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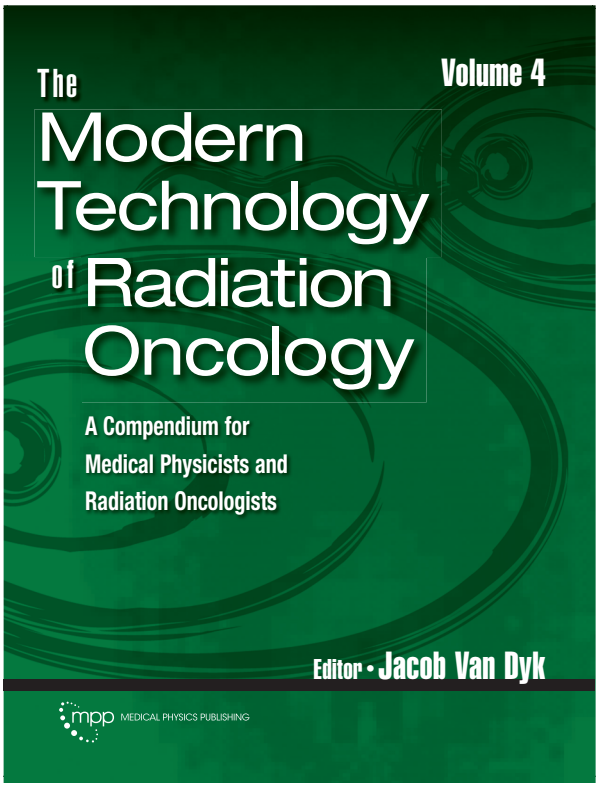

Here is a sample chapter from *The Modern Technology of Radiation Oncology, vol. 4*©.

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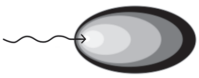
Chapter 1

Technology Evolution in Radiation Oncology: the Rapid Pace Continues



Jacob Van Dyk

1.1 Evolution of the Radiation Treatment Process

The history of radiation therapy can be described in a variety of ways. In Chapter 1 of Volume 2 of this series of books (Van Dyk 2005), five phases of major technological developments in radiation oncology were described:

1. the low-energy x-ray period from 1895 to the 1940s;
2. the megavoltage era of the 1950s with the implementation of cobalt-60, low-energy linacs, and high-energy betatrons;
3. the development of multimodality linacs, computerized radiation treatment planning systems, and simulators in the 1960s and 70s;
4. the development of computerized tomography (CT) scanners combined with 3-D treatment planning capabilities for conformal radiation therapy in the 1970s and 80s; and
5. the development of computer-controlled dynamic treatments with multi-leaf collimators (MLCs) and intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT), and further improvements in imaging for therapy planning with CT-simulators, magnetic resonance imaging (MRI), positron emission tomography (PET), and its hybrid combination of PET-CT since the 1980s.

James Slater uses an analogous but different historical evolution of radiation therapy where he described the "discovery era" (1895 to about the 1920s–30s), the "orthovoltage era" (late 1920s–1950), the "megavoltage era" (1950–1985), and the "ion beam era," which already began in the 1950s but has grown dramatically in recent years (Slater 2012).

One of the quantitative measures of technology evolution is the number of journal publications on specific topics per year. Thus, in Volume 2 (Van Dyk 2005), Figure 1.2 demonstrated the rapid evolution of IMRT. Similarly, Figure 1.1 of Volume 3 (Van Dyk and Battista 2013) showed the continued rapid development of IMRT and VMAT, Figure 1.2 demonstrated the growth of tomotherapy, Figure 1.4 the development of adaptive radiation therapy (ART), Figure 1.5 the growth of heavy particle (light ion) radiation therapy, Figure 1.6 the growth of robotic radiation therapy, and Figure 1.7 the increased interest in patient safety and medical errors.

1.2 Does New Technology Make a Difference?

The question has been raised as to whether the advances in technology have made a difference in patient outcome. In 2007, Robert Schulz, in a *Medical Physics* Point/Counterpoint article argued that "despite the myriad technical advances over the past decade, their contributions to survival rates are undetectable, albeit there have been reduced levels of toxicity in some cases." In Chapter 1 of Volume 3, we referred to some reviews of clinical studies assessing the impact of IMRT and modern treatments, with the general conclusion that there appeared to be reduced toxicity, but the findings regarding local control and overall survival were generally inconclusive. There have been multiple papers addressing the question of whether the additional sophistication and cost of radiation therapy is worth the benefit (Bentzen 2008a; Loeffler 2008; Nystrom and Thwaites 2008; Veldeman et al. 2008; Vergeer et al. 2009; Verma, Mishra, and Mehta 2016).

The European Society for Radiotherapy and Oncology (ESTRO) has developed the Health Economics in Radiation Oncology (HERO) project with the overall aim to develop a knowledge base and a model for health economic evaluation of radiation treatments at the European level (Lievens and Grau 2012) (also see Chapter 15 of this volume). The outcome of this project is that it has provided data and guidelines on equipment and staffing in the European context (Dunscombe et al. 2014; Grau et al. 2014; Lievens et al. 2014). Defourny et al. (2016) performed a thorough literature review of publications between 1981 and 2015 to analyze critically the type and quality of radiotherapy cost information available in cost calculation studies. Their search yielded 52 articles. These studies displayed large heterogeneity in scope, costing method, inputs, and outputs. They conclude that these results call for developing a well-defined and generally accepted cost methodology for performing economic evaluation studies in radiotherapy. Very recently they have published the time-driven activity-based costing model to determine the national costs and resource requirements of external beam radiotherapy for the ESTRO-HERO project (Defourny et al. 2019). It is suggested that with real data, tailored to the specificities of individual countries, national societies of radiation oncology will be able to support their strive for adequate investment planning and access to innovative radiotherapy.

Arguments for and against the use of more advanced and more expensive technologies have varied dramatically. One argument is that radiation therapy is an efficient, effective, and also highly cost-effective treatment modality in comparison to surgery and chemotherapy (Nystrom and Thwaites 2008). These authors conclude

> ...from that information and on the evidence discussed, we believe that the role of physics and technological developments in radiotherapy is still vital and that these will continue to contribute significantly and cost-effectively to improvements in radiotherapy outcomes in the foreseeable future.

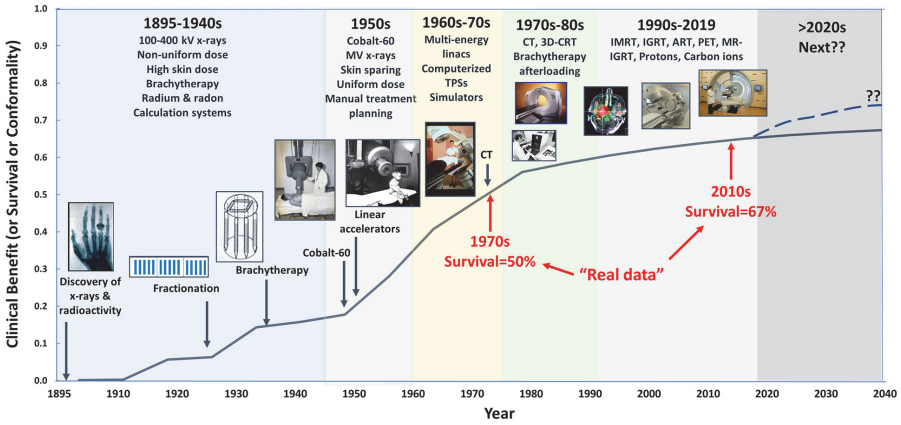


Figure 1.1
Schematic of clinical benefit improvements by year since the discovery of x-rays in 1895. Different time periods are shown representing five different phases of technology development. The clinical benefit curve is fictional except for two data points: the survival of 50% in the 1970s and the survival of 67% in the 2010s. These two data points come from (Ritchie 2019) with their summary data shown in Figure 1.2.

