REVIEW

Cancer risk assessment in modern radiotherapy workflow with medical big data

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Abstract: Modern radiotherapy (RT) is being enriched by big digital data and intensive technology. Multimodality image registration, intelligence-guided planning, real-time tracking, image-guided RT (IGRT), and automatic follow-up surveys are the products of the digital era. Enormous digital data are created in the process of treatment, including benefits and risks. Generally, decision making in RT tries to balance these two aspects, which is based on the archival and retrieving of data from various platforms. However, modern risk-based analysis shows that many errors that occur in radiation oncology are due to failures in workflow. These errors can lead to imbalance between benefits and risks. In addition, the exact mechanism and dose–response relationship for radiation-induced malignancy are not well understood. The cancer risk in modern RT workflow continues to be a problem. Therefore, in this review, we develop risk assessments based on our current knowledge of IGRT and provide strategies for cancer risk reduction. Artificial intelligence (AI) such as machine learning is also discussed because big data are transforming RT via AI.

Keywords: cancer risk, radiotherapy, workflow, big data

Introduction

With the growth of cancer survivors, there was more than 15.5 million on January 1, 2016, in USA and is projected to reach more than 20 million by January 1, 2026.[1] Electronic health records for them are skyrocketing. The US Cancer Moonshot Initiative recommends large-scale genetic analysis of tumors and clinical trial networks to better harness the information gleaned from cancer patients and to optimize care, pushing forward the personalized medicine.[2]

In radiotherapy (RT), cancer data are firmly in the realm of big data mainly due to ubiquitous images constituting one-third of total global storage demand. Medical imaging is crucial to RT. Its application in RT, referred to as image-guided RT (IGRT), encompasses tumor diagnosis, staging, prognosis, treatment planning, radiation targeting, and follow-up care.[3] Enormous digital data are created in the workflow, so IGRT can be redefined as information-guided RT. Large setup errors, ranges of organ motion, and changes in tumor position, size, and shape are most likely to be detected during the course of RT with frequent imaging, which has been becoming a requirement to attain the best tumor coverage improving local control and the most healthy tissue sparing, thereby improving quality of life.[4,5]

For decades, cancer patients have benefited from advances in IGRT. Survival times are likely to be longer for them, and the number of cancer survivors is increasing. Late sequelae of RT are becoming the next concern. Second malignant neoplasms

(SMNs) are among the most serious and life-threatening sequelae for the growing number of cancer survivors, especially for younger patients who have a longer life expectancy. Numerous epidemiological cohort studies have demonstrated radiation-related risks of thyroid and breast cancers, leukemia, and other neoplasms.[6,7]

However, the exact mechanism and dose–response relationship for radiation-induced malignancy are not well understood. The cancer risk associated with RT is still an area of controversy in clinical radiation oncology with impact on treatment decision making and on patient management. Many debates on cancer risks have existed for a decade or more.[8–10] In addition, modern risk-based analysis shows that many errors that occur in radiation oncology are due to failures in workflow and process.[11] These errors may further exacerbate the risk. In any case, research on cancer risk has substantially expanded our knowledge of clinical radiation oncology.

In this review, we highlight the latest research on IGRT workflow and discuss cancer risks in four key areas: screening and diagnosis, contouring and planning, targeting and delivery, and follow-up care and re-irradiation (Figure 1). Ethics approval for this study was obtained from Ethics Committee of Chongqing Cancer Institute. All methods were performed according to the relevant guidelines and regulations. These insights will help clinicians better understand the technology and the IGRT process in general and have an effect on personal trade-off between the risks and benefits of treatment options, improving safe RT delivery and patient treatment outcomes. In addition, these insights have the potential to decrease health care costs with a more rational use of medical technology. To transform these data into knowledge, data-driven machine-learning approaches such as automatic diagnosis, automated RT planning, and medical image retrieval are being utilized in the modern RT, so they are also discussed in this review.

