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ADVANCES IN RADIOTHERAPY SPECIAL FEATURE: COMMENTARY

Does a too risk-averse approach to the implementation of new radiotherapy technologies delay their clinical use?

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ABSTRACT

Radiotherapy is a generally safe treatment modality in practice; nevertheless, recent well-reported accidents also confirm its potential risks. However, this may obstruct or delay the introduction of new technologies and treatment strategies/techniques into clinical practice. *Risks must be addressed and judged in a realistic context*: risks must be assessed realistically. Introducing new technology may introduce new possibilities of errors. However, delaying the introduction of such new technology therefore means that patients are denied the potentially better treatment opportunities. Despite the difficulty in quantitatively assessing the risks on both sides of the possible choice of actions, including the “lost opportunity”, the best estimates should be included in the overall risk-benefit and cost-benefit analysis. *Radiotherapy requires a sufficiently high level of support for the safety, precision and accuracy required*: radiotherapy development and implementation is exciting. However, it has been anxious with a constant awareness of the consequences of mistakes or misunderstandings. Recent history can be used to show that for introduction of advanced radiotherapy, the risk-averse medical physicist can act as an electrical fuse in a complex circuit. The lack of sufficient medical physics resource or expertise can short out this fuse and leave systems unsafe. Future technological developments will continue to present further safety and risk challenges. The important evolution of radiotherapy brings different management opinions and strategies. Advanced radiotherapy technologies can and should be safely implemented in as timely a manner as possible for the patient groups where clinical benefit is indicated.

Whilst the statistics confirm that radiotherapy is a generally safe treatment modality in practice,¹ recent well-reported accidents and incidents also confirm its potential risks.² These necessitate careful approaches to testing, implementation, commissioning and quality assurance (QA) throughout, building in safety and radiation protection at every level. This needs appropriate time and resource. However, there is an argument that too strong a focus on these issues can potentially overestimate the risks and lead to a too risk-averse approach of overtesting and/or lack of confidence. This, in turn, may obstruct or delay the introduction of new technologies and treatment strategies/techniques into clinical practice. Considering the significant improvements in possible treatment methods and the potential for improved patient outcomes, there is a present feeling among some professionals that such delays mean that patients are denied timely access to these better care possibilities. This may vary with national health system situations or local circumstances in a particular centre.

After the last few decades of very rapid evolution in radiotherapy technology and techniques, we may have reached a critical situation that divides professional opinion. Wide and rapid availability of advanced techniques to the relevant patient groups is required, to support maximum benefit. However, this must be provided within an optimized and appropriate safety and radiation protection testing framework, which is sufficiently, but not overly, risk-averse. The occurrence of accidents, resulting in injury or death of one or more patients, continues to challenge professionals to find the correct balance. These issues were aired in a recent debate at the ESTRO meeting in Vienna (April 2014), summarized here.

RISKS MUST BE ADDRESSED AND JUDGED IN A REALISTIC CONTEXT

Risks must be assessed realistically. However, this is not an easy task when the risks discussed are associated with

ionizing radiation. Indeed, many other hazardous areas of human endeavour appear to suffer generally lower levels of scepticism in relation to potential risks. For example, the chemical industry is known to contain many toxic or explosive hazards, but people are generally less afraid to live next to a chemical facility than to a nuclear facility, or, even further, to possess or consume products with potentially hazardous elements. Some factory explosions have not generated such widespread and generalized fears as seen linked to the hazards, real or perceived, of nuclear sites. Medical uses of radiation, including radiotherapy, suffer to a significant extent from the excessive anxiety in the public mind about ionizing radiation. Of course, radiation can cause damage, including at dose levels far below those giving rise to acute toxicity. Indeed, this characteristic is being harnessed to provide the beneficial effects of radiation from radiotherapy. The effects are well investigated, documented and known. However, partly owing to the human history with radiation, including atomic and nuclear bombs, as well as nuclear power accidents, the perceived risks of radiation often have only a loose connection to the real risks. In addition, anyone trying to discuss the risk perception of radiation and put it into a relevant contextual perspective, may often be accused of vested interests or other hidden motives; at least, this is one possible conclusion from discussions of nuclear energy production over recent decades.