While others argue that phase III controlled clinical trials should be used to validate the cost-effectiveness of more advanced technologies, the problems of requiring such trials for every technological improvement and the concerns about equipoise in the two arms of such trials have also been described (Bentzen 2008b). Recognizing these limitations, Bentzen notes that non-randomized, or "observational," studies should be seen as a complement to, rather than a substitute for, randomized controlled trials of treatment outcome. In a similar vein, Lievens et al. suggest the use of "blended evidence" and "real-world evidence" as a compliment or alternative to controlled clinical trials (Lievens, Grau, and Aggarwal 2019). A more detailed discussion on financial and economic considerations in radiation oncology can be found in Chapter 15 of this volume.

From a historical perspective, we can readily see that radiation therapy has had a major impact in cancer control rates. Figure 1.1 is a ***schematic*** drawing of clinical benefit versus year since the introduction of x-rays in 1895. The curve is purely hypothetical based on the author's imagination, except for two points: the survival of 50% in the 1970s and the survival of 67% in the 2010s. These two points are based on data from the Surveillance, Epidemiology and End Results (SEER) program (Figure 1.2). According to Hannah Ritchie (2019), there are two key factors that could contribute to improved five-year survival rates: earlier detection and improved treatment. Defining the exact attribution of each is difficult and varies depending on cancer type. Some studies have attempted to quantify this distinction. For example, Scott Alexander published an overview of the relative impact of detection versus treatment (Alexander 2018). However, such "crude" survival data give no indication of quality of life after fairly complex treatment modalities that have the potential of causing some harm and impacting quality of life. As treatment technologies become more sophisticated, they have the capability of reducing complications and improving quality of life in addition to increasing life expectancy. Furthermore, as new technologies are developed, they become more efficient, more compact, and have the potential of becoming more cost effective.

Another study (Arnold et al. 2019) reported on progress in cancer survival, mortality, and incidence in seven high-income countries (HICs) between 1995 and 2014 and found that the 1-year and 5-year net survival increased in each country across almost all cancer types. Figure 1.3 shows age-standardized 5-year survival by clinical site and by country for the period of diagnosis of 1995–2014 (Arnold et al. 2019). The authors postulate that progress likely stems from earlier diagnosis and improved treatment, alongside policy reforms that have ensured improved pathways to diagnosis and treatment.

The extent to which these overall improved survival data relate directly to improvements in radiation therapy

is very difficult to quantify since there are multiple variables at play. However, there are various specific studies that demonstrate improved clinical results. For example, in a review of technology-driven research for radiotherapy innovation, Fiorino et al. (2020) summarize the results of three randomized clinical trails for the treatment of oligometastatic cancer using image-guided, stereotactic body radiation therapy (SBRT). They indi-

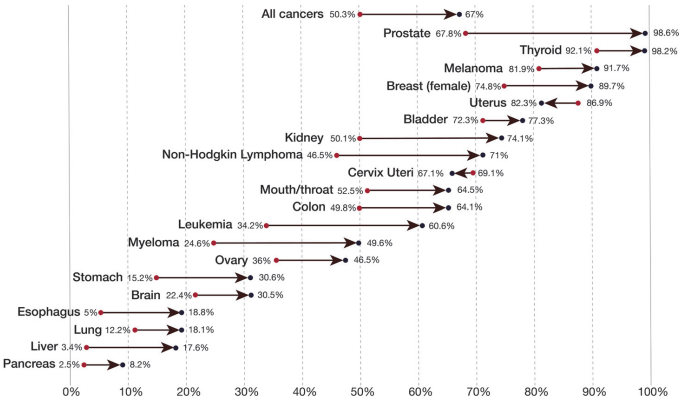


Figure 1.2
Average five-year survival rates from common cancer types in the United States shown as the rate over the period 1970–1977 (red dots) and over the period 2007–2013 (blue dots) This five-year interval indicates the percentage of people who lived longer than five years following diagnosis. Based on data by the *Journal of the National Cancer Institute*; Surveillance, Epidemiology and End Results Program. The data visualization is available at OurWorldinData.org. Licensed under CC-BY-SA by authors Hannah Ritchie and Max Roser (Ritchie 2019).

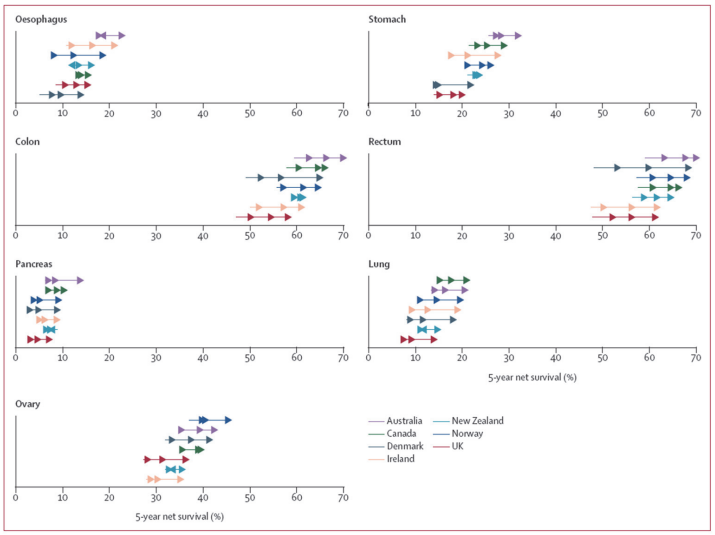


Figure 1.3
Age-standardized five-year survival by site, by country, and period of diagnosis, 1995–2014. With permission from (Arnold et al. 2019).

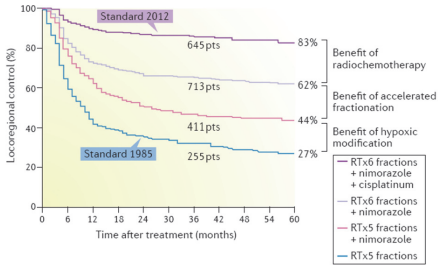


Figure 1.4
Illustration of biological modification of radiotherapy (RT) seen in a series of continuous clinical trials in the treatment of advanced head and neck squamous cell carcinoma. Locoregional tumor control was significantly improved between the 1980s and the 1990s by adding the hypoxic cell radiosensitizer nimorazole to conventionally fractionated RT. Further improvement was reached in the early 2000s by treating with six radiation fractions per week and, thereby, reducing the overall treatment time to compensate for radiation-induced accelerated repopulation of cancer stem cells. Finally, the current standard was defined in approximately 2011 and includes targeting intrinsic radioresistance by adding concomitant cisplatinum chemotherapy. With permission from (Baumann et al. 2016).

cated that the technological advances of SBRT and its improved accuracy translated into an improved therapeutic ratio with low risk of toxicity and simultaneously high rates of local tumor control.

The outcome of radiotherapy has been improved not only by technological improvements, but also by integrating radiobiological and biological knowledge into more effective treatment approaches (Baumann et al. 2016). A good example comes from sequential prospective randomized clinical trials performed over the past few decades by the Danish Head and Neck Cancer Group in patients with head and neck squamous cell carcinoma (Bentzen et al. 2015). First, they showed the benefits of increasing the total dose of radiation by using better conformity of the dose to the clinical target volume (CTV) while better sparing normal tissues. Next, to reduce the negative impact of hypoxia on the radiosensitivity of tumor cells, the hypoxic cell radiosensitizer nimorazole was successfully introduced (see Figure 1.4). Then to counteract repopulation of cancer stem cells, the overall treatment time was reduced, which again increased local tumor control. Finally, simultaneous chemotherapy with cisplatinum was introduced, which further improved outcome. Overall, the locoregional tumor control after primary radiotherapy was achieved in approximately 30% of patients in the 1980s, while current radiochemotherapy achieves approximately 80% tumor control. This is a clear demonstration that while technical improvements are an important component of improvements in clinical outcomes, other (radio)biologically related parameters are also relevant.

Another group analyzed how often innovations in healthcare are evaluated regarding *output*, especially in radiotherapy, where they defined *output* as any of the following: survival, toxicity, safety, service, efficiency, or cost-effectiveness (Jacobs et al. 2017). They performed a systematic literature review and found that 65% of papers reported significant results on patient outcome, service, or safety; this rose to 76% if confined to radiotherapy reviews. This review highlights that benefits of new technologies involve more than overall survival and reduced toxicities. They include issues like safety, service, and cost-effectiveness, parameters of which the benefits are sometimes difficult to quantify and certainly are not reflected in data such as demonstrated in Figures 1.2 to 1.4.

