Abstract

A NEW METHOD OF ASSESSING THE DOSE-CARCINOGENIC EFFECT RELATIONSHIP IN PATIENTS EXPOSED TO IONIZING RADIATION. A CONCISE PRESENTATION OF PRELIMINARY DATA

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Radiotherapy and risk of secondary cancer

Over 100 million individuals each year undergo radiodiagnostic or functional examinations. Despite a huge number of studies, a cancer excess has only been evidenced in young women followed-up for lung tuberculosis by repeated fluoroscopies in the 1930s. The risk of computed tomography (CT) scans that deliver 15 to 30 mGy remains a matter of debate. Over one million patients with cancer are treated each year by radiotherapy (RT), a second cancer is observed in about two to seven percent of them, and the risk is correlated with dose and the mass of irradiated normal tissue. Currently, data regarding the dose-carcinogenic effect relationship are too imprecise to contribute to the design of the RT protocol. The controversies regarding risks associated with conformal and intensity-modulated RT illustrate this problem.

In the 1960s, the linear no-threshold (LNT) relationship was introduced in radioprotection because it was convenient for administrative purposes, but it remains controversial. In view of the current epidemiological dilemma, including the confounding factors regarding the Japanese data following the atomic bomb survivors and regarding the new experimental data on the lack of fidelity of the LNT-model extensively discussed at this workshop, it seemed necessary to explore new ways to understand the dose-risk relationship concerning oncogenesis.

The variation of the relative carcinogenic efficiency (RCE) with dose remains to be assessed, especially for medical practice. The LNT model assumes that RCE does not vary with dose even for a second cancer after RT ($R = a\ D$ where R here is the risk of second cancer, D the absorbed dose, and a is the proportionality coefficient, which is assumed to be constant in the LNT model). The current study is to assess in human beings the value of a. This new method provides data directly on the carcinogenic risk per unit mass of normal tissues abscopally exposed in RT. Centers of excellence treat hundreds of thousand patients each year with accurate dosimetry in the tumor volume and throughout the body, with doses ranging from 60 to 70 Gy in the tumor volume to less than 50 mGy in distant regions of the body. These patients are followed up even over decades until their death. Toxic effects, in particular second cancers, are registered, and many studies have already provided fascinating information.

The construction of the dose-risk relationship

The new method uses cumulated absorbed doses to distant tissues for assessing the risk of second cancer per unit mass of the distant tissue. In each patient in the study, the isodose curves were drawn (for example 40 Gy, 20 Gy, 1 Gy). Usually RT was delivered in 30 sessions over 6 wk; the dose per session was 2 to 2.5 Gy in the target volume or near it, and as low as 25 mGy in distant tissue. For a cumulated distant tissue dose of 5 Gy, the dose per session was about 160 mGy. The mass of tissue wedged between two isodose curves can be determined, for instance between isodoses 5 Gy and 10 Gy = M_{5-10}. The integral dose Σ D (M_{5-10}) delivered to this tissue was calculated, as well as the average dose in

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this tissue mass D_{5-10} [Σ D (M_{5-10})/M_{5-10}]. Knowing the number N of second cancers that had occurred in those normal tissues in all the patients of the cohort, the risk per unit mass for a dose ranging from 5 to 10 Gy can be calculated (R_{5-10}). Hence, the variation of the carcinogenic risk can be assessed for doses ranging from $D > 50$ mGy to $D \geq 40$ Gy.

This study was carried out on a French-United Kingdom cohort of 5,000 survivors of a childhood cancer cohort treated in eight centers in France and the UK before 1985 and followed on average for 29 y. Detailed information on chemotherapy was also collected for each patient: date and dose of each drug used in each course for initial treatment or treatment of recurrence or metastasis. A total of 369 cases of second malignant neoplasms (SMN) were diagnosed and validated. Radiation treatment was retrospectively reconstructed for all patients of the cohort, except for 105 patients for whom RT data were incomplete. Isodose profiles were estimated using an improved version of the homemade DOS_EG software.

The above-described new approach method was complemented with a conventional case-control study by individually matching each of the 369 SMN to three controls of the same gender, date of diagnosis (± 2 y), and age at diagnosis (± 2 y), with follow-ups being at least equal to the follow-up time of the SMN case. For each case, the dose was estimated at the site of the SMN. Local radiation dose was defined as the cumulative radiation dose received at the site of SMN of each case and at the corresponding site for the controls. Statistical analysis was performed for all cases and controls together, and separately for sarcoma ($n = 90$) and carcinoma ($n = 271$). Conditional logistic regression analysis was used to investigate the dose response associated with local radiation dose.

