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Is the linear no-threshold (LNT) model relevant for radiotherapy?

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Abstract – Initially considered as a kind of radiobiological law, the linear no-threshold (LNT) model, which by definition supports the absence of any threshold for cancer risk induction after irradiation, is nowadays more reasonably described as a pragmatic and prudent approach by the International Organizations. However, it remains today a dogma in radiological protection. Actually, this model had been essentially developed for the radiological protection of a general population against low, and sometimes very low, doses of irradiation. Radiation oncologists are dealing with a totally different situation since they deliver, on purpose, high doses of radiations in more or less limited volumes of the body of cancer patients, patients for whom no other alternatives do exist to get rid of their malignant tumors. Simultaneously, the radiation oncologists inevitably give low and even very low doses at distance from the so-called target volumes. In such a specific situation, what is the carcinogenicity of these low doses and the relevance of the LNT model in radiotherapy? Thus, this paper addresses three critical questions: 1) what is the risk acceptability of the radiation doses delivered by radiotherapy of malignant tumors? 2) what is the real carcinogenic risk of (very) low doses delivered at distance from the target volume? 3) are the clinical radiotherapy data, *i.e.*, the number of second primary cancers, accumulated since more than a century, consistent with the LNT model? In conclusion, the LNT model appears to be poorly adapted to the high doses locally delivered to cancer patients and dramatically overestimates, in most cases, the risk of secondary radio-induced cancers. *In fine*, the real risk of the LNT model in radiotherapy would be to promote radiophobia in cancer patients and to see some of them turning away from a life-saving treatment.

Keywords: linear no-threshold model / LNT / radiological protection / radiotherapy / carcinogenesis

1 Introduction

Although challenged in the recent years, the linear no-threshold (LNT) model, which by definition supports the absence of any threshold for cancer risk induction after irradiation (thus meaning that some cancer risk does exist even at very low doses and with a linear relationship) still stands today as a kind of dogma in radiological protection (Boice, 2017; Shore *et al.*, 2019). In spite of a number of criticisms, and even petitions, against the use of the LNT model, most international bodies (such as UNSCEAR, BEIR, ICRP and NRC, only to mention those ones) still favor today this LNT model.

However, at present, more than 70 years after its birth, we have to recognize some evolution in the interpretation of the LNT model. While it was initially described and considered as a kind of radiobiological law it is now more and more often rather described as a pragmatic and prudent approach (ICRP Publication 103, 2007; Shore *et al.*, 2019). For international radiological protection bodies, whose task is by definition to protect the general population against all detriments due to irradiation, such an attitude (most probably overestimating – by large? – the risk) could be, at least partly, understood.

Nevertheless, this (over?) prudent attitude may pose problems in some specific situations.

For example, the ICRP 60 recommendation has set the effective dose limit for the general population at only one millisievert (mSv) per year, a dose which is, as well known, the level of the natural irradiation in most countries on Earth (ICRP Publication 60, 1990). Actually, the ICRP 60 recommendation meant that it was the excess dose – above the natural background – which should not exceed 1 mSv per year.

However, as honestly recognized by Roger Clarke himself (who acted as chairman of the ICRP main Commission from 1993 to 2005), this very low limit "has not been understood". For example, we could read in some – usually serious – newspapers: "1 mSv, the dose above which the cancer risk is unacceptable"... Such a statement would therefore mean that the natural background dose received by almost all inhabitants of our planet is unacceptable.

Such a misunderstanding had direct (and sometimes devastating) consequences, including in the medical world, even if ICRP 60 reasonably recommended not to use any dose

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limit for medical radiation exposures (ICRP Publication 60, 1990). In an attempt to overcome this misunderstanding, ICRP tried to substitute to the dose limit a new concept of controllable dose (Clarke, 2003), which actually was not very successful, the 1 mSv limit unfortunately remaining deeply stuck in most of the minds...

In such a context of (understandable) public fear of even very low doses of radiation, a context largely exploited by various anti-nuclear lobbies, the radiation oncologists, who have to deliver, on purpose, very high doses to their patients in order to cure their cancers, have to face specific and sometimes difficult situations.

Radiation protection experts, used to deal with a few mSv of effective dose, are clearly not comfortable with radiotherapy absorbed doses by the tumor, given in Gy since they are localized to a small part of the body. Although we cannot directly compare the localized absorbed dose of radiotherapy in Gy and the total body effective doses in mSv, radiation therapy doses reach up to hundreds to one thousand times the limit set for the general population (and still more for brachytherapy). In each chapter of this article, we will try to meet the challenge by using the more adapted unit corresponding to the point in question.

Let us remind here that, in the case of total body irradiations before bone marrow grafting for leukemia, radiation oncologists have even to deliver lethal doses, a situation properly terrifying and beyond understanding for our radiological protection colleagues (Cosset *et al.*, 1995).

Surprisingly enough, the wide experience of the millions of patients treated worldwide by radiation therapy for more than a century has been rather poorly studied by the radiation protection international bodies. In the 332 pages of the ICRP 60 document, the therapeutic exposure experience is somehow limited to a short statement on page 183: "*Therapeutic exposures often involve doses in excess of 5 Gy, where cell killing may lead to an under-estimation of the cancer risk per unit dose.*" (ICRP Publication 60, 1990)

As we will see later on, the rules (and the risk models) have been essentially based on radiobiological (sometimes obsolete) and epidemiology data obtained in the Japanese A bomb survivors forming the Life Span Study (LSS) cohort (Preston *et al.*, 2007), as well on large studies of nuclear workers (Cardis *et al.*, 2007). None of these studies take into account medical exposures.

In addition, we note that very few radiation oncologists (and in a number of cases none of them) were or are still participating in the international groups specifically involved in radiological protection.