1.3 Developments in the Last Decade

At the present time, most modern and advanced radiation therapy departments are fully capable of IMRT/VMAT, image-guided radiation therapy (IGRT), and some form of motion management allowing for breathing and other motion considerations, thus addressing the effects of time, i.e., the fourth dimension (4-D). While each of these advances has been in development over the last 15 years or so, the applications keep evolving. The intent of these new technologies is to minimize random and systematic uncertainties. These technologies have been well-described in the previous three volumes of this series of books. Figure 1.5 is a schematic summary of the evolution of the application of these radiation treatment technologies and their impact on reducing the margin between the clinical target volume (CTV) and the planning target volume (PTV). The figure shows the corresponding impact on the therapeutic index: same or increased tumor control probability (TCP) and/or same or decreased normal tissue complication probability (NTCP) (Chargari et al. 2016).

The evolution of these margin-reducing technologies continues. The underlying hypothesis continues to be that a reduction of the treatment volume reduces the amount of normal tissue irradiated (Suit 2002), allowing for dose escalation and/or higher doses per fraction and, thereby, increasing the TCP without increasing or even reducing the NTCP.

Examples of these evolving technologies are covered in this volume's chapters. The following summarizes some highlights of these topics.

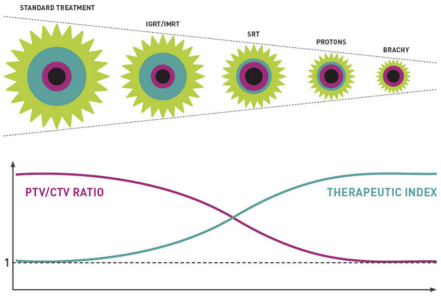


Figure 1.5
The interplay between radiation delivery techniques, with different levels of accuracy based on imaging and dose delivery, treatment margins, and the volumes of non-tumor tissues irradiated. The increasing availability of repositioning and on-board imaging systems has allowed decreasing margins around the gross tumor volume (GTV, in black) and around the clinical target volume (CTV), which accounts for microscopic tumor extension (in purple). Thus, the planning target volumes (PTV), which consider positioning uncertainties (darker green circle), is progressively reduced. The consequence is a decrease in normal tissue irradiation (lighter green star). The progressive decrease in the PTV/CTV ratio is expected to be associated with an improvement in therapeutic index (toxicity decreased; dose escalation enabled). With permission from (Chargari et al. 2016). SRT = stereotactic radiation therapy.

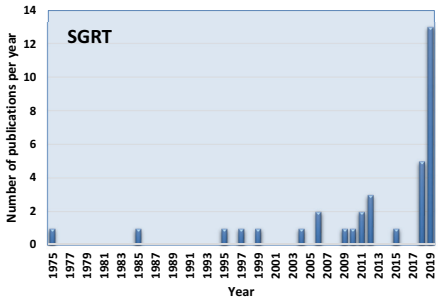


Figure 1.6
The number of publications per year on SGRT between 1975 and 2019. Fifty-three percent of these publications occurred from 2018–2019.

1.3.1 Surface guidance technologies (Chapter 2)

While surface guidance technologies have been under development already since the 1970s (Connor et al. 1975), it is only during the last decade that these have become more routinely and commercially available. Surface-guided radiation therapy (SGRT) involves the use of real-time patient position data before and during simulation with imaging modalities such as CT, MR, and PET, and for radiation treatment delivery on the treatment machine. This also includes positioning for respiratory-correlated procedures. SGRT uses sophisticated 3-D camera technologies to track the patient's skin surface, giving it the ability to not only position the patient accurately and reproducibly, but also allow for motion management. It provides a positioning accuracy of better than 1 mm and can detect rotational offsets of less than 1 degree. Developments under consideration include collision detection and biometric measurements. In view of the non-ionizing nature of this 3-D imaging modality, it enables the collection of vast amounts of real-time data about patient treatments that is expected to benefit the field in novel ways in the future. As can be seen in Figure 1.6, it is only in the last two years (2018–2019) that publications on the use of SGRT have started to appear more frequently, with 53% appearing in those years compared to the total published since 1975.

1.3.2 Hybrid PET/MRI for radiation oncology (Chapter 3)

In Chapter 1 of Volume 3 of this series of books, under *future developments*, we already alluded to more hybrid technologies and noted that PET/MRI scanners were just becoming available. The application and benefits of this technology is now addressed in detail in Chapter 3. PET/MRI is a hybrid imaging technology that incorporates MRI soft tissue morphological imaging and PET functional imaging providing information on metabolic activity. While this hybrid technology has been in a developmental stage already since 1997 (Meyer et al. 1997), it was first introduced commercially in 2011. One recent study compared PET/MRI to PET/CT in whole-body oncological imaging for lesion detection and classification using 1003 examinations (Martin et al. 2019). Their conclusions were that PET/MRI improves lesion detection and potentially reduces additional examinations in tumor staging, and especially younger patients may benefit from the clinically relevant dose reduction of PET/MRI compared to PET/CT. However, as indicated in Chapter 3, the significant cost of whole-body PET/MRI (approximately double that of a standalone 3 T MRI or PET/CT systems with similar specifications) has limited its implementation in the clinic. They do point out that with further advancements in technology, future PET/MRI systems may target a more affordable price point.

1.3.3 Hybrid linear accelerator with MR imaging (Chapter 4)

Image-guided radiation therapy using 3-D CT imaging has been in the clinic since the early 2000s. Helical tomotherapy was already described in detail in Volume 1 of this series of books in 1999 (Olivera et al. 1999). Since then, cone-beam CT (CBCT) has been implemented for IGRT on conventional linacs (Jaffray et al. 2005). The CT imaging on both of these technologies is usually done prior to treatment. Upon review of the images, the patient is repositioned and treated. The total process of imaging and review may take several minutes. These systems cannot provide any real-time feedback during the actual treatment to see if there is any change in position while the beam is on. More recently, the combination of a linear accelerator (linac) with an MR scanner has become available clinically. The development of this technology was already described as part of Chapter 4 in Volume 3. By integrating an MR imaging system with a linac, one not only obtains high-quality 3-D images, but one can also obtain real-time imaging while the beam is on. Thus, the radiation oncologist can see if there is a change in tumor volume and surrounding structures on a daily basis and determine if the treatment plan needs to be adapted to the modified anatomical shape. Also, the real-time images will allow tracking of the tumor position during treatment, with the possibility of the beam position being adjusted to follow the motion of the tumor, especially for cases such as lung tumors, where there is significant breathing motion during the treatment.

1.3.4 Stereotactic body radiation therapy (SBRT) (Chapter 5)

Stereotactic radiation therapy was already described in Volume 1 of this series (Podgorsak and Podgorsak 1999). Volume 3 contained a chapter on stereotactic and robotic radiation therapies (Dieterich and Fahimian 2013). In the meantime, SBRT has become a clinical standard of practice in nearly every modern radiation therapy department. SBRT delivers precise, high doses of radiation to the tumor—especially for tumors in the lung, prostate, pancreas, liver, spine, and kidney—while minimizing damage to the surrounding normal, healthy tissues. It allows for high doses per fraction and relatively fewer fractions. For non-small cell lung cancer (NSCLC), the preponderance of evidence suggests that SBRT is associated with excellent local control (~90% at three years) and a favorable toxicity profile (Chehade and Palma 2015). In patients with higher operative risks, such as the elderly and patients with severe chronic obstructive pulmonary disease (COPD), SBRT may provide a less-toxic treatment than surgery with similar oncologic outcomes. Ongoing studies are evaluating the use of SBRT for locally advanced or oligometastatic NSCLC.