Screening and diagnosis

Technologies have improved, and cancers are being detected earlier. Cancer survival rates have improved over the past several decades.[12] The specific contribution of screening has been debated for lung cancer (low-dose computed tomography [LDCT] or chest radiography), breast cancer (mammography), colorectal cancer (computed tomography [CT] colonography, CTC), and other cancers.[13–16] Several trials have demonstrated that screening can reduce death from both lung cancer and breast cancer by 20% with LDCT and mammography, respectively.[17,18] Epidemiological analyses also show a steady decline in mortality rates of colorectal cancer over the past several decades, which are attributed to screening.[19]

However, concerns have been raised about these routine screening and diagnostic evaluations because of the potential harms, including the radiation risks. The mean effective dose from an LDCT or a CTC is 1.6–2.1 mSv or 7.0–8.0 mSv, respectively.[20,21] Mammography screening doses range from 2.0 to 5.0 mSv.[22] The total radiation dose for a diagnostic CT can vary widely ranging from 2.2 to 14.0 mSv.[23] The dose is so low that these risks are not precisely quantifiable. Most of the quantitative information comes from studies of survivors of the atomic bombs and cohorts of radiation workers but it is characterized by a great uncertainty. The theoretical risk is estimated as follows: doses below 20 mSv have a minimal risk of cancer of less than one in 1000 patients, doses of 20–100 mSv have a moderate risk greater than one in 1000 patients, and doses above 100 mSv have clear evidence of radiation-induced cancer.[24]

Above 100 mSv: most scientific review groups consider that this dose is appropriate to use a linear dose–response model; below 100 mSv: it is difficult to get consensus on dose–response due to considerable uncertainties. Currently,
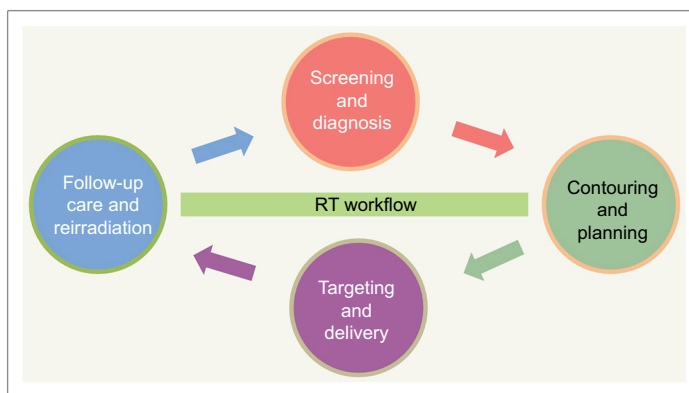

Figure 1 Modern RT workflow from diagnostic imaging to treatment.
Abbreviation: RT, radiotherapy.

the most commonly used model is a linear no-threshold (LNT) model, wherein dose–effect data at high dose are simply extrapolated linearly downward to zero without a threshold dose (Figure 2).[25] The LNT model is recommended by many expert advisory bodies for setting radiation protection regulations. Lifespan study (LSS) of atomic bomb survivors also shows that dose–response is consistent with the LNT model over 0–2 Gy range for all solid cancers as a group.[26] However, the LNT model focuses only on molecular damage, while ignoring protective, organismal biological responses. There is a growing body of experimental and epidemiological evidence that does not support its usage for estimating cancer risks.[27] Moreover, LNT sometimes causes considerable stress-related casualties.[28] The French Academy of Sciences believes that the use of LNT for assessing carcinogenic risks induced by low doses below 100 mSv is unjustified and should be discouraged.[29]

Apart from LNT model, there are various other contradicting models. A sub-linear model such as the linear–quadratic model based on "dual radiation action" theory which reflects the effect of dose and dose rate can explain current leukemia data from the LSS.[30] A hormesis model predicts protective effects below a threshold dose, even for noncancer deaths. It belongs to an adaptive response triggered by low-dose radiation, which is supported by multiple animal studies revealing the extension of lifespan of various mammalian models and many retrospective human studies exhibiting the reduced cancer rates or negative excess relative risk.[27,31,32] A threshold model predicts a negligible risk below a threshold dose such as immune suppression. This model is also compatible with leukemia data and sarcoma data, suggesting that thresholds cannot be larger than ~60 mSv for cancer or ~0.9 Sv for noncancer disease.[33] A supra-linear model fits well with the current cancer incidence data explained by hypersensitivity or bystander effect, and the low-dose hypersensitivity decreases with increasing dose and then disappears at doses of >0.5 Gy due to the biological defense system.[34]