There are similarities in this respect between radiotherapy and the aviation industry. The demand on flight safety is unparalleled as compared with other modes of transport. As a consequence, flying is the safest transport method, irrespective of how the comparison to other modes is made. This does not change the fact that a significant proportion of the population suffers from some flight anxiety and quite a few to such a degree that they cannot fly. Part of this may be owing to feelings of lack of personal control or understanding of the technology, as compared with the alternatives, as well as with the (justifiable) publicity given to the rare events that do occur.

We may conclude that flight anxiety, just as radiation anxiety, is due in part to non-rational feelings, rather than a realistic evaluation of real risks. This conclusion, however, does not help those suffering from the anxiety. This must be recognized, and people's fear of radiation must be dealt with and, on good grounds, respected. Any systematic use of ionizing radiation will always be viewed and judged with different standards than other similar human activities; this is a part of the radiotherapy professions' reality that has to be lived with and dealt with.

This is not the same as saying that we must simply give up our efforts to inform the general public as well as our patients; this is a necessary part of our work. Unfortunately, this too is not an easy task. For a patient with cancer referred for radiotherapy, there is in most cases an understandable primary, immediate and overriding fear of dying from the effects of the disease. Since radiotherapy can often also be a quite toxic treatment, there are additional risks of suffering from side effects owing to the treatment. These are of varying probability and severity, although rarely with potential life-threatening sequelae.¹ It is understood that the risk of dying from the disease or suffering

injury by expected/unavoidable side effects is inherent to the disease/treatment interplay and hence nobody's fault nor should they attract blame. However, from the point of view of the patients and their families, it is hard to see a significant difference between adverse outcomes, whatever the cause. Unlike a passenger with flight anxiety who can choose to take other means of transport, the patient with cancer does not generally have many options or alternatives.

New technologies, *e.g.* intensity-modulated radiotherapy (IMRT) or particle therapy, have been introduced because it was believed from the initial investigations and dose distribution modelling to be of benefit for patients, and this has been generally supported by clinical experience.³⁻⁵

The goal of IMRT or particle therapy, as compared to three dimensional conformal radiotherapy, was and is to provide treatment with either higher probability for tumour control (dealing with the major immediate risk to the patient; *i.e.* the disease progressing and not being cured) and/or lower rates and severity of side effects (dealing with the next worst risk for the patient; *i.e.* suffering injury from known side effects). The issue of whether the level of evidence of the superiority of IMRT was strong enough for wide-scale clinical implementation^{3,4} is an important and relevant issue; however, it is less important in the present debate context. It requires a discussion, outside the scope of this commentary, of the issues and arguments around the use of randomized clinical trials (RCTs) to compare such technologies,^{6,7} where similar issues may be considered for IMRT, or for the advantageous use of protons (and ions) to treat childhood cancers, despite their much higher cost. Whether RCT proven or not, IMRT and particle therapy were introduced for the benefit of the patients. The present debate also does not consider the issues, discussed widely in other medical specialty areas as well as in radiation oncology, of whether a specific new technology may negatively impact the cost-benefit balance of its use and outcomes in a range of ways, including overuse (*e.g.* compare with the debate on medical imaging use) or overtreatment.

Introducing new technology, in particular if it is technically advanced and complex, may introduce new possibilities of errors. As part of the implementation process, the risk of mistakes, accidents and errors must be carefully analysed, and the severity of possible risks judged. These must then be balanced and evaluated against relevant risk measures and not against unrealistic or utopian visions of being "100% safe" because, being dispassionate and fair about this, nothing in life is. Denying that fact, however complicated it may be to communicate with journalists and the general public (and even the radiation protection authorities), is dishonest and unscientific. Of course, such risk assessment and analysis must be within a context of the already established and additionally developed (for a specific new technology) safety and quality systems and the procedures put in place to mitigate risks and their clinical impact to acceptable levels.