1.3.5 Radiation treatment uncertainties and robust optimization (Chapter 6)

Accuracy considerations for radiation oncology and a discussion on treatment uncertainties were addressed in some detail in Chapter 11 of Volume 3 (Van Dyk et al. 2013) as well as in an IAEA report (International Atomic Energy Agency 2016). Giving the highest dose possible to the tumor while constraining normal tissue doses to acceptable levels are two of the main considerations in developing an optimized treatment plan. However, it is now well recognized that treatment uncertainties can vary dramatically depending on the nature of the treatment plan's technique and technology used. The concept of *robust optimization* has been under consideration for a number of years. Indeed, it was already in 1985 that Goitein proposed the calculation of three treatment plans in parallel, one using the nominal values and two others using extreme values of the parameters upon which the dose depends (Goitein 1985). In 1997, our group also began addressing issues related to uncertainties and their impact on developing optimized treatment plans (Wong et al. 1997). The field has advanced to robust optimization, whereby plans are calculated and optimized in such a way that they are minimally affected by uncertainties. Robust optimization is now available on commercial treatment planning systems. The number of publications per year on robust planning in radiotherapy can be seen in Figure 1.7, which shows that nearly 50% of these publications occurred in the last five years.

Robust planning has become especially relevant for particle therapy, where range uncertainties can have dramatic effects on dose delivery, both to the target and the

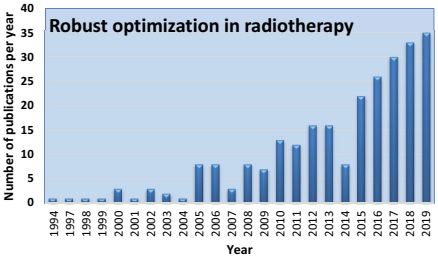


Figure 1.7
The number of publications per year on robust optimization in radiotherapy. About 50% of these publications occurred in the last five years.

normal tissues. This has led to probabilistic estimations of dose distributions. These distributions can now be calculated and possibly replace the PTV concept since the generation of the CTV-to-PTV margin is performed based on the uncertainty distributions (Unkelbach et al. 2018). We already proposed the direct calculation of treatment plans without using the PTV concept in 2001 (Craig et al. 2001).

1.3.6 Automated treatment planning (Chapter 7)

The entire radiation treatment process has multiple steps, as summarized in Figure 1.8, with the treatment planning components being shown in beige and the major steps that stand to benefit from automation shown in green. With the recent rapid advancements in computer technology and the development of improved and faster optimization algorithms, the calculation component of generating a treatment plan has improved significantly. In addition, auto-segmentation for tumor and normal tissue delineation allows the time taken by the radiation oncologist and the treatment planner to be reduced significantly. Many treatment planning systems now provide scripting capabilities, where it is possible to record a sequence of messages or keystrokes while the user is operating the system. Scripts can be used within the radiation treatment planning system to reduce human error, increase treatment planning efficiency, reduce confusion, and promote consistency within an institution or even among different institutions (Holdsworth et al. 2011). Scripting has been used for automated IMRT planning, both for simple cases, such as localized prostate and whole breast cancers (Purdie et al. 2011), as well as more complex cases, such as head and neck, anal canal, and prostate with pelvic nodes (Xhaferllari et al. 2013). The Xhaferllari paper makes a comparison between the time to generate a manual plan versus the time to generate an automated plan. Their results are shown in Table 1.1 and demonstrate a huge time savings by automation. In addition, because of the self-consistency of the scripting process, the scripts can reduce variations of plan quality due to the differences in experience of the planners.

Software for auto-contouring of images and automatic generation of treatment plans is becoming more

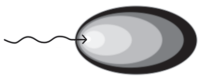


Table 1.1
Time required to generate complex IMRT plans. From (Xhaferllari et al. 2013).

CLINICAL SITE	MANUAL PLANNING	AUTOMATED PLANNING
Head and neck	>4 hrs	~8 min
Anal canal	>2 hrs	~6 min
Prostate with pelvic nodes	>1.5 hrs	~6 min

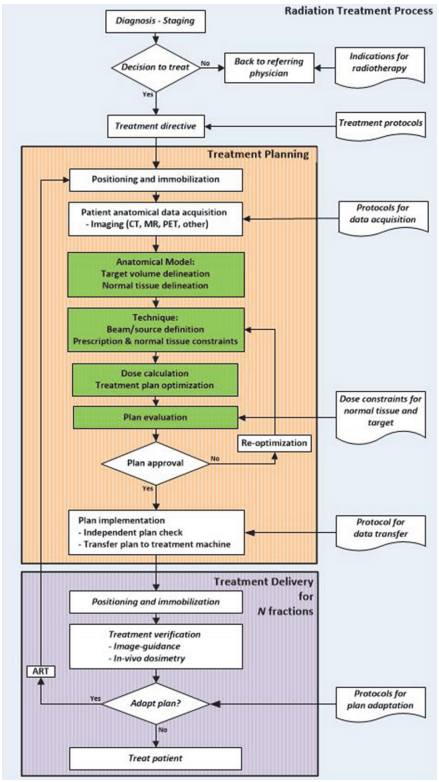


Figure 1.8
Flow chart of the steps in the radiation treatment process. The treatment planning component is shown in the beige box, and the major steps that benefit from automation are in the green boxes. Also shown is the treatment delivery component in light purple and the adaptive radiation therapy (ART) pathway. This figure is updated significantly from International Atomic Energy Agency 2004.

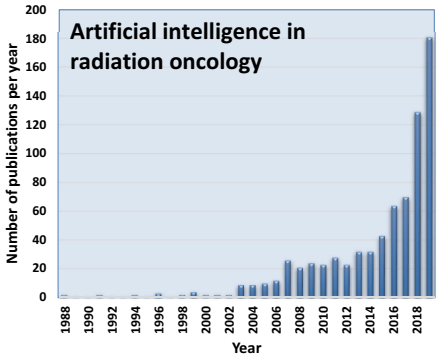


Figure 1.9
The number of publications per year on artificial intelligence in radiation oncology. About 50% of these publications occurred in the last four years.

readily available on commercial treatment planning systems. Furthermore, computer speed is increasing such that it allows for online adaptation of the treatment during every treatment fraction. A critical step is the validation and clinical approval of the auto-segmentation and automatically generated treatment plans by radiation oncologists and medical physicists. To reach the goal of online biological image-guided adaptive radiation therapy, this validation and approval needs to be streamlined so that it can be done in a few minutes rather than in hours (Fiorino et al. 2020). As pointed out in Chapter 7, this type of software that supports automation of the contouring and treatment planning process is especially useful in lower-income contexts since it provides the potential for scaling up radiation therapy capacity to meet global needs.

1.3.7 Artificial intelligence in radiation oncology (Chapter 8)

An online search for the general definition of artificial intelligence (AI) yields multiple hits. The following is one of those results (TechTarget 2020): Artificial intelligence (AI) is the simulation of human intelligence processes by machines, especially computer systems. Specific applications of AI include expert systems, natural language processing (NLP), speech recognition, and machine vision. AI programming focuses on three cognitive skills: learning, reasoning, and self-correction.

- **Learning processes.** This aspect of AI programming focuses on acquiring data and creating rules for how to turn the data into actionable information. The rules, which are called algorithms, provide computing devices with step-by-step instructions for how to complete a specific task.
- **Reasoning processes.** This aspect of AI programming focuses on choosing the right algorithm to reach a desired outcome.
- **Self-correction processes.** This aspect of AI programming is designed to continually fine-tune algorithms and ensure they provide the most accurate results possible.

Figure 1.9 shows the annual publication rate for "artificial intelligence in radiation oncology" and demonstrates a clear dramatic growth in the last few years, with 50% of these publications occurring between 2016 and 2019.

The applications in the context of radiation oncology are numerous. Automated treatment planning is a clear application of AI. Again, the rapid increase in computational power, as well as advances in data collection and sharing capabilities, provide multiple opportunities for AI applications in radiation oncology. Treatment planning, auto-segmentation, image processing, and QA activities can all be aided by AI (Deig et al. 2019; Wang et al. 2019). Applications of AI to improve the quality and safety in radiation therapy are also in progress (Pillai et al. 2019).

1.3.8 Adaptive radiation therapy (Chapter 9)

Adaptive radiation therapy (ART) was already discussed in Chapter 1 of Volume 3, where it was described as the treatment plan being readjusted "on the fly" based on the changes that occurred in the patient or tumor anatomy during the course of a multi-fraction treatment. Figure 1.8 also shows the ART pathway in the total radiation treatment process. While ART was first described in 1997 by Di Yan (1997), the onset of multiple publications per year started in about 2005. Chapter 9 of this volume addresses ART directly, although aspects of ART are also discussed in several other chapters, e.g., Chapter 4 on real-time image guidance, Chapter 5 on SBRT, Chapter 6 on robust optimization, Chapter 7 on automated treatment planning, Chapter 8 on AI, Chapter 10 on machine learning, and Chapter 11 on big data applications.