To better understand the nature of the dose–response in the low-dose zone, it is necessary to use biological models with low variability and high reproducibility. In addition, it is much more important to review the risks and benefits of screening and diagnostic tests. This may serve as an indication for the individual to make a more informed decision to undergo these procedures. For breast cancer risk associated with mammography, the estimated risk is 86 cancers and 11 deaths per 100,000 women screened annually from 40 to 55 years of age
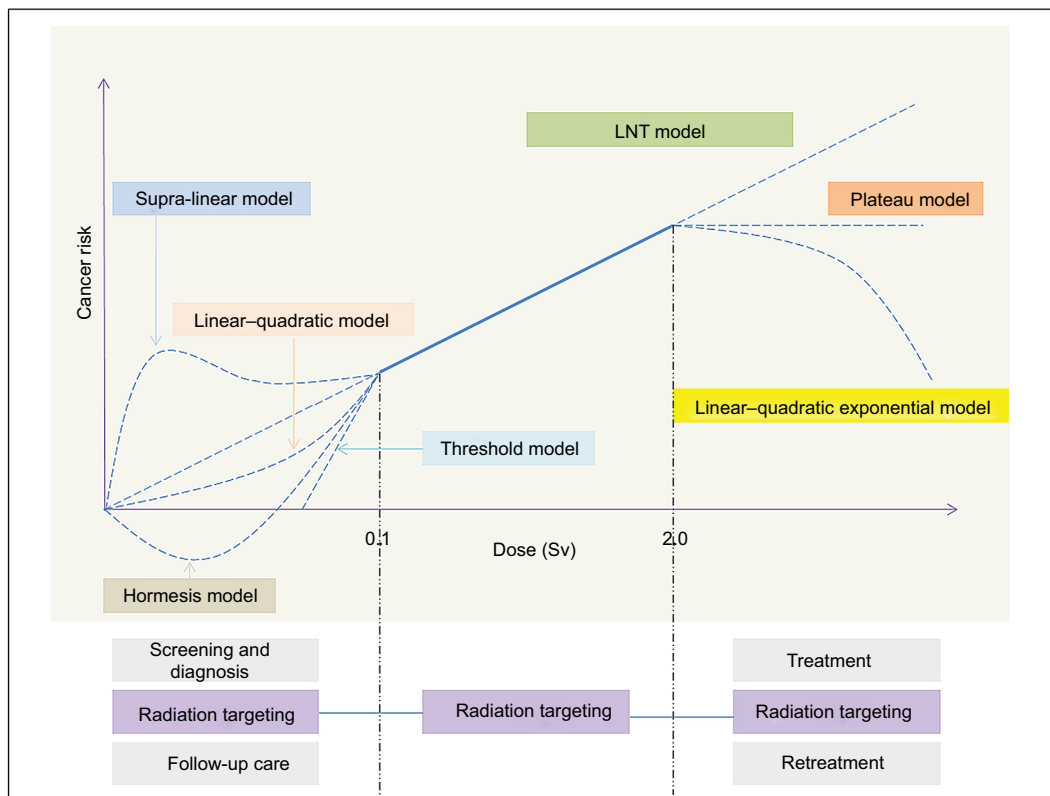

Figure 2 Dose–response curve for carcinogenesis and dose range of the IGRT workflow.
Abbreviations: IGRT, image-guided radiotherapy; LNT, linear no-threshold.

and biennially thereafter; the ratio of benefit to risk is 4.5:1 for lives saved and 9.5:1 for life-years saved.[35] The estimated number of radiation-related cancers from CTC every 5 years from age 50 to 80 years is 150 cases/100,000 individuals; the estimated number of colorectal cancer prevented by CTC ranges from 3580 to 5190/100,000, yielding a benefit–risk ratio that varied from 24:1 to 35:1.[21] The benefit-to-risk ratio of lung cancer screening with CT depends on several factors including efficacy of screening, smoking habits, sex of the screened subject, CT technology, and patient age at the commencement of screening. It can reach about 10:1 for special cohorts and screening efficacy, and it increases with advancing age.[36]

The radiation-related cancer risk is not well understood at the levels of screening and diagnostic radiation, but there are clearly risks associated with not performing an examination, such as missing a diagnosis and/or initiating treatment too late to improve the medical outcome. Currently, there is rigorous evidence supporting the value of screening and diagnosis, and it is important to implement screening and diagnosis in a manner that is focused on maximizing benefits and minimizing harms. For example, the dose to the fetus resulting from most conventional radiography or nuclear medicine procedures is <0.01 Gy for pregnant women, and it has a risk of childhood cancer and leukemia with an incidence of about 3–4/1000;[37] if the dose exceeds 0.01 Gy, it can be reduced with proper tailoring of the examination or adopting another type of examination, such as ultrasonography or magnetic resonance imaging (MRI).