The occurrence of a SMN in a volume was assumed to follow a Poisson distribution. Generalized Estimating Equations were used to take into account the hierarchical structure of the data; i.e., the sequential position of several volumes to the same patient. The dose responses were investigated by the integral dose method and case-control method and adjusted to the type of the first cancer, chemotherapy (yes/no), alkylating agents (y/n), antracycline (y/n), and stratified by gender, date and age of diagnosis and follow-up duration.

Dose and secondary cancer

The conventional case control method for all SMN′s together yielded no increase in risk for doses lower than 1 Gy (331 controls were included in this dose category). The upper level of the 95% confidence interval of the relative risk in this category was only 1.2, and therefore excludes a significant risk. Also for both carcinomas ($n = 271$) and sarcomas ($n = 72$) separately, there was no excess risk from doses less than 1 Gy. At very high doses (>20 Gy), the risk was higher for sarcomas than for carcinomas.

Fig. 1 presents the incidence of SMNs per unit mass as a function of dose calculated with the integral dose method. As in the conventional case-control approach, no excess cancer incidence (as compared to patients without RT) was observed in the tissue volumes which received 0.0 to 0.5 Gy and 0.5 to 5 Gy. The data for doses below 0.5 Gy strongly suggest the existence of a hormetic effect for both carcinoma and sarcoma. For doses between 0.5 and 5 Gy, the cancer incidence is similar to that of non-irradiated areas. For doses above 5 Gy, the incidence of both sarcoma and carcinoma increases with dose, seemingly in a linear fashion (a constant between 5 Gy and >40 Gy); again, a appears to be higher for sarcoma than for carcinoma.

Figs. 2 and 3 give the complementary results separately for carcinomas and sarcomas. As with all SMN, there is no excess cancer incidence in volumes having received 0 to 0.5 and 0.5 to 5 Gy, compared to the control incidence in patients without RT. Above 5 Gy, both sarcoma and carcinoma incidences increased with dose, and the rate of increase was higher for sarcomas than for carcinomas.

Non-linear dose-risk relationship

This preliminary study demonstrates the feasibility of the integral dose method to assess the second cancer risk and the RCE. Note that this method is applied to patients with a second cancer and only provides data on the relationship between dose and carcinogenic effect, but not second cancer risk. Comparing the data from the

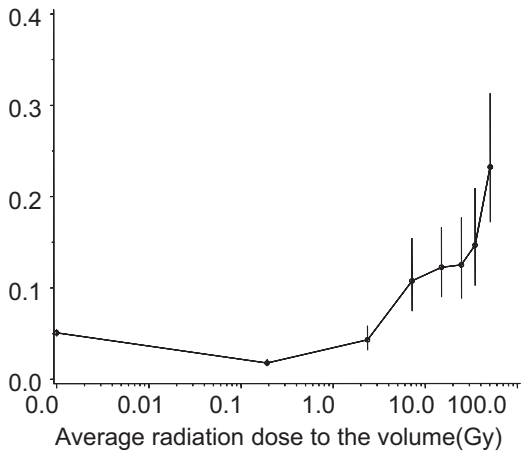

Fig. 1. Second cancers per kg according to the mean dose received in volume All SMN/kg.

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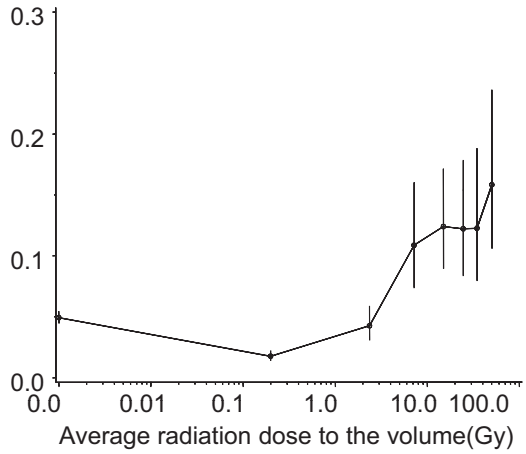

Fig. 2. Carcinomas per kg according to the mean dose received in volume Carcinomas/kg.