In such a situation, what should be the attitude of radiation oncologists facing the rules or models set by the international bodies, and particularly when considering the LNT model? Among the number of possible questions that radiation oncologists may (or should) pose to themselves when "forced" to take into account the LNT model, we will consider three of them:

1 What is the cancer risk acceptability of the radiation doses delivered by radiotherapy of malignant tumors in such a context?
2 While delivering doses considered as very high by the radiation protection experts, radiotherapy unavoidably delivers much lower doses in large parts of the patient's distant body. What is the real carcinogenic risk of such (very) low doses delivered at distance from the target volume? Here, it is clearly the level of risk of those (very) low doses at distance from the target volume(s) which is questioned.
3 With the (much) higher doses given in the target volume or in its "penumbra", *i.e.*, several grays (Gy) in the surrounding millimeters/centimeters, what is the real risk of radio-induced cancer after radiotherapy in those areas? If we keep in mind the LNT model, which implies a direct proportionality between risk and dose – whatever the dose level – a (large?) number of secondary cancers is clearly to be expected. Are the clinical radiotherapy data accumulated since more than a century consistent with the LNT model?

The goal of this paper is to address these three questions.

2 Risk acceptability of radiotherapy for malignant tumors

2.1 "Normal" population *vs.* radiotherapy population

A first point to be emphasized when discussing the risk of a radio-induced cancer is to stress the obvious difference between a "normal" population of healthy people, on the one hand, and a cancer patient population undergoing radiotherapy, on the other hand.

In a normal population of healthy people, it appears obvious that the acceptable risk of a radio-induced cancer should be if possible nil, or as low as reasonably achievable (according to the ALARA principle). It is clearly the reason why ICRP had recommended dose limits which are particularly low for the "normal" general population (see above).

The situation is obviously totally different for a population of cancer patients having to undergo a therapeutic irradiation. Nowadays, in most cases (see the rare exceptions later on in this chapter) radiotherapy is prescribed and delivered for a malignant disease.

In spite of a number of recent therapeutic advances, let us remind that cancer remains in a majority of cases a therapeutic challenge for the oncologists, with in most cases an almost constant 100% mortality in the absence of treatment. In such a life-threatening situation, the acceptability of some risk (including the risk of second primary radio-induced cancer) cannot obviously be compared with what could or should be accepted in the general population.

As a logical consequence, the level of "acceptable" risk of radio-induced cancers is clearly (much) higher in a cancer patient population (having to face a life-threatening disease, and who would die in the absence of treatment) than in a "normal" population of healthy people.

Actually, all cancer therapies whatever their type (surgery, chemotherapy, radiotherapy, immunotherapy...), imply some risks of side effects and/or complications. Professor Maurice Tubiana used to say: "*We cannot treat cancer with rose water*". Those risks are to be accepted in the absence of any reasonable alternative because it is the one and only way to obtain the eradication of the tumor of a cancer patient.

Thus, to compare the radio-induced cancer risks in the general population and in a cancer patient population is obviously irrelevant.

If looking for a comparison, one should better turn towards the potential risks of oncologic surgery (per and peri-operative mortality) and of antineoplastic chemotherapy (hematological toxicity, secondary leukaemia, etc.): those risks are to be accepted with a concurrent known benefit, in the same way we have to accept in most instances some risk of secondary malignancies (fortunately usually very low, as we will see later on) after radiotherapy.

In keeping with those assumptions, one of the authors who reported on the potential increased secondary cancer risk after modern radiotherapy techniques reasonably recognized that "*the risk of secondary malignancy is a minor consideration for radiotherapy patients as compared to tumor control and acute toxicity effects*" (Kry *et al.*, 2005).

However, we have to recognize that nowadays such a statement, based on common sense, does suffer a few exceptions. Since the 1950s–1960s, radiation oncologists know that a number of parameters have to be considered when evaluating the risk of radio-induced cancers in their patients.

2.2 The effect of age

Among those parameters, age is clearly one of the most important. A huge number of data accumulated since the early years of radiotherapy have confirmed that patient's age is one of the main parameters radiation oncologists have to take into account when choosing a given technique of irradiation and particularly when trying to evaluate its secondary cancer risk. It is now well known that children (and to a much lesser extent young adults) are much more prone than older adults to develop a radio-induced cancer after a given dose of irradiation. They are also in parallel more prone to develop some serious deterministic effects such as the stopping of bone growth.

There is no "cut-off" for the carcinogenic risk depending on age. The risk being very high for the newborn decreases progressively with age. ICRP Publication 60 (1990) and Hall (2006) reported for example that for a female population, the attributable life-time risk (% per Sv) is 15% for the new born, 10% for a girl of 10, 5% for a woman of 30, 2% at the age of 60, and almost nil after 80. This figure is due to a number of causes: among them, a higher "general" radiosensitivity of children, with more frequent genetic syndromes linked to a higher genetic susceptibility to irradiation at that age (ICRP Publication 79, 1998), and also a higher impact of scattered dose due to the smaller size of the children's body (Hall, 2006).

Therefore, when irradiating a child, the risk of a secondary tumor must always be kept in mind in order to adapt the technique to the particular susceptibility of children. The "acceptability" of radiotherapy for a child is therefore very different from what can be accepted for an adult (or an older) patient. Actually, the secondary cancer risk in children has already led to the introduction of significant changes in a number of current paediatric oncology protocols; radiotherapy has sometimes been totally excluded from the treatment strategy for some malignant tumors for which adequate alternatives could be developed (most often chemotherapy for example for hematologic malignancies).

In other cases, radiotherapy had to be accepted in the absence of alternatives but in order to reduce the carcinogenic risk, significant efforts have been made to reduce both the irradiated volumes and the doses. Significant examples of those (successful) efforts can be found in the paediatric Hodgkin's disease protocols for which the reduction of the irradiation volumes and doses has been proposed more than three decades ago, based on the higher deterministic effects rates in children, and also on the (already detected at that time) higher risk of secondary tumors. Moreover current efforts are ongoing to more and more propose proton therapy to those patients. Those efforts have allowed to very significantly decrease the radio-induced cancer risks in those patients (De Bruin *et al.*, 2009; Tubiana, 2009; Schaapveld *et al.*, 2015).

