The spectrum hypothesis and the technical revolution in radiotherapy at the origin of a major paradigm shift

P.A. Coucke

"Predicting is difficult, especially predicting the future…."

The evolution in radiotherapy nowadays allows highly conformal treatment. Even for moving targets, the radiation therapy can be given with high precision, avoiding as much as possible the irradiation of healthy tissue. This allows reduction of the number of fractions and increase of the biological effect of the treatment. The literature shows us that this increase in biological effect opens the perspective of ablative radiotherapy as an alternative to surgery, whether this is for selected primary tumours or for limited metastatic sub-sites. This ablative radiotherapy will change the treatment paradigms in oncology radically. It is cost-effective, non-invasive and, as the treatment is given in a limited number of fractions not requiring a hospital stay, it has no negative impact on the quality of life of the patient.

(Belg J Med Oncol 2012;6:151-156)

Introduction

In the history of treatment of cancer, surgeons such as Halstedt developed aggressive loco-regional treatment modalities (ablative treatment) to eradicate cancer.[1] They advanced the hypothesis that cancer is progressing in an orderly fashion, emphasising the importance of ablation of the primary tumour and adjacent lymph nodes. This theory was replaced by Fisher who claimed that cancer is a metastatic disease at onset. If this is true, the ablative treatment aiming at local and regional control of the disease cannot impact survival.[1] This theory prevailed for several years during the golden era of development and widespread use of systemic treatment. However, cancer is neither a local disease nor a systemic disease, but it represents a spectrum of diseases. This spectrum hypothesis was first launched by Sam Hellman and Ralph Weichselbaum in 1995.[2] The metastatic phenomenon is not random and does require the acquisition of capabilities of invasion and metastasis. It is the result of a complex interaction between cancer cells that acquired these capacities for dissemination and invasion and the host, especially the niche in which those cells will ultimately settle and proliferate (seed and soil hypothesis of Paget).[3] This theory of a pre-metastatic niche located in the receiving host organ explains the non random distribution of metastatic deposits and illustrates the importance of a continuous cross-talk between the tumour cells and the homing organs.[4,5] If metastases are not de facto full-blown there might be an opportunity for an aggressive ablative approach of offering the potential of a significant survival benefit.

Author: P.A. Coucke MD PhD, [illegible] Domaine Universitaire du Sart-Tilman [illegible] Liège, Belgium [illegible]
Conflict of interest: the author has nothing to disclose [illegible]
Keywords: oligo-metastases, stereotactic body radiation [illegible]

Oligo-metastases and the potential impact on outcome of an ablative treatment approach

Surgeons have tested the potential of a curative resection in case of limited metastatic disease (referred to as oligo-metastatic disease = OMD).[5-7] For example, in the case of breast cancer, it has been shown in several clinical series that an aggressive local surgical approach for solitary metastatic sites located in the brain, liver and lung can yield survival figures ranging from 10% to 50% at 5 years.[8-11] On the one hand, these publications are characterised by differences in patient populations, treatment techniques and modalities of follow-up, but on the other hand they demonstrate how treatment can be tailored according to a specific patient and disease profile.

A pre-requisite for a long survival probability in these surgical series is the complete eradication, i.e. a radical resection labelled as R0 resection by the pathologist (no microscopic or macroscopic residual disease left behind after surgical resection). In general, more information is available in the published literature on surgical modalities to remove metastatic sub-sites as compared to any other local modality, but apparently very little of this research has been conducted in a prospective fashion.[12]

In view of these surgical publications, two clinical situations can be identified that could well generate opportunities for aggressive local ablative treatment approaches: de novo OMD or induced OMD. In the first situation, de novo OMD, the disease is characterised by the presence of synchronous (i.e. at the time of diagnosis), or metachronous (i.e. after initial diagnosis has been set and an initial treatment has been given for the primary disease) limited number of distant metastatic sub-sites. In the second scenario, if the systemic treatments usually applied in the context of widespread metastatic disease are able to control almost all metastatic sub-sites, yielding a limited number of macroscopically detectable metastatic remnants, one should be able to apply ablative treatment approaches to the latter. If this is the case, a single course of ablative treatment might be able at the end to transform a partial response (which in fact is synonymous to a total failure) into a complete clinical response which could eventually stand for a couple of years and potentially influence positively survival and quality of life. Therefore, if the efficacy of the systemic treatment is increasing constantly, one might envision an ever-growing importance of local ablative treatment modalities. Moreover, a debulking procedure with a potent local therapy could result in a remaining burden more sensitive to chemotherapy.[12]