Recently, a new emerging field referred to as radiomics not only provides a quantitative way to assess tumor phenotype but also has shown promise in automatic detection of cancers, staging determinations, and predicting treatment response by applying a large number of quantitative features from screening or diagnosis images.[38] This new field will make CT, MRI, and positron emission tomography (PET) more standardized, reproducible, and quantitative. Its potential has been demonstrated in many cancers, in turn allowing for adapting and individualizing treatment at low cost.[39] In light of this, cancer risks may be more accurately predicted by radiomic changes, which are assessable prior to the development of observable changes on standard diagnostic imaging. Combining radiomics with genomic data, the so-called radiogenomics could provide the highest level of personalized risk stratification.

Contouring and planning

In IGRT, pretreatment images constitute the inputs to the treatment planning process, which is vulnerable to the GIGO effect (garbage in, garbage out). For this reason, a series of scientific articles on CT have been raising increasing concern about image quality.[40] However, the higher the dose contributing to the image, the less apparent is image noise and the easier it is to perceive low-contrast structures. In view of possible cancer risk, CT dose reduction strategies and scanning protocols have been suggested to match CT dose with the necessary image quality by many organizations.[41–43] In contrast to therapeutic irradiation, the CT planning doses are too small to judge whether cancer patients benefit from the reduced dose strategies. Hence, it is not of great concern to these patients and their attending radiation oncologists. The acquisition of optimal CT data set fused with other imaging modalities, such as MRI and PET, to allow the radiation oncologist to accurately contour the tumor targets, is always the subject of the RT procedure.

Various studies indicate that inconsistencies in anatomy contouring may be larger than errors in the other steps of the treatment planning and delivery process.[44] They also could potentially lead to reduction in the dose to the tumor, increased locoregional recurrence and worse survival. Up to now, a large number of contouring consensus guidelines have been established, and structured training on image interpretation has been offered. In addition, semiautomatic and automatic contouring methods, such as probabilistic atlases and machine-learning technologies, have been proposed to minimize manual input and increase consistency in delineating target volume. Various margins are recommended to generate clinical target volume (CTV) or planning target volume (PTV). Frequent image guidance is suggested allowing margin reduction to several millimeters and dose escalation while maintaining sparing of healthy tissue. Standards for quality assurance (QA) of IGRT devices and reconstruction algorithms are implemented to quantify image quality in adaptive RT (ART) and online/offline planning process, improving positioning or registration accuracy.

However, traditional CT images show respiratory motion as artifacts, and target volumes based on these images may be distorted. Four-dimensional (4D) CT (4DCT) technology allows clinicians to view volumetric CT images changing over time for the observation of intra-fractional target motion and assessment of lung function in RT and to predict treatment response even better than static pretreatment images. Although a prospective 4DCT simulation can allow radiation exposure to be minimized to almost the same as that in helical CT, the measured effective dose was 28.7–33.2 mSv during a retrospective 4DCT simulation, approximately four times higher than that for helical CT.[45] From the radiological

protection point of view, it is important to optimize the 4DCT scan protocol to minimize patient exposure.

To enhance target definition and RT planning, IGRT takes full advantage of these imaging advances. It markedly impacts the amount of radiation dose and volume of irradiated tissue as well as cancer risk. Large clinical studies have highlighted that patients who received RT had a higher risk of SMNs.[46] SMNs usually occur near volumes irradiated to intermediate doses (~2–50 Gy) or in volumes receiving full-dose radiation.[47] Although LSS shows that a linear relationship exists between cancer and dose from ~0.1 to ~2.0 Sv, there are great uncertainties at higher doses (Figure 2). The bell-shaped Gray model (linear–quadratic–exponential model) hypothesizes that the relative increase in risk declines above a threshold dose (thyroid cancer, ~20 Gy) in terms of a balance between cell mutation and killing; a plateau model based on various biological parameters, such as cell sterilization, proliferation, and carcinogenic effects, speculates that there is a plateau beyond a threshold dose (breast cancer, ~10 Gy).[48] However, several epidemiological studies indicate that SMN risks increase significantly from 1 to 45 Gy for stomach and pancreas, but 1–60 Gy for bladder and rectum or 1–15 Gy for kidney.[46] It seems that the risk continues to rise as a linear function of dose.[47]

In IGRT, especially for planning process, many factors such as fractionation schedule, linear accelerator (linac), RT techniques, beam energy, and dose/dose rate may affect SMN risks. Carcinoma and sarcoma risks are decreased by ~10% and ~15% per gray with increasing fractionation dose.[49] The out-of-field dose is likely to be highly facility dependent due to leakage and scattering from head and accessories.[50] Intensity-modulated techniques increase the risks because of more monitor units (MUs), increasing leakage and scattering radiation; dynamic mode or cross-plane motion also increases SMN risks compared to segmental or in-plane mode; more fields are correlated with higher risks.[51–53] Higher energies (>6 MV) produce larger scattered X-rays and small but significant neutrons due to photonuclear interactions with thresholds of 6–13 MeV for most materials.[54] Although the model-dependent SMN risks have been presenting in many literatures according to the Gy, plateau, or linear dose–response model, large discrepancies exist among them.[55]