One issue of *Zeitschrift für Medizinische Physik* was devoted to ART (Yan and Georg 2018). Biologically adapted radiotherapy can be considered as the most advanced form of ART, since it involves functional imaging to extract biological tumor surrogates or features, and thus needs a multidisciplinary approach. Thorwarth illustrates the complexity by discussing the whole development chain of biologically ART from radiobiologically relevant processes, to functional imaging techniques that visualize tumor biology non-invasively, to the implementation of biologically adapted radiation therapy in clinical practice (Thorwarth 2018). It is clear that ART will be a main contributor to the

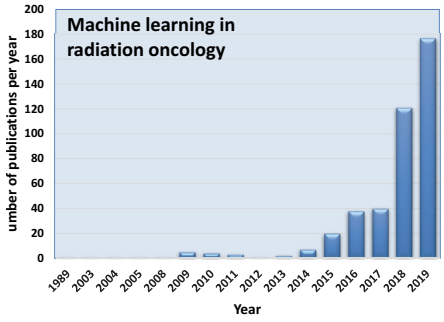


Figure 1.10
The number of publications per year on machine learning in radiation oncology. About 70% of these publications occurred in 2018 and 2019.

radiation oncology process, with geometric and anatomical adaption being available and biological adaption evolving such that it becomes a true contributor to personalized medicine.

1.3.9 Machine learning in radiation oncology (Chapter 10)

As a significant component of AI, machine learning is the development of data-driven algorithms that learn to mimic human behavior based on prior examples or experience (Jarrett et al. 2019). Figure 1.10 shows the recent rapid increase in machine learning publications, with 70% of them occurring in 2018 and 2019.

Applications of machine learning (Jarrett et al. 2019) (see also Chapter 10) include

- improvements in low-dose imaging for therapy planning,
- the use of MRI for the generation of CT-like electron densities for treatment planning (Dinkla et al. 2018; Dinkla et al. 2019; Maspero et al. 2018),
- multimodal image fusion for radiation therapy planning (Cao et al. 2016; Kearney et al. 2018),
- image segmentation for tumor and normal tissue delineation (Rigaud et al. 2019),
- treatment planning (see Chapter 7),
- plan approval and QA (Stanhope et al. 2015; Tol et al. 2015), and
- dose delivery and treatment adaptation (Tseng et al. 2018).

Table 1.2 summarizes the components of the treatment process that have had considerable research in the context of machine learning and its corresponding challenges. One of the main challenges is knowing the ground truth. Learning-based models are only as good as their training data. Machine learning is evolving rapidly, and it is an excellent means of providing consistency and efficiency, facilitating both transfer of best practices between physicians and clinics and greater process automation.

1.3.10 Big data (Chapter 11)

The complexity of the radiation therapy process is evident from Figure 1.8. The new advances in technology allow enormous amounts of data to be generated for patients during their total treatment process, as shown in Figure 1.11. The comparison is like a snowball rolling down a hill. It is the accumulation of these data, for which the radiation oncologists need help for translation into knowledge, that supports decision-making in their clinical practice.

The research analysis of these large amounts of data relies on analytical methods from the emerging science of "big data" informatics. This "big data" refers to extremely complex datasets characterized by the four Vs:

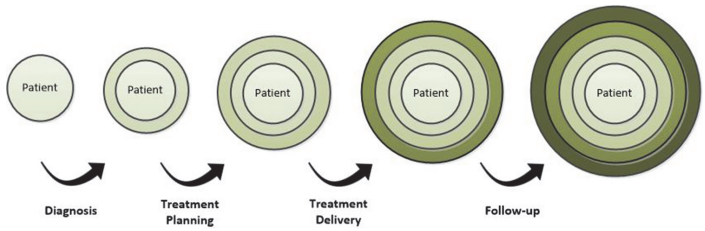


Figure 1.11
With each step along the radiation therapy process of Figure 1.8, more patient information is generated. Figure adapted from (El Naqa and Murphy 2015).

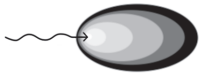


Table 1.2
Summary of current ML research focus in the radiation therapy process. Adapted from (Jarrett et al. 2019).

CLINICAL APPLICATION	CLINICAL NEED	CURRENT ML FOCUS	WELL-DEFINED PROCEDURE?	WELL-DEFINED GROUND TRUTH?	QUANTITATIVE MEASURE OF CORRECTNESS?
CT simulation	• Image reconstruction quality • Dose reduction	• Image reconstruction quality • Dose reduction	Yes	No	No
MRI simulation	• Pseudo CT creation	• Pseudo CT creation	Yes	No	Yes
Image fusion	• Estimate spatial uncertainty • Accommodation of anatomical changes	• Registration efficiency • Appropriate similarity metric	No—depends on use-case	No	No
Contouring	• OAR/target contouring efficiency • OAR/target consistency • Target contouring accuracy	• OAR/target contouring efficiency • OAR/target consistency	Yes	No—subjective clinical contours used	Yes
Treatment planning	• Planning efficiency • Plan consistency • Determining the plan to deliver the best clinical outcome	• Planning efficiency • Plan consistency	No—depends on clinical satisfaction criteria	No—subjective treatment plans used	No
QA	• Efficiency and automation • Identification of clinically meaningful errors	• Efficiency and automation	n/a	n/a	n/a
Delivery	• Dose accuracy in the presence of motion • (See image fusion, contouring, and treatment planning) • Determining who will most benefit from replanning	• Dose accuracy in the presence of motion • (See image fusion, contouring, and treatment planning)	No	No	No

- *volume*, which refers to the sheer number of data elements within these extremely large datasets;
- *variety*, which describes the aggregation of data from multiple sources;
- *velocity*, which refers to the high speed at which data is generated; and
- *veracity*, which describes the inherent uncertainty in some data elements (Kansagra et al. 2016).

In 2015, a workshop was organized by the American Society for Radiation Oncology, the National Institutes of Health, and the American Association of Physicists in Medicine on *Exploring Opportunities for Radiation Oncology in the Era of Big Data* (Benedict et al. 2016). Some of the important opportunities to explore further included:

1. Widening the potential for interlinkage of cancer data registries and developing strategies to include

analytics for a broad range of treatment approaches (widely variable dose/volume strategies).
2. Developing technology and adopting a culture change to enable inter-institutional pooling of data to form large analyzable databases.
3. Engaging with legislative and regulatory groups to find effective and inexpensive electronic methods to gather long-term follow-up data on survival, recurrence, and patient-reported outcomes while still respecting the need to protect patient health care information.
4. Understanding and identifying the key clinical decisions and questions where big data can be most useful.

In summary, the promise of big data in radiation oncology is to provide improved access to the collective experience of treating patients to improve care for new and future patients. This improvement can take the form of actions such as (1) reducing geographic disparities in care, (2) ensuring continual quality improvement for individual practices, and (3) ideally, personalizing treatments based on the outcomes of prior, similar patients. Each of these objectives requires different levels and resolution of clinical data that may be contained in registries, electronic medical records, tissue banks, and treatment planning and imaging systems (Benedict et al. 2016).

1.3.11 Radiomics in radiation oncology (Chapter 12)

A very recent, new field of study in radiation oncology and diagnostic imaging is known as *radiomics*. The publication rate is shown in Figure 1.12, with the onset of "radiomics" occurring in 2012. Seventy-one percent of the publications occurred in 2018 and 2019. Radiomics is based on the extraction of a large variety of features from medical images using data-driven algorithms to characterize tumors (Reuze et al. 2018). The image data are further processed with a variety of reconstruction algorithms to obtain images that generate tumor-characteristic features. Automatic image segmentation is used to generate appropriate volumes of interest. The tumor characterization algorithms should have several specific features, including (1) reproducibility, i.e., if used on the same data, the outcome should remain the same; (2) the algorithm must be able to detect disease; (3) it must be accurate, i.e., minimum false positives and minimum false negatives, with a maximum of true positives and true negatives; and (4) in view of the amount of data involved, it must be efficient.