The decision not to apply a new and superior treatment option for a patient is also clearly not a risk-free option. If the new treatment is accepted to provide the planned improvements,

then it is equivalent to deliberately accepting a higher risk of side effects and/or a higher risk of not controlling the tumour. Delaying the introduction of such new technology therefore means that patients are denied the potentially better treatment opportunities. Despite the difficulty in quantitatively assessing the risks on both sides of the possible choice of actions, including the “lost opportunity”, the best estimates should be included in the overall risk–benefit and cost–benefit analysis.

RADIOTHERAPY REQUIRES A HIGH LEVEL OF SUPPORT FOR SAFETY, PRECISION AND ACCURACY

During the first few decades of the modern era of radiotherapy, *i.e.* following the wider availability of megavoltage X-ray beams, roughly from the late 1950s to the early 1980s, the development and implementation of technologies and technique, as well as the daily treatments, were generally directly in the hands of medical physicists, radiotherapy technicians (RTTs; otherwise denoted as therapy/therapeutic radiographers, radiotherapy nurses or radiation therapists, RTs) and radiation oncologists. Safety was an integral part of all their activities. The treatment machines were accessible and often repaired by the physicists. Software either did not exist or was written and developed in-house and based on clear and simple concepts. The overall treatment and dosimetry systems in use were generally intuitively understandable, in terms of linkages between patient set-up, treatment and machine parameters applied and doses delivered.

The following decades brought a dizzying and continuing pace of impressive developments. To participate in radiotherapy development and implementation in this period has been (and still is) exciting, to contribute to systems and methods that support significant treatment improvements. However, it has also been anxious, with a constant awareness of the consequences of possible mistakes or misunderstandings, where this feeling has been heightened by well-publicized accidents and incidents. The introduction of advanced and complex new technologies has been carried out with many QA procedures, both traditional and newly developed. Risk analysis of the new methods has also been employed. All of this has been largely based on existing experience and has required significant time and machine access. Unfortunately, the general expectation was that such QA would ensure safety. However, there have been a number of accidents, whether from inadequate QA procedures or, more likely, their incorrect or insufficient application, where one factor may be owing to a lack of medical physics resources. Faced with this evidence, radiotherapy professions have begun to learn from other safety-critical industries how to manage the safety of complex systems and processes in multilayered ways. For example, the implementation of the failure modes and effects analysis (FMEA) method helped to show how much more sophisticated safety procedures must be to deal with much more sophisticated systems and how existing experience on simpler systems may be limited in application.⁸ Many of the relevant processes are now much more secure and robust owing to the numerous corrective actions that have been adopted into daily work practices. Unfortunately but obviously, this new activity also needs further significant time to be implemented and embedded. FMEA, or any similar complex-system risk management

tool, is an ongoing work process that should continue to be practised, evolved and adapted to keep pace with the continuing development of treatment technology and methods. In industry, the safety cost can be recovered in the product price, but in medical centres that are often not in explicitly commercial settings (depending on the health system and specific centre), this is not always so simple. There can be pressure to take on new technologies with no additional resource. However, whatever the local health economic model for radiation oncology, adequate safety costs should be fundamental and sufficient resources should be carefully evaluated in relation to the clinical service required and should be provided. Such resource not being available would be a clear reason for slow implementation or non-introduction of complex technology. At present, 10 years or so after the emergence of a series of accidents,^{2,9} Europe overall still does not display a consistently good economic management of radiotherapy.¹⁰

Amongst other industries, transport generally may be viewed as having similarities to the high-technology radiotherapy sector. Two transport examples can be cited.

- (1) As above, aviation has similarities of risk perception and also of the criticality of accidents that do occur and of increasingly sophisticated technology. Planes have become much more fly-by-computer and hence less intuitive to operate. Automation has improved safety levels but decreased pilots' direct control and “feel” for the systems.¹¹ The investigation into the 2009 loss of an Airbus 330 between Rio and Paris reported that this followed an auto-pilot failure and that in those circumstances the pilots suffered “a total loss of cognitive control of the situation”.
- (2) Train/rail systems and processes may often also have some close similarities. In recent years, high-speed trains were built with many innovations and high technologies and with mixes of public and private infrastructure and funding, developed from old-established systems and technologies. Unfortunately, a recent (2013) French railway accident highlighted the lack of understanding of the overall system. The official investigations that analysed the accident highlighted the decrease in resources, modified practices and a low level of care (QA) on conventional train lines such as the presence or tightness of track bolts.¹²

Unfortunately, there is a danger that radiotherapy may be under similar pressure that may potentially produce similar consequences. Resources are needed not only for equipment but also for the necessary supporting human activities. Radiotherapy requires a sufficiently high level of support for the levels of safety and precision/accuracy required. It can be argued that it is better for the quality and outcome of treatment to use modalities and methods that are well tried, tested and supported than newer ones for which the resources are not sufficient to implement them well.