Clinically, choosing the least toxic radiation modality is of utmost importance. Previous studies have also demonstrated that increased risks for RT-related SMNs vary in different organs/tissues (Figure 3);[56–61] both size and shape of the PTV influence SMN.[62,63] While providing equally good PTV coverage and following the specific organ-at-risk

(OAR) constraints, the probability of SMN incidence should be carefully examined and weighed against the possibility of developing acute side effects for each patient individually as well as treatment efficacy. According to the target characteristics, a major decrease in the volume receiving a moderate radiation dose by any strategy (e.g., patient positioning, linac choice, and shielding strategies) is the appropriate way to substantially decrease the second cancer risk while designing the treatment plan. In addition, clinical trials have demonstrated that plan quality is associated with survival and local tumor control.[64] There have been intense research activities in planning quality evaluation using machine-learning approaches based on prior plans.[65–67] Further, automatic treatment planning solutions such as knowledge-based planning and multi-criteria optimization have been proposed to improve the plan quality and workflow, including automatic learning-based beam angle selection and automatic optimized intensity for individual patients based on their unique anatomy.

Targeting and delivery

For decades, radiographic images have been the standard method of verification, providing localization, displacement, and deformation of tumors and/or OARs in two dimension (2D), three dimension (3D), or 4D to achieve the beam-and-target alignment, dose verification, and adaptation, which are dependent on both image quality and imaging frequency.[68] Nowadays, the emerging delta radiomics, a longitudinal fashion for radiomics, can be based on routine images to serve as a biomarker for treatment monitoring and optimization or active surveillance. An increase in the number of images will ensure accurate and precise RT delivery and yield smaller setup errors and CTV-to-PTV margins reducing SMN risks in distant tissues, but add more imaging radiation doses to target and adjacent healthy tissues. About 70% of SMNs occur in those regions.[69,70] At some point, a cost/benefit balance needs to be reached, which is highly individualized to RT site and protocol. In fact, geometric precision is only one aspect of treatment, and its desire should be balanced with clinical gains and modest workloads on RT contouring, planning, and delivery.