At the other end of the age scale, elderly cancer patients pose a totally different problem: they are much less susceptible to develop a radio-induced cancer (see above), and they often will not live long enough to allow us to observe the emergence of such tumors, due to the well-known delay (usually more than 10–15 years) between the irradiation and the emergence of a secondary solid tumor.

In the same line, for palliative treatments proposed to patients whose life expectancy does not exceed a few months, considering the secondary cancer risk would obviously be irrelevant.

In between the children and the elderly, for adults with a life expectancy exceeding (often by large) 10 years, the risk of a secondary tumor, although much smaller than in children, must be kept in mind, and the technique must be adapted, at least when this is possible without altering the primary aim of radiotherapy, *i.e.*, the eradication of the primary cancer.

2.3 Dose optimization in cancer radiation therapy

This being said and recognized, it is obvious that everything should be done to optimize and reduce the risk of secondary induced cancers after radiotherapy, down to a level "as low as reasonably achievable". The lower limit here cannot be a kind of "threshold" dose level delivered to some organ or tissue, but the "level" below which the measures taken to reduce the second cancer risk would reduce the anti-tumor efficacy of radiotherapy (thus leading to an increased risk for the patient of dying from his/her primary tumor).

This "level" will vary according to a large number of parameters, including the type of cancer, the patient's age, the irradiated organs and the various irradiation parameters. In such a situation, the balance of risks (*i.e.*, second cancer risk *versus* mortality from the primary tumor) has to be assessed by taking into account the specificities of each patient, and therefore no precise "dose limits" can (or should) be given.

A number of papers have discussed the main recommendations to optimize radiotherapy delivery and thus to reduce to an "as low as reasonably achievable" level the risk of secondary malignant tumors after modern radiotherapy (Cosset *et al.*, 2016; Recorad, 2022).

As previously emphasized, considering this specificity of the medical therapeutic irradiations, ICRP reasonably recom-

mended not to use any dose limit for medical radiation expositions (ICRP Publication 60, 1990).

However, with (very) rare exceptions, cancer patients never read the ICRP 60, and a percentage among them only kept in mind the risk of minimal radiation doses, risk which has been largely (and often wrongly) advertised by some lobbies promoting radiophobia for a variety of reasons.

Consequently, radiation oncologists have sometimes to face patients who refuse, by fear of a subsequent cancer, a radiotherapy which represents the only way of curing their cancer. Such a situation is fortunately rare in our clinical practice but may happen as an indirect, and unfortunate, misunderstanding of the linear no-threshold (LNT) model.

Strangely enough, we note that the same "opinion leaders" who promote radiophobia, and are therefore directly responsible for those unreasonable treatment refusals, do not usually hesitate to accept radiotherapy when their own life is threatened by a cancer.

In line with those treatment refusals, some authors have even questioned the use of radiographies (for example the mammographic screening aiming at detecting breast cancers), because of the possible theoretical risk of radio-induced cancers. Such an excessive proposal had forced the former chairman of ICRP Committee 3 to publish a paper demonstrating that, even with the more pessimistic hypothesis (*i.e.*, the LNT model), the (proven) benefits of mammography are exceeding by far the (theoretical) risk of a secondary induced malignancy, and this by a factor ranging from 25 to 100 (Mettler *et al.*, 1996).

The previous paragraphs are dealing with the usual use of radiotherapy in 2022, *i.e.*, its almost exclusive use for malignant tumors.

2.4 The anti-inflammatory effects of radiotherapy

Nowadays, it is frequently forgotten that historically, the very first targets of therapeutic irradiations were not cancers, but a large series of benign lesions. For example, the first "brachytherapy" was performed by H. Danlos at the Paris Hospital St. Louis for a tuberculosis lupus. Thereafter, and this for decades, radiation therapists took advantage of the anti-inflammatory capacity of ionizing radiations to (quite successfully) treat a large number of nonmalignant lesions.

In France, until the 1980s, the French University regularly asked the author of the present paper to give conferences to students on "Anti-inflammatory effects of ionizing radiations". At that time the following diseases were often treated with irradiation: painful arthrosis, Dupuytren's disease, Plantar fibromatosis, keloids, Peyronie's disease, symptomatic vertebral haemangiomas, synovitis, heterotopic ossification, Graves' orbitopathy, hemorrhoids, herpes zoster, etc. (Seegenschmiedt *et al.*, 2015; Cosset and Deutsch, 2021).

However, a number of secondary tumors were then registered several years after such irradiations and consequently those "anti-inflammatory" radiotherapies almost disappeared from the radiation oncologist armamentarium in the 1980s–1990s (Cosset and Deutsch, 2021).

Nevertheless, in 2022, a sharp contrast does exist between the strategies chosen in various countries in Europe; for example, while it is considered as almost totally "outlaw" in France, anti-inflammatory irradiations are still largely proposed in Germany (Seegenschmiedt *et al.*, 2015). The fact is that our German colleagues somehow refused to "throw the baby out with the bath water", and are still proposing (wisely) this type of irradiation to selected elderly patients, for whom the medical alternatives (such as steroids) would be dangerous and for whom the secondary cancer risk is almost nil as indicated above.

So, with strict selection of patients and well-balanced indications, irradiations of some non-malignant lesions can be probably considered as "acceptable".