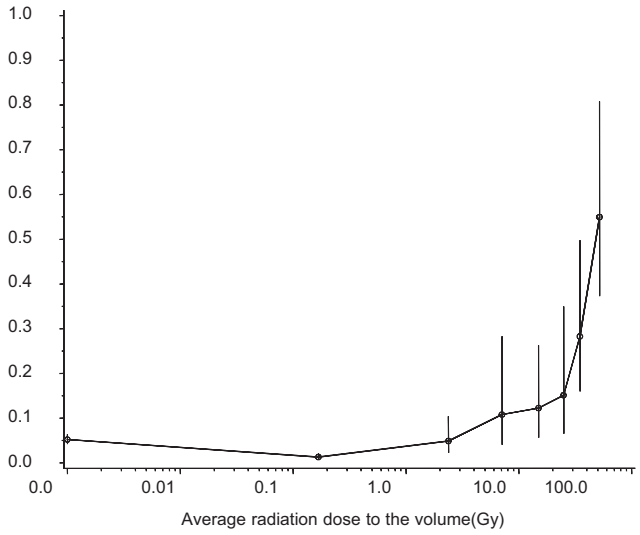

Fig. 3. Sarcomas per kg according to the mean dose received in volume Sarcomas/kg.

conventional case-controlled studies with those using the integral dose method indicates no major divergence between the results. Both methods show a clear influence of dose on SMN, with the sarcoma incidence rising with dose steeper than the carcinoma incidence.

The new method provides information on the cancer risk per unit mass of irradiated normal tissue, whereas the case-controlled studies compare the incidence of cancer in irradiated and non-irradiated individuals without taking into account the dose distribution in the exposed body. Indeed, a few conventional studies that have already shown the impact of the mass of irradiated tissue have shown that following radiotherapy for Hodgkin's disease, reduction in the size of the irradiated volume reduces the SMN risk. Below a cumulative dose of 5 Gy of fractionated irradiation, there are no detectable SMNs, with this dose having been delivered in 30 sessions of about 160 mSv (five sessions per week). This may be comparable to data on efficient DNA repair after protracted irradiation, which is, for both whole and partial body irradiation, much less carcinogenic per unit dose than for acute irradiation. This is in line with data showing that non-tumor dose is about 10 times greater for protracted irradiation than for acute irradiation. The fact that 30 sessions of 160 mGy are not carcinogenic suggests that most probably a single acute dose of 160 mGy also is not carcinogenic, even with cancer patients being additionally exposed to frequent x-ray examinations delivering doses as high as several hundred mGy. This observation also complies with the absence of any excess cancer incidence—except thyroid cancer following the Chernobyl accident and in several other studies.

The current study does not refer to hormonal stimulations that can increase the risk of relatively small doses; e.g., in women of less than 40 y, a dose of 1 Gy can increase the risk of breast cancer, whereas it has no effect on women aged above 40 y. Moreover, the relatively small risk of breast and thyroid cancers among children after very low acute doses ($\sim$100 mGy) may not be apparent in this study.

Both methods reveal a lower incidence of second cancers in regions having received a small dose ($<$500 mGy) than in non-irradiated regions. This finding, even if preliminary, complies with a hormetic effect and should be confirmed on a greater number of patients.

Expressing cancer per unit mass of normal tissue can be misleading, since normal tissues are a mix of muscle, bone, bone marrow, mesenchymal tissue, blood, etc., with different susceptibilities to carcinogenesis. Yet segments of the body always are a mix of specific tissues with radiosensitivities not well-known and varying with the type of radiation. In fact, the assessment of the results obtained for various parts of the body comprising different proportions of tissues might provide information regarding the relative oncogenic sensitivity of those tissues.

The advantages of the integral dose method

With most accurate and easy-to-use dosimetry, the integral dose method has the following advantages:

a) It can directly provide data regarding RCE as a function of dose without need of controls;
b) By providing relative risk of cancer induction as a function of dose, it can help to optimize dose distribution in radiotherapy and minimize the risk of second cancers;
c) It has the potential of establishing the probability of cancer induction by doses lower than 500 mGy, such as those delivered during a CT scan;

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d) Its accuracy can be improved by pooling data from several cohorts and by comparing RCE as a function of the type of primary and second cancer, and the type of irradiation (fractionated or low dose rate); and
e) It has the potential of providing answers to several questions associated with medical procedures accompanying RT, such as those caused by the impact of various genetic dispositions, age, and hormonal factors, and various adjuvant drugs or hormonal therapy.

The current data do not provide information on the absolute cancer risk per unit dose. Future studies with larger numbers of patients and different types of cancer in various age groups receiving RT may increase the significance of the results and search for evidence of a variation of susceptibility to cancer induction among normal tissues in patients. Detailed references are available from the authors. Detailed references are available from the authors. Health Phys. 100(3):296–299; 2011

Key words: dose, low; health effects; hormesis; radiation dose

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