Besides imaging frequency, the organ-absorbed doses also depend on imaged region, imaging parameters, and techniques provided by different vendors (Figure 4).[71] Generally, 2D imaging dose is concentrated at the skin, while 3D/4D tomography dose is distributed nearly uniformly throughout the imaged volume. If imaging parameters are not optimized, out-of-field doses from imaging can be comparable to doses from the scatter and leakage radiation associated
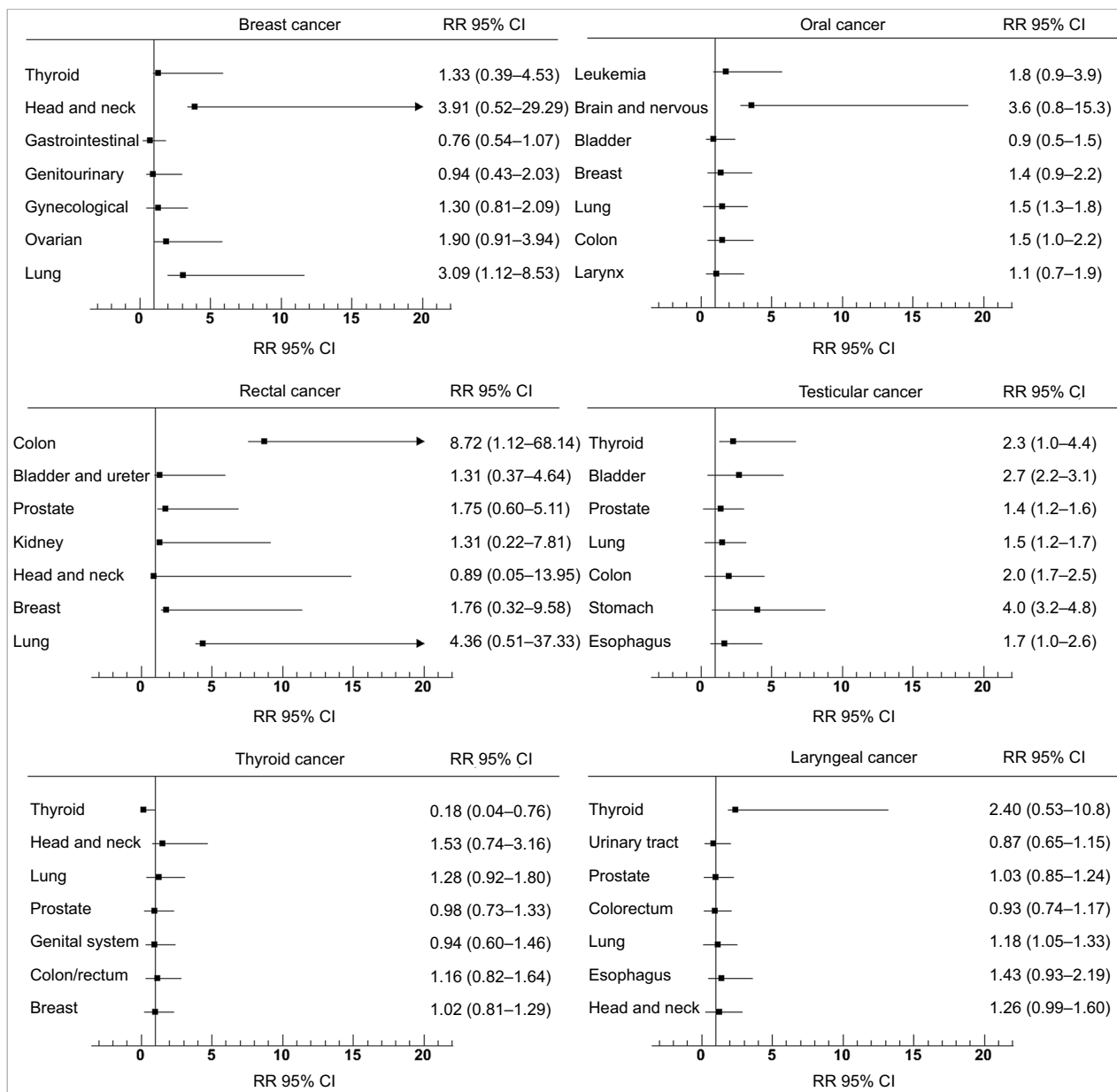
Figure 3 RRs of second cancers in patients treated for breast, rectal, laryngeal, oral, testicular, and thyroid cancers.
Abbreviations: CI, confidence interval; RR, relative risk.

with therapeutic beam. There is an estimated probability of 0.08–3.59% of SMN.[72] Therefore, the imaging dose and its distribution need to be taken into account in the treatment planning, which results in about 4–5% reduction in MUs and control points,[73] or it is appropriate to optimize the image quality and minimize the imaging dose to ≤2% variation of the therapy dose, which is the internationally accepted beam output variation of RT linac, through varying the beam directions, field of view, number of projections per imaging, the tube voltage (kVp), current (mA), or mAs/frame. Especially for pediatric patients, it is necessary to perform personalized

imaging according to patient characteristics considering the type of imaging, such as two orthogonal images or cone beam CT (CBCT), and acquisition modes, for example, CBCT head modes can be used to image the thorax, abdomen, or pelvis to selectively avoid irradiation of superficial organs.[74]

Unlike the diagnostic/planning imaging, radiation targeting adds the additional dose to an already high level of therapeutic radiation except for the first fraction (Figure 2). The joint effect of targeting and delivery, which is additive or not, is not readily tested through randomized clinical trials. In theory, due to enhanced accuracy, the observed
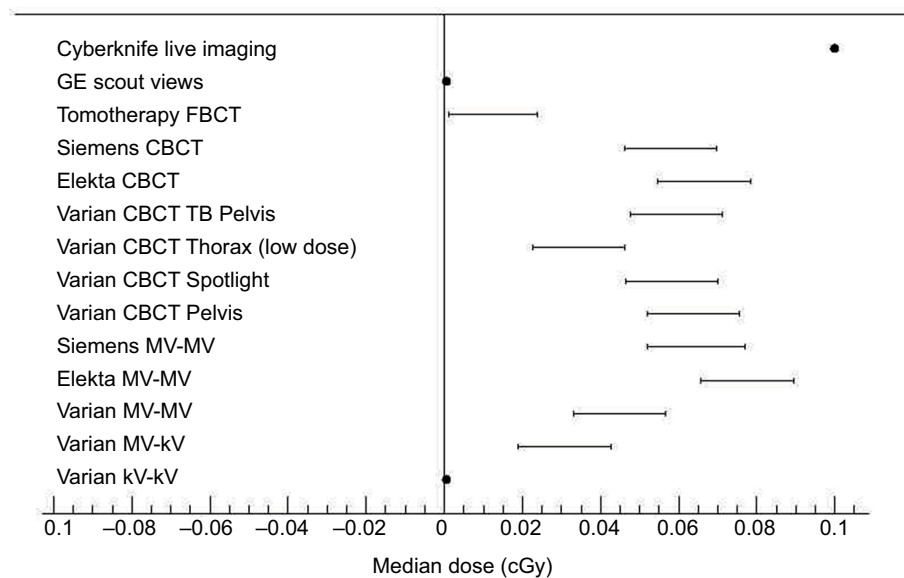
Figure 4 The median dose of various imaging modalities.
Abbreviation: CBCT, cone beam computed tomography; FBCT, fan beam computed tomography; GE, general electrics; MV, megavoltage; kV, kilovoltage; TB, truebeam.