3 What about low doses in radiotherapy?

The "high" absorbed doses (several tenths of Gy) delivered by radiotherapy in the target volume and close to it will be considered in a subsequent chapter, but in 2022 the radiation oncologist cannot totally escape considering the "low doses" delivered in parallel by radiotherapy. As a direct consequence of most therapeutic irradiations, large volumes of the body are actually receiving doses considered as "very low" by radiation oncologists but not so "very low" by our radiological protection colleagues. For a long time such low doses have been considered as quite negligible and often totally ignored in the context of cancer radiotherapy.

In addition to their almost complete absence in international bodies texts (see above), an indirect proof of the relative "lack of interest" of radiation oncologists for those dose levels is the absence of "isodoses" lower than 5% (of the prescribed dose), *i.e.*, 100 mGy for a dose of 2 Gy, in most of the available dosimetry softwares. In fact one has to acknowledge that the theoretical calculation of those doses far away from the target volumes is quite difficult, with, apart from (very rarely performed) direct measurements, huge uncertainties.

However, should radiation oncologists completely forget what happens with the very low doses they deliver at distance from the treated volumes? Certainly not.

Again, we will only consider in this chapter doses received at distance from the target volumes, which in most cases will exceed several mSv, *i.e.*, again doses mostly considered as quite negligible by radiation oncologists, but considered as relevant in terms of radiological protection. If trusting the LNT model, those doses (actually unavoidable because mainly linked to scattered irradiation from the patient body and from the treatment machines) will be systematically – theoretically – responsible for some increased cancer risk at distance from the target volumes in irradiated patients.

So the radiation oncologist must therefore ask the question: is the LNT model really relevant for those very low (and unavoidable) doses? A huge number of articles/reviews/letters have been published for more than 70 years on this topic. As stated above, the LNT model still remains the one which is still officially recognized as the "best choice" by international bodies. However and particularly in recent years, it has been more and more questioned.

3.1 LNT concept: the history

It is worth reminding that the studies on which the LNT model has been built (somehow "validated" by the Nobel Prize

of H.J. Muller in 1946) were performed on a fruit fly model (drosophila) and more precisely on spermatozoa of this specific fly. Moreover, the experiments were performed at high doses (2 to 3 Gy) and at high dose rates. Last but not least, subsequent data have shown that mature spermatozoa are lacking the capability of DNA repair.

Apart from the (daring?) extrapolation to man of those data obtained from the drosophila spermatozoa, and apart the (also daring?) direct extrapolation to zero dose, the Muller Nobel Prize of 1946 suffers from an "original sin", *i.e.*, a suspicion of dishonesty. It happens that we do have available exchanges of letters between Muller and other colleagues, proving that, before his Nobel Lecture, Muller was aware of experimental results challenging his LNT response paradigm and strongly suggesting a threshold to the mutagenic effect of radiation. Strangely enough, rejecting those studies, Muller claimed in his Nobel Lecture that "*There is no escape from the conclusion that there is no threshold dose*" (Calabrese, 2017, 2018, 2019).

A second "original sin" of this early period relies on the strange interpenetration (*i.e.*, the same scientists with top responsibilities in both groups) between the National Academy of Sciences (NAS), Biological Effects of Atomic Radiation (BEAR) genetics panel and the Rockefeller Foundation, with – significant – financial supports to the research groups supporting the LNT model (Calabrese, 2019). Therefore, the "no threshold" concept was ironically financially supported by the "Oil lobby", and this, up to the 1970s.

Only considering the "low doses", hundreds of papers, in the following decades, have suggested that the LNT model was clearly over simplistic. It was true that the relationship between dose and carcinogenesis was subsequently found to be linear in the LSS cohort of the survivors of the atomic bombs, but this was true between about 0.5 and a few Gy (Preston *et al.*, 2007). Later on, ICRP Publication 103 (2007) suggested that the carcinogenic risk is directly proportional to the radiation dose down to 100 mGy.

There is (at least) a rather large consensus to consider that this dose level of 100 mGy (actually frequently reported as 100 mSv) constitutes the "threshold" below which epidemiology cannot be contributive. For those doses below this 100 mSv "threshold", a number of uncontrollable biases "tends to obscure evidence concerning radiation-related risk" (ICRP Publication 103, 2007). For this part of the dose-risk curve (*i.e.*, below 100 mSv) discussions are still going on.

Actually, for those very low doses, some authors have emphasized the role of the "bystander" effect, claiming that the shape of the curve in this low dose part could be supra-linear; in such a situation, the LNT model would underestimate the risk (ICRP Publication 103, 2007). On the contrary, there are "*long-standing arguments on whether some form of low-dose simulation of anti-tumorigenic components of the immune system might serve to reduce cancer risk*" (ICRP Publication 103, 2007). In such a situation, together with defense mechanisms able to deal with limited DNA lesions, the LNT model would overestimate the risk.

To make the problem still more complex, cancer induction varies with the tissue or organ involved, so that "*the existence of a low-dose threshold for cancer induction in certain tissues is not implausible*" (ICRP Publication 103, 2007). Last but not least, some authors proposed a "double threshold", taking into account the now well-studied "radiation-induced adaptive response" at low doses (Waltar and Feinendegen, 2020). Based on the "triggering" of defense systems by low doses of radiation, this mechanism would be likely to explain the "low dose hypersensitivity", followed by a relative radioresistance, well known by radiation oncologists since the publications of Joiner *et al.* (1996, 2001).

In conclusion, it seems clear in 2022 that the application of the LNT model looks over simplistic. ICRP itself recognizes that "*the possibility of a threshold for cancer induction at some unknown low dose cannot be ruled out*" (ICRP Publication 103, 2007). The French Academies (Tubiana *et al.*, 2006) emphasized evidence on the potential dose-dependence of post-irradiation cellular signaling, DNA repair, apoptosis and other adaptive anti-tumorigenic process, and argued for the existence of a "practical" low-dose threshold for radiation cancer risk.

While still considering the LNT model as a prudent basis, the international bodies honestly recognize a large number of uncertainties, sometimes devoting entire specific chapters to those uncertainties (ICRP Publication 103, 2007).