The technical evolution allows for ablative radiotherapy

To obtain the same ablative effect as the surgeon, the radiation oncologist should be able to apply a very high dose on a limited volume.[13] However, increasing the physical radiation dose (number of fractions time dose per fraction) by conventional conformal techniques results in an increased risk of normal tissue complications. Even using treatment under image guidance (IGRT=Image-Guided Radio Therapy) and beam intensity modulation for optimised dose delivery (IMRT=Intensity-Modulated Radio-Therapy), the limits of applicability of a high physical dose will be defined by the tolerance levels of the healthy tissue surrounding the target.

It is well known that the dose response relationship for tumour and normal tissue to ionising irradiation is best represented with a sigmoid dose response curve. Both dose response curves - in an ideal world - should be separated as much as possible to offer a therapeutic index as large as possible and hence increase the probability of increasing dose and cure without complications. However, both curves are in reality not that much separated. Therefore, any increase in physical total dose will, without any doubt, result in an increase of the probability of side-effects in healthy tissue. One of the main reasons for the limitations of the physical dose increase is linked to the necessity of taking - within the irradiated volume encompassed by the prescription isodose - not only the gross tumour volume (GTV) and the possible microscopic extension (clinical target volume=CTV), but also safety margins which are necessary to cope with movement of the target (internal target volume=ITV) and uncertainties which are positional (daily repositioning uncertainties) or mechanical (technically linked to the device) in nature (planning target volume=PTV). The end result is a rather large volume to be irradiated at a

therapeutic dose level in order to obtain local control. Therefore, this large volume encompasses a significant amount of non-target tissue. If one would be able to reduce these safety margins, he could potentially envision a physical dose escalation without taking significant increased risk of late normal tissue complications. To do so, one has to eliminate the impact of and/or movement of the target and/or positional and/or mechanical uncertainties. A reduction of the thickness of the shell taken around the target by a couple of millimetres will have a tremendous effect on the amount of normal tissue within the volume encompassed by the prescription isodose. This can be highlighted by a straightforward example: if you remove the peel of an orange without dropping it away in the basket, the total volume of this collected peel corresponds to the volume of the fruit itself.[4] Therefore every reduction of the shell thickness results in a significant reduction of the volume of healthy tissue within the prescription isodose.

One of the largest shells added to the CTV is the one required by the respiratory-related movement of the target. If there is a possible gain to look for to reduce the amplitude of the safety margins, reducing the shell required to cope for respiratory-related movement of the target is obviously a logical choice. There are two ways to eliminate respiratory movement: either you consider gating or you choose tracking. In gating you ask the patient to breath-hold and you switch on the beam during this breath-hold period. It is obvious that here you have to rely on perfect collaboration from your patient which might be a tricky issue especially in older and frail patients with respiratory disorders. To avoid this compliance problem you can opt for tracking. In tracking the patient does not provide a special effort and you ask him to breathe normally. The key for tracking is to register continuously the potential impact of the respiratory movement on the target position. Therefore you rely on a correlation model built up by external markers and internal markers. External markers alone, such as for example infra-red emitters positioned on the patient chest wall coupled to a detector somewhere in the room capturing the infrared signal from the moving emitter, are not reliably giving the position of the target. This is especially true as there is no way to assess whether movement of external and internal markers are linearly linked. Moreover, external markers alone do not account for complex internal target movements (for example hysteresis). The best thing to do is to couple the information provided by the external markers to assessment of positional changes of internal markers. These internal markers can be either surrogates for the target (e.g. bony structures) or, more interestingly, directly the target itself, provided the latter can be localised with radiological imaging. An alternative to the target itself is the use of several gold fiducials implanted under CT-guidance at the boundaries of the target in a particular geometrical position one to each other so that even complex movement can be tracked adequately. Whatever is used as internal marker, to avoid continuous imaging during beam on time, one should establish a correlation model between external markers and internal markers. If this correlation model is built, one can rely on external markers registered continuously and internal markers registered at different time points during the beam-on time. An example of such an approach is the CyberKnife® system which allows continuous and real-time tumour tracking with an overall precision in case of a moving target of 0.7+0.3mm. This precision is even better for non-moving targets (precision for a brain location is 0.4mm).

