potential of (at least partially) automatizing the planning phase is also very attractive [15] and could open the possibility of implementing these techniques in small to medium sized centers as well.

At the same time, tools permitting the rapid selection of plans, correct delivery of the dose and safe storage of the data referring to each fraction would be appropriate. However, more research is warranted regarding the residual error following this approach and in robustly defining margins to take it into account, including intra-fraction changes [6,16,17].

### **New tools for rapid on-line re-planning – dream or reality?**

An important general point concerns the rapid development of tools for ART applications, including deformable registration, daily dose calculation, dose summation and fast re-planning. In the case the CTV is coincident with the whole organ (as often happens for prostate and bladder cancers), the benefit of frequent adaptive re-planning does not seem to be of primary clinical significance. However, it is also clear that the scenario may change over time due to the likely increasing availability of tools for automatic segmentation/contouring and rapid planning which could lead to the

concrete possibility of considering the actually delivered “dose-of-the-day” at each fraction and, if necessary, of off-line and, possibly, on-line re-planning.

A paradigmatic scenario where on-line re-planning could have important applications is the emerging field of stereotactic radiotherapy which could have a growing role in the treatment of pelvic tumors, mainly for low-risk prostate cancer patients and for the treatment of single/multiple positive nodes. A crucial point regarding the future of on-line adaptive re-planning is the increased importance of residual uncertainties, firstly intra-fraction changes.

### **Boosting the residual tumor – expanding ART indications?**

ART is unquestionably evolving rapidly toward the inclusion of individual biological biomarkers into the process. The possibility of predicting or directly measuring the tumor response to therapy is opening extremely promising areas of refinement to the original ART concept. Within this scenario, an effective and already available approach consists in the direct measurement of tumor regression during therapy followed by “adaptation” of the treatment plan in the remaining portion of therapy through an “adaptive” boost to the residual tumor. This approach is widely applied when delivering adaptive boosting with brachytherapy for gynecological cancers, generally using magnetic resonance imaging (MRI). Very interestingly, the possibility of boosting residual tumors in the case of external beams radiotherapy for pelvic malignancies has been explored for rectal cancer during neo-adjuvant radio-chemotherapy [9,18]; this ART strategy may in principle be exploited to substantially escalate the dose to the tumor with a view to increase the rate of pathological complete responses and improve the chance of conservative surgery in distal rectal cancer or, potentially increase the fraction of patients that could benefit from a wait-and-see approach as an alternative to immediate surgery, after radio-chemotherapy. Very promisingly, in a very recent watchful waiting prospective trial, Appelt et al. [19] delivered an integrated brachytherapy boost on the residual tumor during the last week of treatment (2Gy equivalent dose: 66 Gy) in 55 patients treated with radio-chemotherapy for distal rectal cancer. They found a very high rate of clinical complete response (78%) with 58% of patients with local control and free of surgery at 2 years from the treatment and relatively mild acute and late toxicity. Similar strategies using external radiotherapy could also be applied to other tumors that exhibit substantial shrinkage during therapy such as, for instance, cervical and anal cancers as well as for advanced, non-resectable rectal cancer [20]. Of course, the appropriateness of such applications should always be confirmed by means of controlled clinical trials.

### **Predictive models of tumor response and ART customization**

As briefly mentioned in the previous section, there is enormous interest in developing models that are predictive of

tumor response and which could have a dramatic impact in orienting/optimizing the ART strategies for pelvic tumors, as well as other districts. Multi-variable models based on tumor/patient characteristics, including genomic and radiomic features, will likely classify patients based on expected outcome/response. However, as discussed above, the quantification of tumor regression during therapy may also orient the type of adaptation, being a quantitative, direct and simple measure of the individual response to therapy. Again, rectal cancer is a paradigmatic example, thanks in part to the availability of a precise assessment of the response to the treatment; models predicting the response based on pretreatment features (including imaging-based parameters) started to appear [21,22] as well as models including tumor regression measured by MRI [23]. The assignment of patients to specific categories based on predictive models has the potential of identifying those patients who could benefit most (or, on the contrary, not at all) from adaptive boosting. Similar considerations may be extended to other types of cancer in the pelvic region, primarily in the gynecological domain.

## Concluding remarks

Despite the relatively limited clinical experience, well reviewed by Thornqvist et al. [1], the points briefly discussed here clearly suggest that a promising future may be expected for ART for pelvic tumors. The availability in the near future of reliable models able to predict outcome based on specific patient and tumor characteristics is likely to lead the evolution of ART toward increasingly customized approaches. However, new tools for automatizing most of the involved procedures (including patient set-up, deformable registration, dose calculation and rapid re-planning) and the availability of morphological and functional imaging before and during radiotherapy will likely support the large scale clinical implementation of ART techniques in many significant applications.

Considering its relatively brief history, ART has evolved from a visionary, albeit cumbersome and expensive way to counteract set-up errors (perhaps “too high cost for too little result”) to its current potential of being the natural evolution of modern radiotherapy to further individualize the treatment by incorporating anatomical and biological information, likely to become “a relatively low cost for a significant result”. As always, time will provide the definitive answers and the responsibility for this answer lies with us.

## Disclosure statement

None to declare.

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