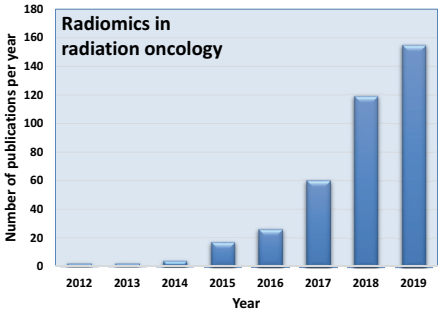


Figure 1.12
Publications per year on radiomics in radiation oncology. The onset occurred in 2012, and 71% of the publications occurred in 2018 and 2019.

Radiomics has the potential for providing guidance on a number of applications in radiation oncology (Wikipedia 2020), including (1) prediction of clinical outcomes (Nasief et al. 2019a; Nasief et al. 2019b); (2) prognostication (Huang et al. 2018); (3) prediction of the risk of distant metastases (Vallieres et al. 2015); (4) assessment of cancer genetics (Grossmann et al. 2016; Gutman et al. 2015); (5) tumor dynamics changes through data generated by IGRT (Yip et al. 2016); (6) distinguishing tumor progression from radionecrosis (Peng et al. 2018); (7) prediction of physiological events with, e.g., the use of functional MRI (Hassan et al. 2016); and (8) the use of multiparametric radiomics for detection, characterization, and diagnosis of various diseases, including breast cancer (Parekh and Jacobs 2020).

The use of radiomics overlaps with applications of AI, machine learning, and big data. Machine learning algorithms of AI boost the powers of radiomics for the prediction of prognoses or factors associated with treatment strategies, such as survival time, recurrence, adverse events, and subtypes. Thus, radiomic approaches, in combination with AI, may potentially enable practical use of precision medicine in radiation therapy by predicting outcomes and toxicity for individual patients (Arimura et al. 2019).

1.3.12 Radiobiological considerations in particle radiation therapy (Chapter 13)

While proton radiation therapy was already proposed in 1946 (Wilson 1946), the first treatments with protons did not occur until 1954 (Lawrence 1957). However, in the early years, proton therapy was only available in very few institutions that had access to high-energy particle facilities that were primarily used for physics research purposes. More recently, however, accelerator technology has been designed very specifically for clinical radiation therapy applications for both protons and heavier particles, and the number of hospital-based clinical facilities is escalating rapidly. Furthermore, new

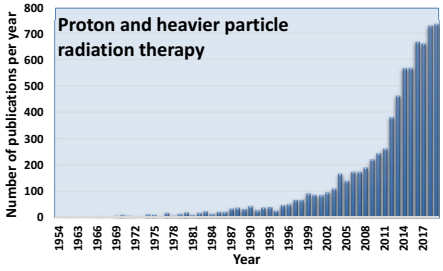


Figure 1.13
Number of publications per year with a PubMed search on "("hadron" OR "proton" OR "heavy ion" OR "heavy particle") AND ("radiotherapy" OR "radiation therapy")." The onset occurred in 1954 and 50% of these articles were published between 2014 and 2019.

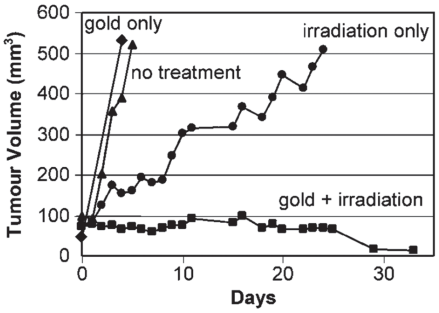


Figure 1.14
Average tumor volume after: (a) no treatment (triangles, n = 12); (b) gold only (diamonds, n = 4); (c) irradiation only (30 Gy, 250 kVp, circles, n = 11); (d) intravenous gold injection (1.35 g Au/kg) followed by irradiation (squares, n = 10). Figure from (Hainfeld, Slatkin, and Smilowitz 2004).

advanced capabilities—such as beam scanning, IMRT, IGRT, along with robust treatment planning—are providing further advances beyond the tight dose distributions provided by particle treatment. While the majority are proton centers, there are also some dedicated carbon ion facilities, as well as several facilities with the capability to treat with either (DeLaney 2018). Figure 1.13 shows the number of publications per year on protons and heavier particle radiation therapy since 1954, with 50% of these articles published between 2014 and 2019. It was estimated that, by the end of 2015, over 130,000 patients had been treated with protons and over 19,000 had been treated with carbon ions (DeLaney 2018).

As already indicated in Chapter 6 of Volume 3, for treatment planning purposes, it is assumed that the relative biological effectiveness (RBE) is a constant 1.1 over the entire irradiated volume for proton therapy. However, as pointed out in Chapter 13 of this volume, RBE values are probably higher at the end of the proton range, potentially affecting normal tissue toxicities, although the RBE variations are likely smaller than the variability in patient radiosensitivity. For heavier particles, however, the change in RBE values are significantly larger and need to be considered as a function of particle species, particle energy, depth of penetration, and type of tissue. It appears that current models, while not mechanistic, seem to be sufficiently accurate for clinical treatment planning purposes.

1.3.13 High-Z nanoparticles in radiation oncology (Chapter 14)

Nanotechnology relates to the manipulation of matter on atomic or molecular scales, generally less than 100 nanometers. The use of nanotechnology in medicine has led to what is now known as *theranostics*, where theranostics involves using nanoscience to unite diagnostic and therapeutic applications to form a single agent, allowing for diagnosis, drug, or dose delivery and treatment response monitoring. Nanomaterials have several characteristics that are relevant for oncology applications, including preferential accumulation in tumors, low distribution in normal tissues, and biodistribution, pharmacokinetics, and clearance that differ from those of small molecules. Because these properties are also well suited for applications in radiation oncology, nanomaterials have been used in many different areas of radiation oncology for imaging and treatment planning, as well as for radiosensitization to improve the therapeutic ratio (Rancoule et al. 2016; Wang and Tepper 2014).

Nanoparticles have been engineered from a wide range of materials that can be divided into inorganic and organic nanoparticles. One unique strategy is to increase the effect of the external beam radiation dose within tumor tissue by using materials with high atomic numbers (Z). This is because the dose absorbed by any tissue is related to some power of Z of the material, depending on the energy. If an agent can increase the overall effective Z of the tumor without affecting the Z of nearby normal tissue, it can lead to increased radiotherapy dose to tumors and higher therapeutic efficacy. The results of one of the first published mice experiments are shown in Figure 1.14, where gold nanoparticles of 1.9 nm diameter were injected into tumor-bearing mice (Hainfeld, Slatkin, and Smilowitz 2004). Tumor volumes were measured under various conditions of irradiation with 250 kVp x-rays. The one-year survival of the mice

treated with both the gold nanoparticles and irradiation was 86%, versus 20% for irradiation alone, versus 0% for gold alone. The gold nanoparticles were found to be non-toxic to the mice. These experiments generated much excitement and further research into applications of gold nanoparticles in radiation therapy. Other *in vitro* studies using 50 nm gold nanoparticles demonstrated a radiation sensitization enhancement factor of 1.66 and 1.17 with 105 kVp and 6 MV x-rays, respectively (Chithrani et al. 2010). Chapter 14 provides a detailed description of the applications of high-Z nanoparticles in radiation oncology.

1.3.14 Financial and economic considerations in radiation oncology (Chapter 15)

While the increasing complexity of the modern technology of radiation oncology has demonstrated improvements in patient outcomes, this comes at a considerable cost. As discussed in Chapter 1 of Volume 3 under "evolving trends," much emphasis has been placed in recent years on the financial and economic considerations in radiation oncology (Van Dyk and Battista 2013). Furthermore, there has been significant discussion in the recent literature on the global needs of radiation oncology, along with the estimated overall costs according to national income levels (Atun et al. 2015; Van Dyk, Zubizarreta, and Lievens 2017; Zubizarreta, Van Dyk, and Lievens 2017). Chapter 15 of this volume provides detailed guidance on economic considerations.