One can argue that repeated imaging during beam-on time is deleterious for a patient's health but the amount of supplementary dose given by this imaging is negligible compared to the dose given for therapeutic reasons and significantly less than the one used by cone beam CT used in routine for positioning checking in conventional radiotherapy. If the dosimetrical problem is solved by isocentric and non-isocentric, co-planar and non co-planar multiple beams, if the amplitude of the safety margin around the target is reduced by tracking, this paves the way to a significant increase of the biological effectiveness of the dose (BED). Without significantly modifying for example the applied total physical dose, the BED will be greatly enhanced by using the same physical dose but a limited number of fractions. Indeed, in the BED formula the biological effect depends upon total physical dose and relative effect. The relative effect is highly weighted by the sensitivity of a given tissue (target tissue or healthy

tissue) to changes in fraction size. If the tissue is sensitive to a change in fractionation, a significant increase in the dose per fraction will greatly impact the BED. If the sensitivity to a change in fractionation is greater in the healthy tissue surrounding the target, one should pay particular attention to limit the applied fractional dose on this healthy tissue by leaving it as much as possible outside the volume encompassed by the prescription isodose. On the other hand, tumours have often sensitivity to fraction changes which are rather close to the ones observed for healthy tissue. If this is the case, one could exploit the significant increase in biological effect by using high fractional doses on tumours, but at the same time taking particular care to eliminate healthy tissue as much as possible. A clinical illustration of this concept is the treatment of early stage NSCLC.

A conventional treatment, although conformal, can usually be applied safely at the total physical dose level of 66Gy in 33 fractions of 2Gy over 6.5 weeks. At this dose level we expect a less than 15% probability of local control at two years. The same tumour can be approached with Stereotactic Body Radio Therapy (SBRT), using Real-Time Tumour Tracking (RTTT) with a total physical dose of 60Gy applied in only three fractions of 20Gy each over an overall treatment time (OTT) of a single week. Besides the obvious reduction of the treatment burden for the patient by reducing the total number of fractions, this dose schedule results in a 70% to 90% probability of local control at two years translating in an actuarial survival of about 60% which is comparable to survival figures after surgery.[15] In these surgical series, however, the patients are highly selected because of their good general condition and tumour characteristics allowing a surgical intervention. This is definitely not the case in SBRT series. Frail, older patients, rejected for surgery because of their general health condition are addressed for SBRT and nevertheless the survival figures in this negatively-selected patient population are comparable to surgery.
The key to success for SBRT therefore, is optimal delineation of the target, based on high resolution multi-modal imaging (combining morphological and metabolic information), and optimised hypofractionated dose delivery through multi-beam approach with image-based RTTT. These techniques, therefore, do allow an ablative radiotherapy to be given with only a very limited risk of side-effects as the dose fall-off is extremely sharp outside of the volume encompassed by the prescription isodose.

Radiotherapy versus surgery in the ablative paradigm

There are several advantages of ablative radiotherapy as compared to surgery: there is no invasive procedure requiring several days in hospital, the treatment is given on an ambulatory basis, the cost of treatment is significantly reduced provided one takes into consideration total direct and indirect costs, the treatment can easily be given for another metastatic sub-site appearing at a later time point, there are virtually no acute side-effects and the treatment is totally painless. The impact on quality of life, in contrast to an invasive surgical procedure, is only small and limited in time as the numbers of fractions are restrained to an absolute minimum.
There is another important advantage linked to the use of ionising radiation to eradicate the tumour target. The ablative surgical procedure should be radical, i.e. if the margins are closed or involved, the survival drops dramatically. In contrast, in case of SBRT, even if the dose fall-off outside the volume encompassed by the prescription isodose is extremely rapid, the dose is not null outside the target volume. There are data showing the link between the number of clonogenic cells to eliminate and the dose to be applied.[16] Therefore, in the area of possible microscopic extension, outside the PTV - which in theory already contains a safety shell to cope with microscopic extension beyond the macroscopically visible target volume - the lower radiation dose might be able to eradicate these isolated cells.