reduction in adverse effects of IGRT might in part be due to an adaptive response of normal tissues to the low doses of radiation from the imaging process before the delivery of high therapeutic doses. By coincidence, tumor cell radioresistance triggered by the imaging dose has been verified recently.[75] According to the generalized linear–quadratic model, the delay time between imaging and treatment also affects local tumor control while incorporating imaging dose into the therapeutic dose.[76] Other modalities such as optical imaging techniques also have an important role in IGRT without exposing the patient to additional radiation dose during RT delivery.[77] In conjunction with X-ray systems providing some information about internal anatomical structures such as bones, they can provide continuous monitoring of patients and detect these changes in the soft tissues, where the tumor is located.

Due to higher rates of medication errors among adult (7.1%) and pediatric (18.8%) patients with cancer, numerous programs for workflow-related QA are established and performed to detect errors to ensure that these personalized treatments are delivered safely.[78] These errors include unauthorized acts, operative errors, equipment failures, initiating events, accident precursors, near misses, and other mishaps.[79] Most of the errors are discovered in setup/treatment and during treatment follow-up phases. There are still errors that are not covered by regular QA checks, so individual clinics should perform a risk analysis of their unique practice, classifying and learning from incidents, and to determine

appropriate testing frequencies to maximize physicist time efficiency and patient treatment quality, improving existing processes or implementing new workflows. But manually intensive procedures are more prone to errors. To further minimize human errors, all kinds of applications using state-of-the-art web technologies, data mining, and machine learning, are being designed to automate and model the clinical workflow and IGRT process.

As one of today's most rapidly growing technical fields, machine learning also brings new treatment technologies via new learning algorithms, such as auto-adaptive margin generation for real-time tracking RT for motion management.[80] However, technological innovations themselves can lead to the development of new potential hazards, so it is important to carry out quality evaluation when they are implemented in the clinic. All aspects of the treatment workflow, from imaging to dose calculation and treatment delivery, should be carefully handled and recorded. A large amount of data will be produced. Although these data are available in one RT center or other centers separately, it is difficult to make comparisons of new treatment technologies on a large scale and explore treatment effects. Nowadays, information availability has become more elaborate and widespread. More and more national or international infrastructures are being developed to enable structured and automated data collection and secure sharing of RT data.[81] To reach the best patient care, most treatment decisions will be based on gathered relevant data, referred to as big data, while treatments can be further

optimized with respect to increased survival, less SMN risk, and less burden on the health care sector.

Follow-up care and re-irradiation

The risk of second malignancies after RT is a subject not without controversy. Generally, all cancer survivors should follow applicable national guidelines for cancer screening. But it is more important than ever for clinicians and patients to have accurate risk estimates of secondary cancers after RT to permit the development of individualized follow-up guidelines and prevention and intervention strategies.

To date, there are many investigations of interactions between RT and potential confounding factors such as age, sex, race, tobacco and alcohol use, dietary intake, energy balance, and other cofactors, as well as genetic susceptibility. One of the most important factors correlated with an SMN is the age of the patient at the time of RT. For the same dose, it shows that children are considered to be 3–15 times more sensitive to radiation-induced SMN than adults, and the cancer risk decreases from about 15%/Sv of whole body uniform irradiation for children under 10 years of age to about 1%/Sv for adults exposed at over 60 years of age.[82] Greater systematic checkup should be implemented after RT for this higher risk population. Compared to the therapeutic benefit, SMN might not be as significant and should not factor into treatment decisions for the older population.