One of the issues that arises out of these discussions goes beyond the dollar cost analysis and has been described as assessing *value* per dollar spent. The discussion on *value* is complex. In the world outside of medicine, a good value is a desirable product or service that can be purchased for a fair price. The definition of value will vary depending on several factors, including the social identity and the social context of the person purchasing the product or service (Teckie et al. 2014). The desirable product or service, as well as the fair price, is in the eye of the beholder. Teckie et al. go on to describe their interpretation of *value* in healthcare. Where value has been described as outcomes per dollar spent, they suggest it should be expanded to include structure and process; thus, transforming the value equation to value equals quality per dollar spent. The key components of value include structure, process, outcomes, and costs, which are outlined in more detail in Figure 1.15. This type of value-based approach requires more involvement of the patient and adds another component to what has become known as personalized medicine.

1.3.15 Global considerations in radiation oncology medical physics (Chapter 16)

Globalization has been defined in a variety of ways, with one definition being "worldwide integration and development." The Wikipedia definition is "globalization is the process of interaction and integration among people, companies, and governments worldwide." Globalization has expanded as a result of advances in transportation and communication technologies. When the pros and cons of globalization are discussed, it is usually considered from an economic perspective. But what about the radiation oncology and medical physics perspective? In a recent debate on globalism versus nationalism in medical physics (Dube et al. 2017), the author in favor of globalism argued that globalism from a medical physics perspective, especially regarding dose calibration protocols, provides uniformity/consistency and efficiency, while the counterargument was that diversity provides more opportunities for advancements. Chapter 16 on global considerations in radiation oncology medi-

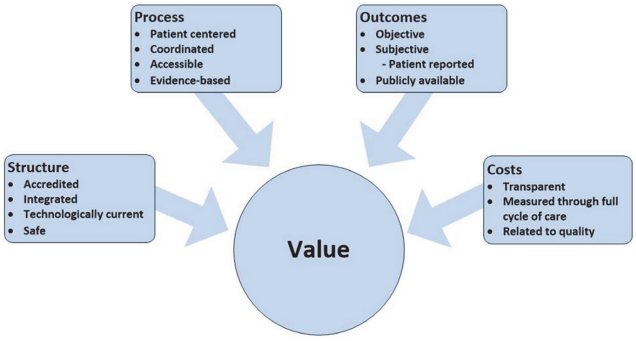


Figure 1.15
Key components of "value".
Adapted from (Teckie et al. 2014).

cal physics is not so much about globalization as it is about looking at a worldwide perspective of medical physics, e.g., what is the status of medical physics around the world, how are medical physicists trained, what are the issues, what are the solutions, etc. For example, as pointed out by the Global Task Force on Radiotherapy for Cancer Control (GTFRCC) (Atun et al. 2015), it is clear that there is a huge disparity of the availability of medical physicists by country, dependent on the country's income level as described by the gross national product.

According to the World Health Organization (WHO), of the 57 million global deaths in 2016, 71% were due to noncommunicable diseases (NCDs), of which 66% are due to cardiovascular diseases and cancer (World Health Organization (WHO) 2020), each of which involves significant support from medical physics, both in diagnostic imaging and radiation therapy. The burden of these diseases is rising disproportionately among lower-income countries and populations, almost double that of HICs. Several of the 2015 United Nations Sustainable Development Goals (United Nations 2018) include proposals to reduce by one third by 2030 premature mortality from non-communicable diseases, such as cancer and cardiovascular disease, and promote education and partnerships in support of sustainable development, all of which are relevant to Medical Physics. Many scientific and professional organizations provide various levels of support to international outreach activities for individuals from LMICs via reduced membership fees, special travel grants, and other specific awards, as well as providing education and training. These organizations include those related to Medical Physics (e.g., International Organization for Medical Physics (IOMP), American Association of Physicists in Medicine (AAPM), American Society for Radiation Oncology (ASTRO), and European Society for Radiotherapy and Oncology (ESTRO). Indeed, many of these organizations are increasing their outreach efforts. For example, the AAPM has had some recent task groups reviewing the international outreach structure within the AAPM with the goal of having a greater international impact along with improved effectiveness and efficiency. Similarly, the American Physical Society (APS) recently developed a strategic plan taking their international efforts to the next level with an indication that international activities cut across essentially all interests of the APS, and that their importance is increasing (American Physical Society 2018). It is clear that future demand for medical physics research and clinical support around the world requires multi-pronged approaches with the global community working together.

1.3.16 Emerging technologies for improving access to radiation therapy (Chapter 17)

The report by the GTFRCC (Atun et al. 2015) as well as others make it very clear that there is a need for additional radiation therapy equipment as the burden of cancer escalates, especially in LMICs. However, the technological demands of radiation therapy equipment are dependent on local circumstances and infrastructure. Several workshops have been held in conjunction with scientists and engineers from various high-level research organizations addressing the issue of how can the technology be redesigned to be more robust and less costly so that it can stand up to the circumstances in various environments (Dosanjh et al. 2017; Dosanjh et al. 2019; Pistenmaa et al. 2018). As noted in these workshop reports, filling the gap in cancer care in underserved regions worldwide requires global collaboration and concerted efforts to share creative ideas, pool talents, and develop sustainable support from governments, industry, academia, and nongovernmental organizations. To build capacity with high-quality capability and with the credibility to conduct research to understand specific diseases and treatment outcomes requires a complex systems approach toward both expertise and technology. Chapter 17 addresses some of these issues in detail.

1.3.17 "FLASH" radiation therapy (Chapter 18)

Recent research delivering radiation doses at ultrahigh dose rates, roughly 50 Gy/s and above, could vastly reduce normal tissue toxicity while preserving antitumor activity (Symonds and Jones 2019). So far, the evidence is growing in laboratory experiments. If the evidence is maintained in human clinical trials, FLASH therapy has the potential of being one of the very significant breakthroughs in radiation therapy of recent times (Bourhis et al. 2019). Details of FLASH radiation therapy are discussed in Chapter 18.

1.4 Evolution of Computer Technology

Radiation oncology involves applications of technologies like no other medical discipline. Because of the involvement of ionizing radiation in medical practice, radiation oncology has historically had a multidisciplinary approach to its evolution. Many of the technical advances have been initiated by medical physicists, and their clinical implementation was performed collaboratively with radiation oncologists. Today, nearly all the steps in the radiation treatment process, as outlined in Figure 1.8, involve computer applications. Table 1.3 highlights some of the computer applications in the treatment process and provides some examples, albeit only a partial list.

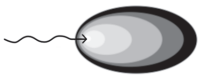


Table 1.3
Sample computer applications in the different stages of radiation treatment process summarized in Figure 1.8. Third column shows the chapters in this volume addressing some aspects of that specific treatment step.

STEP IN RADIATION THERAPY PROCESS	SAMPLE COMPUTER APPLICATIONS	CHAPTERS
Diagnosis	• Imaging • Transfer data to PACS • Interpretation of image data through machine learning and artificial intelligence to guide diagnosis	12
Patient positioning	• Possible use of SGRT	2
Imaging for treatment planning	• Use of CT, MRI, PET, other • 4-D considerations • Transfer of data to PACS or radiation oncology information system • Target volume and organ at risk delineation – Possibly guided by AI, ML	3, 7, 8, 10, 11
Treatment planning	• Treatment planning software • Possible use of SGRT data • Dose calculation – IMRT, VMAT – MLC leaf configuration generation – Optimization (robust) – 4-D considerations • Automated QA • Data transfer	2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 17
Treatment delivery	• Possible use of SGRT • Image guidance • Computer-assisted accelerators • 4-D considerations • Plan adaptation • Automated QA	2, 4, 5, 8, 9, 10, 11, 16

PACS = picture archiving and communications system

Increasing computer power and access to large amounts of data continue to allow further developments, such as automation and real-time adaptation. The co-founder of Intel, Gordon Moore, already in 1965 predicted that computing power would grow exponentially, doubling approximately every two years. The measure of "power" could be a variety of aspects of computer technology, one being the number of transistors on integrated circuits. Figure 1.16 is an example graphic of what has become known as "Moore's Law" (Moore 1965). It has generally been accepted that Moore's Law would be valid for a limited time, although in 2012, Mark Bohr, a later CEO of Intel, indicated that "the end of Moore's Law is always 10 years away. And, yes, it's still 10 years away." Past data continue to show the same trend; however, some computer specialists indicate that "as transistors reach atomic scale and fabrication costs continue to rise, the classical technological driver that has underpinned Moore's Law for 50 years is failing and is anticipated to flatten by 2025" (Shalf 2020). Be that as it may, computers and their corresponding applications continue to advance at a rapid rate.