In the recent years, a large number of papers openly questioning the validity of the LNT model has been published (Scott, 2018; Marcus, 2015; Sutou, 2015; Cardarelli and Ulsh, 2018; Doss, 2018; Pennington and Siegel, 2019; Calabrese, 2021), only to mention a few ones. Overall, there are more than 1000 articles which have been published so far, suggesting a non-linear dose response at low doses (Luckey, 1982; Cardarelli and Ulsh, 2018).

In 2015, three petitions were filed to the Nuclear Regulatory Commission (NRC) asking to give up relying on the LNT concept. Following those petitions (actually rejected by NRC), the exchanges between the "pro" and "anti" LNT scientists reached a surprising level of violence; both parties speaking of "lies", "hogwash", "false science", or even worse...

Somebody honestly trying to understand this fight might be lost: actually, both the "pro" and "anti" LNT authors are usually referring to the same sets of data (essentially the Japanese LSS of atomic bomb survivors cohort and the nuclear worker's one) to reach seemingly opposite conclusions.

3.2 The Life Span Study

We have to recognize that precious data have been brought to the scientific community by the huge study of the Japanese bomb survivors (Preston *et al.*, 2007). We must recognize that those data actually showed a "proportionality" between dose and cancer risk between about 0.5 Gy and a few Gy.

But what happens for doses lower or higher than this range still remains largely questioned and discussed. In fact, even the huge LSS studies suffer from a number of problems and uncertainties. We will only mention a few of them.

– The incidence of some cancers is very different between the Japanese population and that of other countries. For example, breast cancer incidence is much lower (by a factor of about 10) in Japanese women than in Europe and in the US. On the contrary, esophagus and gastric cancers are (far) more frequent in Japan than in Europe and in the US. These differences may obscure the understanding of the carcinogenicity of the Japanese bombs irradiation, or at

least may complicate the extrapolation of those Japanese data to other populations.
- The exact dose received by the Japanese bomb survivors was – understandably – difficult to evaluate. The neutron component, with its high relative biologic effectiveness (RBE), posed a number of problems, so that two successive dosimetry systems had to be successively proposed. The more recent one, DS02, has been considered as a "considerable improvement" by ICRP 103, when compared to the previous system (DS86), which was indicating lower doses, with an about 10% difference. However, discussion are still going on about this neutron component, particularly about the neutron RBE which should be chosen (Cullings *et al.*, 2014).
- Some authors also pointed out that LSS ignored the part of dose received by the subsequent fallouts in the area around the epicenter of Hiroshima (the so-called radioactive "black rains"): in such a situation, the "in-the-city control" people, exposed to such a fallout cannot be considered as a "non-irradiated" control group (as it is the case in LSS). The result might be that "*cancer risk in the LSS was largely overestimated*" (Sutou, 2017).
- Another problem is that the relationship between dose and cancer risk appears to be very different for solid tumors and for leukemia; the analysis of the Japanese bombs survivors showed that "*the leukemia results indicated that there was a nonlinear dose response for leukemia other than chronic lymphocytic leukemia or adult T-cell leukemia, which varied markedly with time and age at exposure, with much of the evidence for this nonlinearity arising from the acute myeloid leukemia risks.*" (Hsu *et al.*, 2013). So the LNT model cannot be applied to leukemia (Cuttler, 2014).
- A last possible question arose recently: in the last years, radiation oncologists learnt that the use of very high dose rates (the so-called "Flash" effect, up to 30–100 Gy/minute) lead to biological results which appear to be very different from those obtained by the dose rates which are usually delivered in the clinic. The "Flash" irradiation is apparently able to achieve a similar efficacy on tumors, but seems to offer a "protection" of a number of normal tissues or organs (Favaudon *et al.*, 2014; Vozenin *et al.*, 2019; Bertho *et al.*, 2020). This could question the biological effects of at least a part of the irradiation received by the atomic bomb survivors, an irradiation delivered at a very high dose rate.

3.3 The Nuclear industry workers

The other large set of data regularly quoted to support the LNT model is the 15-country collaborative cohort study which was conducted on 407 391 nuclear industry workers monitored individually for external radiation exposure, with not less than 5.2 million person-years of follow-up (Cardis *et al.*, 2007). This large cohort also poses several problems.

First, when looking at the French part of this cohort, we discover that cancer mortality in the nuclear workers is significantly decreased (by about 30%) when compared to the general population (Leuraud *et al.*, 2017). Such a finding, also observed in other cohorts, has been dismissed by the international bodies who explain that such an improvement is clearly linked to a "*strong healthy worker effect*". Such an explanation may be understood as due to an obvious "selection" of healthy nuclear workers. But what is less understandable is that our international bodies systematically refused to consider that such a lesser cancer mortality could also be linked (at least in part) to some beneficial effects of low-dose irradiation, and not only to the drastic selection of the workers in nuclear industry (Scott, 2018).

Apart from ignoring such a mechanism, the authors inexplicably ignored other sources of radiation which could have been received in parallel by the nuclear workers. The natural background (obviously very different in the 15 participating countries) is not taken into account. Still more confusing, the medical exposures have been ignored; how can we accept the hypothesis that no one of those 407 391 nuclear industry workers never benefited, in this period of time, from some type of radiographic examinations, or never had to undergo some diagnostic radiology exposures or radiotherapy? Moreover, some workers may have received internal contamination by various radionuclides (isotopes of uranium, plutonium, etc.), but doses from such exposures could not be evaluated and therefore were not accounted for in the assigned radiation doses.

Last but not least, this study failed to address the parallel exposure to other carcinogens, some of them obviously being more dangerous and "potent" that low dose irradiations, such as smoking (Scott, 2018).