It has been known that there is a significant dependence of tissue and organ to SMN risk. According to the National Council on Radiation Protection and Measurements (NCRP) report No. 116, stomach, lung, and colon are the most common sites for developing a fatal second cancer after radiation exposure. In addition, the thyroid gland is known to have a low threshold for radiation-induced cancer, especially in children and young adults (a mean organ dose as low as 0.05 Gy).[83] For a given dose, females have a higher SMN incidence compared to men due to the increased risk of breast and thyroid cancers in females.[84] Therefore, follow-up care should be managed on a case-by-case basis, but the cost to both the health care system and patients need to be evaluated.

The greatest challenge in determining risk is that second cancers after RT have a latency of onset of 5–10 years for leukemia and about 10–60 years for solid tumors after the initial treatment.[85] Only longer follow-up will allow a true assessment of the SMN risk. Taking into account what is known with regard to first primary cancers and adding evidence on SMN risks, a detailed survivorship care plan should be made to record the patient's treatment and anticipated long-term effects.[86] In addition, a risk-adapted strategy can

be made to optimize the routine follow-up policy such as screening frequency and follow-up duration and to minimize the probability of second cancers according to the follow-up care guidelines.

Indeed, new SMNs now are representing about 16% of all cancers reported to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program.[87] Further, SMNs particularly solid tumors are a major cause of mortality among cancer survivors. Fortunately, technological advances in RT and imaging have made treatment of patients with re-irradiation possible. However, re-irradiation with overlapping volumes of previously irradiated tissues is not without risks because of severe toxicity. Due to some disease- and patient-related factors, such as previous treatment, second cancer site, and performance status, the identification of who might derive the most benefit from which technology with what kind of dose and fractionation schedules is of utmost importance.

Nowadays, although the selection criteria for re-irradiation remain poorly defined and vary across centers, a careful second course of irradiation might provide a symptomatic and survival benefit in special patients. A single institutional experience shows that thoracic re-irradiation with conventional RT appears to deliver a meaningful survival benefit in new primary or recurrent lung cancer with low target volume (PTV <300cc).[88] Re-irradiation also may be considered an option for recurrent or new primary cancer of the head and neck, rectum, breast, cervix, or other sites in carefully selected patients using a variety of techniques and fractionation schedules, providing good local control rates while toxicity remains acceptable.[89–94] Despite a paucity of large randomized studies, re-irradiation has been adopted in different clinical scenarios by many institutions, and the role of contemporary methods, such as IGRT, remains an area of active investigation in re-irradiation. Regardless of these aspects, careful attention to RT planning and delivery is critical to optimize the outcomes, so the corresponding guidelines are beginning to emerge for certain indications.

In recent years, enormous advances in RT have been achieved, for instance, introducing particle therapy into clinical routine, or the development of MRI-guided radiotherapy.[95,96] These high-energy particle beams can often achieve excellent disease control while delivering minimal radiation dose to healthy tissue near cancer targets, offering a significantly lower second cancer incidence rates than photons. In a ROCOCO in silico clinical trial, a reduction in mean dose to OARs is also demonstrated using particle therapy compared to photons in the re-irradiation of patients with

squamous cell carcinoma of the head and neck.[97] However, due to the high cost of the particle therapy facility, the cost/benefit ratio is being debated. MRI provides the gold standard for defining soft tissue structures during RT planning, and the use of MRI-guided treatment delivery is providing a further argument for an MRI-only workflow, which will eliminate setup and registration error while also reducing workload and strain on the patient, especially additional radiation in the RT workflow. But the dosimetric errors in an MRI-only RT workflow need to be considered due to the specific geometric distortion from MRI.[98]

Conclusion

This review describes the cancer risks in numerous processes of IGRT, including screening and diagnosis, contouring and planning, targeting and delivery, and follow-up care and re-irradiation. Although we do not know the exact mechanism and dose–response relationship for radiation-induced malignancy, enormous advances in IGRT will help clinicians better understand the technology and the process in general and have an effect on individualized RT guidelines and strategies for cancer risk reduction, improving safe RT delivery and patient treatment outcomes. This review only describes external beam radiation therapy, and it is conceivable that brachytherapy faces a similar challenge. In the future, we believe that utilizing artificial intelligence (AI) to translate and combine all data sources into knowledge will enable health care to move to individualized, high-quality, and safe cancer treatments.

Acknowledgment

Disclosure

The authors report no conflicts of interest in this work.

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