The paradigm shift and the complexity of evidence-based medicine

It seems obvious that SBRT will play an important role in the treatment of selected patients. There is no doubt that progress in medicine has been made thanks to the use of randomised controlled trials. In various fields the implementation of individualised treatment tailored according to a wide variation of patients and tumour characteristics, highlighting the complexity and heterogeneity of the disease, will reduce our ability to run large randomised trials.

Key messages for clinical practice

1. Stereotactic body radiotherapy (SBRT) allows high dose delivery in a limited number of fractions, resulting in a significant increase in biological effect.
2. In selected patients, harbouring primary tumours or oligo-metastatic disease, SBRT is an alternative to surgery.
3. SBRT is safe, cost-effective and limits the burden of the treatment on patients and therefore preserves quality of life.
4. SBRT with real-time tumour tracking (RTTT) paves the way to major paradigm shifts in oncology.

If one considers comparing two treatment modalities, the prerequisite is obviously a mandatory informed consent. If one has to inform a patient thoroughly on two very different treatment modalities with a big differential in invasiveness, there will be without any doubt a very high refusal rate as patients will spontaneously ask to be treated with the less invasive procedure! This is the case for SBRT. A typical example is the abortion in the United States of America (USA) of a randomised trial designed to compares, radical surgery to ablative radiotherapy performed in three fractions in one week in early stage non-small cell lung cancer. Once the patients are informed about the possible side-effects of surgery, they no longer want to be randomised and ask for SBRT. One could argue ironically that there has never been a randomised trial on the use of parachutes and yet its use saves lives! More seriously, the reduced possibilities of running randomised controlled trials put the pressure on the radiation oncological community, in order to perform comprehensive prospective outcome analysis. And outcome is not only a story of local control, disease-free survival (DFS) and overall survival (OS) but includes also quality of life and cost-effectiveness!

Conclusion

The technical revolution, specifically in the fields of imaging, informatics and robotics, has opened the gates to highly conformal IGRT. The possibility to track the tumour in real-time reduces the magnitude of the safety shell to be taken around the target to make sure that the latter at any time is within the prescription isodose. The increase in resolution of the imaging and the combination of morphological and metabolic information will provide the possibility to reduce the amount of healthy tissue even further.

This elimination of healthy tissue from the high-dose volume allows the use of large doses per fraction. This results in a significant increase in biological effect without an increased risk of acute and late complications. Stereotactic image-guided SBRT therefore allows a treatment with an ablative potential comparable to surgery. It offers the advantages of being safe, non-invasive, and cost-effective, with almost no deleterious impact on a patient's quality of life. This treatment option will originate major paradigm shifts in oncology, not only for the treatment for primary tumours but also for the eradication of limited metastatic disease.

References

1. Fisher, B, Anderson, S. The breast cancer alternative hypothesis: is there evidence to justify replacing it? J Clin Oncol 2010;28:366-74.
2. Weichselbaum, RR, Hellman, S. Oligometastases revisited. Nat Rev Clin Oncol 2011;8:378-82.
3. Paget, S. The distribution of secondary growths in cancer of the breast. 1889. Cancer Metastasis Rev 1989;8:98-101.
4. Mareel, M, Constantino, S. Ecosystems of invasion and metastasis in mammary morphogenesis and cancer. Int J Dev Biol 2011;55:671-84.
5. Psaila, B, Lyden, D. The metastatic niche: adapting the foreign soil. Nat Rev Cancer 2009;9:285-93.
6. Simmonds, PC, Primrose, JN, Colquitt, JL, et al. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. Br J Cancer 2006;94:982-99.