3.4 New epidemiological data?

We previously saw that epidemiologic studies have been for decades somehow dismissed, because of the number of possible interpretation biases (ICRP Publication 103, 2007); those biases being considered to "*tend to obscure evidence concerning radiation-related risk*".

However a recent huge study covering the entire US population of the 3139 US counties and encompassing over 320 million people recently brought new data forcing us to reconsidered such a position (David *et al.*, 2021). The authors show that life expectancy was approximately 2.5 years longer in people living in areas with a relatively high *versus* low background radiation, the difference being very significant ($p < 0.005$). The same study revealed a negative correlation between cancer mortality rate and background radiation level ($p < 0.001$).

Actually, several previously published papers had noted such a lower cancer mortality rate in areas with higher background radiation level: this had been reported in some areas in India, Iran, and China and even previously in the US (David *et al.*, 2021). So, those new epidemiological data do suggest that not only very low levels of radiation are not harmful, but that they could even be beneficial, possibly by reducing the cancer mortality rate (?).

3.5 Which risk of the low doses at distance from the radiotherapy target volume?

Finally, what should we conclude in the specific frame of radiotherapy about the risk of those very low doses received at distance from the target volumes?

First of all, the real carcinogenicity of those "very" low doses (less that 100 mSv) remains questioned, the LNT model being more and more discussed. This carcinogenicity is most probably nil for most of our patients, simply because of their age (cancer is most often a disease of the elderly), and a number of papers even suggest some possible beneficial effects of those very low doses (hormesis, adaptive response...).

This assumption may suffer a few exceptions; we probably have to be prudent when having to treat children, and to a lesser extent young adults (see supra), and we have probably to work to reduce those low doses at distance down to a reasonable level (thus without any risk of decreasing the cure rate) for those patients.

In such a situation (irradiation of children and young adults), radiation oncologists must take into account those doses far away from their treated volumes: they have to reduce as much as possible the "scattered" dose, by adapting the technique.

They also have to be aware of any possible "leakage" through the head of their machines. In the past, such leakage from the machine head (in some cases a simple "pencil" beam) sometimes escaped the attention of the commissioning physicists. We have examples where the head shielding had to be reinforced because of such a leakage; this mainly happened with cobalt machines and old linear particle accelerators (linacs), but could also be observed with more recent machines (Petti *et al.*, 2006).

4 What is the real risk of radio-induced cancer in the "high-dose volumes" after radiotherapy?

4.1 Localization of radio-induced cancers after radiotherapy

The review of available data on second cancers occurring after RT (and diagnostic exposures in some series) generally confirms the usual clinical experience, according to which "*the majority of second induced cancers occur in or close to the high-dose treatment volume*" (Hall, 2006). More precisely, Xu stated that most studies have identified second tumors to be located "*adjacent to the target volume in the intermediate-dose level*" (defined as in a 5–50 Gy range) (Xu *et al.*, 2008).

An exception to this evidence-based conclusion is secondary sarcoma, which usually appears within the high-dose volume(s), actually "in-field" (Huang and Mackillop, 2001; Rubino *et al.*, 2005; Kirova *et al.*, 2005).

Therefore, in a majority of cases, radio-induced cancers appear to emerge in the volumes adjacent to the target volumes, in the area usually called the penumbra by the radiation oncologists. So the question is: can a linear extrapolation (following the LNT model) explain the observed risk in those areas?

4.2 LNT calculation of cancer risk after radiotherapy

When speaking of cancer risk after irradiation, a huge number of papers mentions the apparently practical percentage of "5% per Sv", thus indicating that the risk of fatal cancer is 5% per Sv received by a patient.

ICRP Publication 103 (2007), after a review of the available data, noted; "*It is therefore the recommendation of the Commission that the approximated overall fatal risk coefficient of 5% per Sv on which current international radiation safety standards are based continues to be appropriate for the purpose of radiological protection.*"

A direct (mis)extrapolation of this statement to radiotherapy would therefore mean that most (all?) radiotherapy patients, who are given up to 80 Gy (with brachytherapy patients still receiving much higher doses) to the tumor and 5 to 50 Gy in the penumbra, are doomed to develop a fatal cancer. Fortunately for those patients, it does not appear to be the case (see below). With the exception of children, the second radio-induced cancers are rare (Cosset *et al.*, 2018).

Actually, ICRP 60 (see above) notes that such an extrapolation is irrelevant, because, as previously noted, "*Therapeutic exposures often involve doses in excess of 5 Gy, where cell killing may lead to an under-estimation of the cancer risk per unit dose*" (ICRP Publication 60, 1990). The wording is here questionable; actually the cell killing at high doses likely explains why the risk decreases with dose at high doses.

The reason for such an observation is simply the obvious fact that a cell which has been killed (so, a dead cell) cannot give birth to a mutated cancerous clone. In fact, this risk decrease at high doses has been discovered and published by L.H. Gray as early as in 1957, with a so-called "bell-shaped" risk curve of the leukemia risk in mice (the risk decreasing when doses exceed a few Gy). This bell-shaped curve has been largely confirmed since that time by a large number of studies (Schneider, 2011).

By itself, this ICRP statement (not to consider doses in excess of 5 Gy for the discussion of the radio-induced cancer risk) by itself implicitly recognizes that the linear risk curve of the LNT model is clearly unadapted when we have to consider radiotherapy.

Another limitation of the LNT model when it comes to radiotherapy is the role (already mentioned in details in previous chapters) of age. The 5% per Sv "mantra" does not mean anything if we do not consider in parallel the age of the patient. As soon as in 1990, ICRP 60 emphasized the huge variation of the radio-induced cancer risk according to age; the mean risk for an adult was rather considered to be 4% per Sv; it could reach up to 15% for a young child, and goes down close to 0% in the elderly.