As above, often health and hospital administrations ask staff to take on new technologies and methods without any new resources and without evaluating the real need. Such implementation of complex new technologies is expected while still continuing and supporting the existing systems and the existing patient and work load. Depending on the health system, radiation oncology personnel may

be pressed to implement such technology quickly to meet real or perceived “competition” issues. Administrations might be deaf when staff discuss money and resource, but may show more hearing and response when staff discuss safety and risk. Recent history can be used to show that for introduction and implementation of advanced and complex radiotherapy technologies and methods, the risk-averse medical physicist can act as an electrical fuse does in a complex circuit, *i.e.* to ensure safety. The lack of sufficient medical physics resource or expertise can short out this fuse and leave systems unsafe.

Bortfeld and Jeraj¹³ argue that cutting-edge research should optimally reach the clinic within around 20 to 10 years, and translational research in a few years at most. Taking IMRT as the example, the seminal early theoretical work began in the early 1980s, and the technology for convenient delivery became available in the 1990s and more widely available after around the year 2000. The time delay between early and late implementation of IMRT is at least 10 years, and this is similar for other such new technologies in the USA¹⁴ and in Europe.¹⁵ The safety works are clearly not responsible, but more likely resource issues, for provision of the required technology, but also for the supporting human activity required.¹⁶ Future technological developments will continue to present further safety and risk challenges, some of which may be increasingly subtle, *e.g.* risk evaluation in implementing automatic tools and advanced rapid-learning systems aimed at improving treatment optimization.

CONCLUSIONS

As in any other human activity, healthcare is exposed to risks, inherent to the interplay of disease and treatment and also of human mistakes. These can have consequences of varying severity, up to and including a fatal outcome. Unfortunately, radiotherapy is no exception to this, even though the statistics show it is a generally safe treatment modality. Fatal, or other serious or severe, mistakes and accidents are unacceptable in any area of human life, whether it concerns traffic accidents, industrial accidents

or health accidents, including in radiotherapy. The only absolutely safe human activity is an activity not taking place, but this carries other risks of not providing or receiving the wider benefits of the activity for the individuals concerned and society as a whole. Both sets of risks must be weighted into a comprehensive analysis and not only one side of this risk balance.

Two opposing extremes of strategy can be seen. The first is to accept a certain level of risk as inherent to human activity, including that for severe consequences, and simply go ahead. The other is to invest heavily in safety regardless of the true need, justifying the necessary resources to implement innovations everywhere at the same time and under the same conditions. Neither is the correct approach. The appropriate response is to find a realistic and reasonable balance between potential risks and the needed resources, based on clear and supported risk analysis, *i.e.* an optimized risk–benefit and cost–benefit strategy for implementation, operation and monitoring of the activity. This requires sufficiently comprehensive safety and quality systems in place that are robust and reliable to manage such an activity and that will detect errors at the earliest point and will mitigate their impact as much as possible. The underlying principle is that errors cannot be totally prevented, but the risk management systems in place should be designed and operated to minimize the probability that any such errors cause significant patient injury. This requires the necessary resource to be available, including adequate training for all relevant personnel and the possibility of mentoring or other support for newly implementing centres from those who have already implemented.¹⁷ In principle, this “acceptably safe” approach can be applied to developing technologies applied to explore new clinical paradigms, *e.g.* the introduction of image-guidance or hypofractionation. Depending on the technology and the applications, this can prove rather challenging to put into practice. However, with such frameworks in place, advanced radiotherapy technologies can and should be implemented in as timely a manner as possible for the patient groups where clinical benefit is indicated.

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