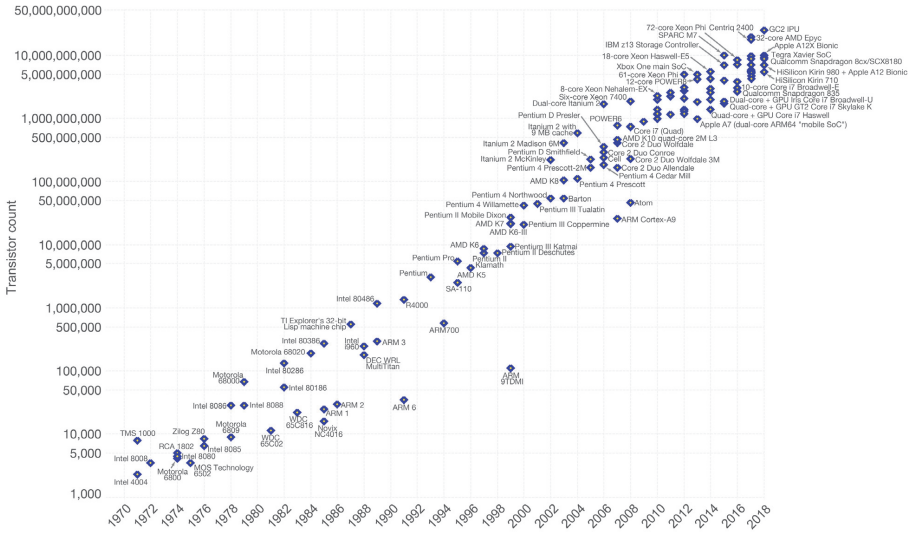


Figure 1.16
Graphic depiction of Moore's Law showing a semi-log plot of MOSFET transistor counts for microprocessors against dates of introduction nearly doubling every two years. From Wikipedia: https://upload.wikimedia.org/wikipedia/commons/8/8b/Moore%27s_Law_Transistor_Count_1971-2018.png.

In a Vision 20/20 paper on automation and advanced computing in clinical radiation oncology, the authors consider the computational advances that are likely to be implemented in clinical radiation oncology in the coming years and how the adoption of these changes might alter the practice of radiotherapy (Moore et al. 2014). Four main areas of likely advancement were explored: cloud computing, aggregate data analyses, parallel computation, and automation. These are issues that in the interim have advanced significantly and have been given considerable attention in the various chapters of this book.

1.5 Trends in Radiation Oncology

Predicting the near future is relatively easy since it is generally a continuation of the recent past and present. Predicting the distant future is much more complex and fraught with difficulties and uncertainties. To quote Niels Bohr, "Prediction is very difficult...especially if it is about the future." The trends listed briefly below are simply a projection of what has been happening in recent years. These are the author's perceptions, and they are listed without a lot of supporting information since many of these items have been discussed in the chapters of this book, as well as in previous volumes.

1.5.1 More hybrid technologies

We have seen the development of hybrid technologies in the last couple of decades, including:

- tomotherapy (external beam radiotherapy plus CT) (Chapter 15 of Volume 1),
- linac plus CBCT (Chapter 7 of Volume 2),
- MRI plus cobalt teletherapy (Chapter 4),
- MRI plus linac teletherapy (Chapter 4),
- PET/CT (Chapter 2 of Volume 2), and
- MRI/PET (Chapter 3).

The concept of a PET-linac system for molecular-guided radiotherapy has already been described by Ishikawa (2010). *In vivo* verification of particle therapy using tissue activation for PET techniques has also been described (Frey et al. 2014; Helmbrecht et al. 2015; Kuess et al. 2013).

1.5.2 More automation

As described in various chapters of this book, we are likely to see an increased use of automation. This will

include daily imaging, perhaps both interfraction as well as intrafraction, combined with real-time replanning, re-optimization and adaptation. This could be combined with more automated patient setups, possibly using robotics. Automated QA procedures will also become more readily available.

1.5.3 Turnkey installations

Tomotherapy is one of the examples where machine commissioning initially takes place in the factory, and the clinical commissioning process is one of verifying that the factory parameters are maintained after installation in the clinic. This results in a much more rapid commissioning process than is normally required for conventional linac commissioning. A similar approach has now also been developed for Varian's Halcyon™ (Gao et al. 2019; Netherton et al. 2019).

1.5.4 Reduced use of planning target volumes

With robust optimization accounting for various treatment-related uncertainties, the PTV concept is no longer needed. As robust optimization becomes mainstream clinical practice, physicians only need to outline CTVs.

1.5.5 Increased emphasis on cost considerations

As a result of the increased complexity of the newly developed radiation therapy technologies, administrators will demand a greater review of cost considerations, and medical physicists and radiation oncologists will have to contribute to such analyses (see Chapter 15).

1.5.6 Increased regulatory oversight

The recognition that we can learn from reporting treatment misadventures, incidents, or errors in radiation therapy has aided in the development of a general culture of patient safety. This was addressed in detail in Chapter 12 of Volume 3. The benefits of such reporting are clear, and various reporting mechanisms have been developed at the local, national, and international levels. Likely, this will also encourage some regulatory oversight to ensure that such procedures are consistently in place in every radiation therapy institution (Amols 2008; Krishnamoorthy et al. 2014; Malicki et al. 2014; Malicki et al. 2017; Malicki et al. 2018).

1.5.7 Increased use of particle therapy

As indicated in Figure 1.13, there has been a significant growth in the number of publications on proton and heavier particle therapy, with 50% occurring between 2014 and 2019. The Particle Therapy Co-operative Group (PTCOG) website (https://www.ptcog.ch/) provides data on particle therapy facilities around the world, both proton and heavier ion facilities. In April 2020, there were 95 operational facilities, 35 facilities under construction, and 28 facilities being planned. Clearly, there is a strong trend of growth in particle therapy around the world.

1.5.8 Increased use of radiobiological models for treatment planning

The use of radiobiological models for general clinical treatment planning has been controversial. The main argument against their use has related to concerns about the capability of the models to predict biological outcome with a sufficient level of accuracy. The concerns relate to limitations of the models and the available model parameters, the incomplete understanding of dose-response, and inadequate clinical data (Li et al. 2012). Radiobiological models were addressed in Chapter 5 of Volume 2, and a further update on dose-volume considerations was given in Chapter 3 of Volume 3. However, the issues described in Chapter 13 of this volume regarding RBE considerations in particle beams, especially heavier particles, make it clear that RBEs are dependent on a number of parameters, including particle type, energy and depth, and the tissue irradiated. The clinical impact of these issues is sufficiently significant that these need to be considered as part of the treatment planning process. The AAPM Task Group Report 166 provides guidance on the implementation of these models into clinical practice (Li et al. 2012). With more clinical data becoming available through "big data" channels, it is likely that the models can be better assessed for accuracy and relevance, and that they will be gradually implemented more and more into the clinical treatment plan optimization process.

1.5.9 Radiomic applications in radiation oncology

As indicated in Chapter 12, radiomics is another area of growth in radiation oncology. The trend toward personalized medicine is likely to include a major radiomics component. The applications of big data and machine learning will contribute to the radiomics developments.

1.5.10 Clinical implementation of FLASH therapy

If the initial excitement about FLASH radiation therapy can be translated into clinical improvements, we are likely to see a tremendous growth in this modality. Existing technologies will have to be upgraded to make FLASH therapy clinically practical.

1.6 Summary

The title of this chapter leaves the impression that the rapid developments of the technology of radiation oncology are continuing at the same pace. Now, having reviewed recent advances, it appears that the pace of development is actually more rapid than it has been in previous years. Thus, the title would have been better as "Technology Evolution in Radiation Oncology: The

Rapid Pace Escalates." It is an exciting period for radiation oncology. Technological improvements abound and the quest for personalized medicine appears to be within practical reach. This chapter has provided a brief overview of these advancing technologies, as well as an introduction to what is provided in much more depth in the subsequent chapters of this book.

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