4.3 Epidemiologic evaluation of radio-induced cancers by radiotherapy

In the extensive 2007 review by Suit, the relative risk (RR) for a second primary cancer in 11 cohorts of cancer patients was 1.31, when comparing the radiotherapy patients (RT) and the general population (GP); *i.e.*: RR RT/GP = 1.31 (95% CI; 1.15–1.49) (Suit *et al.*, 2007). However, this RR does not appear to be only due to irradiation, since the RR for the non-irradiated cancer patients is 1.12 (RR nonRT/GP), strongly suggesting that the risk of a second malignant tumor in cancer patients is higher than in the general population. The real risk of second cancers after radiotherapy is therefore better evaluated by the RR "RT/nonRT", which compares the cancer

patients who received radiotherapy to those that did not receive such an irradiation. Actually, in such a situation, this RR "RT/nonRT" goes down to 1.08 (95% CI; 1.00–1.17), thus with a confidence interval overlapping the value 1. This RR "RT/nonRT" most probably gives a better indication of the carcinogenic role (actually borderline significant) of radiotherapy.

De Gonzales *et al.* (2011) aimed to estimate the proportion of second cancers attributable to radiotherapy in adults, using data from the US Surveillance, Epidemiology and End Results (SEER) cancer registries. Those authors used nine of the SEER registries to systematically analyze 15 cancer sites that are routinely treated with radiotherapy (oral and pharynx, salivary gland, rectum, anus, larynx, lung, soft tissue, female breast, cervix, endometrial, prostate, testes, eye and orbit, brain and CNS, and thyroid). The cohort was composed of patients aged 20 years or older who were diagnosed with a first primary invasive solid cancer reported in the SEER registries between Jan 1, 1973, and Dec 31, 2002. Relative risks (RRs) for second cancer in patients treated with radiotherapy *versus* patients not treated with radiotherapy were estimated with Poisson regression adjusted for age, stage, and other potential confounders. An impressive number of 647 672 cancer patients who were 5-year survivors were followed up for a mean 12 years (SD 4.5, range 5–34); 60 271 (9%) developed a second solid cancer. For each of the first cancer sites, the RR of developing a second cancer associated with radiotherapy exceeded 1, and varied from 1.08 (95% CI 0.79–1.46) after cancers of the eye and orbit to 1.43 (1.13–1.84) after cancer of the testes. In general, the RR was highest for organs that typically received greater than 5 Gy, decreased with increasing age at diagnosis, and increased with time since diagnosis. This study estimated a total of 3266 (2862–3670) excess second solid cancers that could be related to radiotherapy, that is 8% (7–9) of the total (of second cancers) in all radiotherapy patients (≥ 1 year survivors), with about five excess cancers per 1000 patients treated with radiotherapy by 15 years after diagnosis. The authors concluded: "*A relatively small proportion of second cancers are related to radiotherapy in adults, suggesting that most are due to other factors, such as lifestyle or genetics*." (De Gonzales *et al.*, 2011).

The same authors had evaluated in 2010 long-term second cancer risks among 182 057 patients who were 5-year survivors of a loco regional invasive breast cancer, diagnosed between 1973 and 2000 and reported to US NCI-SEER Program cancer registries (De Gonzales *et al.*, 2010). They observed that: "*There was no evidence of elevated risks for sites receiving 'medium' doses (0.5–0.99 Gy, RR = 0.89 (0.74–1.06)) or 'low' doses (< 0.5 Gy, RR = 1.01 (0.95–1.07))*", and concluded that "*most second solid cancers in breast cancer survivors are not related to radiotherapy*".

A last important point is that the "relative risks tend to be lower in the medical series than in the Japanese A-Bomb survivors" (Little, 2001). A similar observation has also been reported by Preston *et al.* (2007). The fractionation/protraction of most of the therapeutic irradiations, in sharp contrast with the extremely brief irradiation linked to the atomic bombs, might explain, at least in part, such a discrepancy. Cell sterilization and larger neutron RBE in the A-bomb data may also account for this difference.

Moreover, Hendry noted that for deterministic effects "*Radiosensitive individuals in the population may contribute to low threshold doses*" (Hendry, 2012); actually, this could also be true for stochastic effects in radiosusceptible patients (Foray *et al.*, 2016).

To summarize, models mostly based on the atomic bomb survivors follow-up, mostly designed to estimate the carcinogenic risk for populations irradiated at low doses *in toto*, appear to be poorly prepared to deal with a population of cancer patients receiving doses ranging from very low to very high levels to limited volumes; by applying the linear no-threshold concept and not taking into account a possible competition with cell killing at high doses, they probably generally overestimate the second cancer risk after radiotherapy.

Models purely based on the follow-up of patients receiving radiotherapy would logically appear to be more relevant in this specific context. The Schneider's model (Schneider and Kaser-Hotz, 2005) is based on such data and takes into account the competition with cell killing at high doses; however, the rapid falling off of the risk after a few Gy could appear questionable and could potentially underestimate the second cancer risk at high doses in some situations.

The model described by Sachs and Brenner considering the competition with cell killing, but introducing a modulation by taking into account repopulation and proliferation during the irradiation, seems to yield intermediate results (Sachs and Brenner, 2005). These results actually show neither a continuous increase of the risk at high doses (as predicted from the LNT models), nor a rapid fall-off after a few Gy (as predicted by some competition models), but rather show a kind of "plateau" of the risk after 20–40 Gy. This seems to better correspond to the clinical experience of radiation oncologists, who have been told for decades that the more "carcinogenic" doses are lying approximately in this range; this also seems to be in reasonable agreement with more recently available clinical data (mostly breast and lung cancers observed after Hodgkin's disease (Sachs and Brenner, 2005); it is also in good agreement with Ron's data reported in the 2006 Hall's paper (Hall, 2006). The recent Schneider study combining A-bomb survivors' data and Hodgkin's disease clinical experience seems to also favor such a "plateau" model (Schneider and Walsh, 2008).

In fine, the risk evaluation of both diagnostic and therapeutic medical exposures to ionizing radiation should be made on the basis of absorbed dose in Gy and not of effective dose in Sv by ICRP in the future (Clement *et al.*, 2021, 2022; Bourguignon, 2021, 2022).

5 Discussion

There is no discussion that secondary radio-induced primary cancers after radiotherapy do exist, but the use of the LNT model to evaluate this cancer risk in such a specific situation deserves to be questioned.

5.1 The LNT model in question

– First of all, radiotherapy (with nowadays only rare exceptions) is proposed to cancer patients, who are

doomed to die if their tumor cannot be eradicated. We are not here in the situation of a general population which should be protected against even a small risk of radio-induced cancers. For cancer patients, in the absence of other therapeutic alternatives, the choice is between a 100% risk of death without radiotherapy and a – fortunately – small secondary radio-induced cancer risk with radiotherapy. In such a situation, this (low) risk is acceptable, while the delivery of the same doses in a general population would be obviously unacceptable. The LNT model had been clearly designed for the radiological protection of the general population, and is inappropriate when some risk should be accepted to save the life of cancer patients.

– But there are other reasons why the LNT model is irrelevant for radiotherapy: the first one is linked to the low (or even very low) doses inevitably delivered to radiotherapy patients at distance from the target volume (s). The extrapolation of the risk to those very low doses has been largely discussed for decades. The Muller's Nobel Price for the LNT model is more and more questioned and even considered by some authors as a scientific imposture, actually strangely supported by lobbies driven by ideology and/or financial considerations. In addition, due to efficient repair and adaptation mechanisms, a number of recent scientific papers denies any radio-induced cancer risk at very low doses, *i.e.*, doses which actually correspond to the level of natural irradiation in a number of countries. Back to radiotherapy, the risk of the scattered low doses received far from the irradiated volumes thus appears to be quite negligible or even nil in some situation (elderly patients for example).
– Last but not least, what about the high (sometimes very high) doses received in the irradiated volumes or around them? Considering the linearity of the LNT model, theoretically until the high doses reached in radiotherapy, it is easy to calculate, using the 5% risk per Sv, that nearly all radiotherapy patients, given 40 to 80 Gy to their tumor, and several tens of Gy in the so-called penumbra, should develop a radio-induced cancer. Fortunately for those patients, the clinical experience of more than a century of radiotherapy, with the analysis of thousands of cancer patients with several decades of follow-up, showed that it is not the case.

5.2 Reasons of the discrepancy between LNT model predictions and clinical observations

What are the reasons for such a contrast between the risk predicted by the LNT model and the overall (rather minimal) risk observed by the clinicians? Actually, a large number of parameters should be considered to "modulate" the results of a simplistic use of the LNT model:

– The age of the patients is one of the most important and has been recognized even by the international bodies still supporting the LNT model. The higher susceptibility of the children to radio carcinogenesis is now largely proven and accepted: for radiotherapy, the secondary cancer risks in children are now taken into account in the design of the therapeutic protocols, with already a very significant decrease of this risk when using the modern protocols, introducing proton therapy, reduction of doses and irradiated volumes, only to mention those possibilities. But what about most cancer patients, who are in their huge majority far from the children ages (cancers in children being fortunately very rare)? Even the international bodies have recognized that the rule "5% risk per Sv" cannot be blindly applied to adults; and for the elderly, the risk is even close to nil.
– The protraction and fractionation of most therapeutic irradiations clearly decreases the second cancer risk. This is most probably why the risk has been shown to be lower in the medical series when compared to the atomic bomb survivors: these survivors received doses in a fraction of second, while cancer patients receiving radiotherapy mostly received fractionated and protracted irradiations (usually 20 to 40 fractions, over several weeks). It happens that the LNT model has been largely based on those Japanese bomb survivors, who therefore received an irradiation very different from what is received by radiotherapy patients.
– The type of radiotherapy beams needs to be considered, knowing in particular the role played by particles with high relative biological effectiveness (RBE) such as neutrons in the Japanese survivors, while neutrons are not used any more in radiotherapy (Razghandi *et al.*, 2021).
– The shape of the risk curve at high doses is obviously the most important point to be considered when trying to evaluate the risk of the "very high" doses of radiotherapy. As it has been previously seen, the LNT model implies a continuous linearity, meaning that the higher the dose, the higher the risk, with a direct proportionality between dose and risk. The clinical results do not fit with such a hypothesis, and by far. Why? A part of the answer had already been given in the fifties by L.H. Gray himself. Actually, the risk decreases at high doses, because of a competition between cell killing and mutagenesis; briefly, a cell which has been killed cannot give birth to a malignant clone. So, while dozens of scientists continue to fight about different shapes of the dose/risk curve below 0.5 Sv, a still more important fight would probably take place to define the shape of the dose/risk curve at doses higher than 10–100 Gy. Some authors support the competition models, with a significant decrease of the risk at high doses, but with the potential risk of underestimating the real risk of radio-induced malignancies. Some others take into account such a competition between cell killing and mutagenesis, but also considered the possibilities of repair and repopulation; for those authors, at a level still to be clearly identified, the risk curve is becoming a plateau, without increasing (neither decreasing) any more. Of note, nowadays, this plateau hypothesis is probably the model which offers the best fit with the clinical data.

6 Conclusion

To conclude, for a large number of reasons, the use of the LNT model in radiotherapy is highly inappropriate. The LNT model has been developed essentially for protection against

low doses in a general population; understandably, it is not at all adapted to the high doses locally delivered to cancer patients. If the LNT model were used for those therapeutic irradiations, it would overestimate in most cases the second primary cancer emergence: the risk would then be to favour or promote some radiophobia in our patients and to see them turn away from a life-saving treatment.

Conflict of interest

The authors declare that they have no conflicts of interest in relation to this article.

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