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Review

OECI Workshop on late side-effects of cancer treatments ☆

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ABSTRACT

This Workshop was organised by the Organisation of European Cancer Institutes (OECI) to provide a forum for discussing the late side-effects resulting from different cancer treatments. One of the main Workshop objectives was to generate recommendations on how to improve knowledge and, consequently, long-term care for cancer survivors.

1. Introduction and overview

This Workshop was organised by the Organisation of European Cancer Institutes (OECI) to provide a forum for discussing the late side-effects resulting from different cancer treatments. One of the main Workshop objectives was to generate recommendations on how to improve knowledge and, consequently, long-term care for cancer survivors.

1.1. Overview on somatic late side-effects

In the Western world the number of cancer survivors is increasing rapidly due to improved treatments, more frequent screening, greater life expectancy and, in some cases, increased cancer incidence rates.

A good example is breast cancer where, in many countries, mortality rates have decreased progressively since the 1980s, despite increasing incidence rates, with 5-year relative sur-

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vival now at 86% for patients diagnosed between 1997 and 2001. Other cancers now also have good survival. For example, relative survival for men with testicular cancer is now over 95%, and relative survival for men with prostate cancer is over 60%. Overall, approximately 60% of patients with a new cancer diagnosis can now expect to survive for 5 years, with a wide variation according to tumour site and stage.[1]

One of the most clinically significant late side-effects of cancer treatment is an increased incidence of *second malignancies*. The increase may be caused by common genetic or environmental risk factors for both first and second tumours, or by treatment. Treatment-related second malignancies have been recorded after a number of cancers,[2–7] including breast cancer after radiotherapy for Hodgkin's disease (HD),[8] and endometrial cancer after tamoxifen treatment for breast cancer.[9] Treatment-induced leukaemia can occur within a few years of exposure, but other radiation-induced cancers mostly occur more than 10 years after exposure.

Late cardiovascular disorders have been related to thoracic radiotherapy and have been described after treatment of HD and breast and testicular cancers.[5,10–12] They mostly appear at least a decade after treatment and may be related to accelerated atherosclerosis of the irradiated vessels, to direct damage to the cardiac myocytes, to valvular stenosis or to constrictive pericarditis.

Chemotherapy-related cardiovascular disorders have been described after the use of CMF (cyclophosphamide, methotrexate, 5-fluouracil) and anthracycline-based chemotherapy, and the risk is clearly dose-related.[12,13] The risk is further increased if chemotherapy is combined with mediastinal radiotherapy. Cisplatin-based chemotherapy may also induce endothelial dysfunction and produce long-term cardiovascular adverse effects.[2,3] The effect of cisplatin on renal function, even if subclinical, may induce hypertension.[3] Treatment-related risks may be substantially larger in smokers whose cardiovascular risk profile is already increased.

The gonads are especially sensitive to irradiation; for instance, a total dose of 8 Gy may induce ovarian failure, and a testicular total dose over 4 Gy may induce irreversible azoospermia.[14] Other well known endocrinal effects caused by radiation are hypothyroidism and pituitary hypofunction. Long-term treatment with a non-steroidal anti-androgen may induce gynaecomastia and aromatase inhibitors may induce osteoporosis.

Knowledge of these late side-effects can be obtained by studying past treatments and can help the development of future treatment strategies with smaller risks of late side-effects. Such knowledge can also provide a sound basis for counselling patients about their likely risks.

1.2. *Overview of psycho-somatic late side-effects*

These effects may have a broad spectrum and cover mental distress, sexual problems (including partner relationships), fatigue and quality of life, and they may be influenced by the patient's personality, especially the trait of neuroticism, and their coping mechanisms.

It is of considerable importance to quantify these late effects, and this is a subject of research at the Norwegian Radium Hospital.[14–18] For instance, the study of long-term testicular cancer survivors showed that the level of anxiety was slightly increased compared with controls, but the level of depression was lower.[16]

A study of chronic fatigue in the same patients showed significant relationships with lack of work, level of somatic symptoms, presence of ototoxicity, including tinnitus, and existence of pre-existing neuroticism,[17] while a study of quality of life in these patients showed no significant differences compared with controls from the general population.[18]

Testicular cancer survivors had significantly worse scores for ejaculatory and sexual function in both young (20–39 years) and middle aged (40–59 years) men compared with controls at a mean of 11 years after primary treatment.[14] At least one sexual problem was reported by 39% of survivors versus 36% of controls. Sexual problems in the survivors were associated with increasing age, lack of a partner, and high anxiety score, while ejaculation problems were associated only with retroperitoneal surgery and neurotoxic treatment.

In summary, long-term survivors of several cancer types (including breast, ovary, cervix, and testis) hardly seem to differ on mental distress or quality of life index from age-matched population samples, although fatigue and sexual functioning may be worse in some groups. As oncologists see long-term survivors with problems rather than patients without, their impressions are inevitably biased. It must be remembered that about 20% of the general population in developed countries have poor lives with multiple problems. It is also of note that the personality trait of neuroticism, existing before the cancer diagnosis, seems to play an important role in the subjective report of long-term morbidity.

2. The dose-response relationship in radiation-induced cancer

The dose-response relationship for radiation-induced cancer has been observed directly in epidemiological studies of the survivors of the atomic bombings of Hiroshima and Nagasaki, in studies of patients who have been treated with radiotherapy, and in occupational studies. These studies show that, following exposure at doses above about 100–200 mGy (10–20 rads) the dose-response relationship is linear for solid cancers and linear-quadratic for leukaemia.[19,20]

Environmental and diagnostic exposures are, however, often at much lower doses. This has generated discussions on radiation risks in normal tissue exposed at low doses of radiation during conformal radiotherapy or from diagnostic exposures, including CT-scans.[21] Some authors have proposed that, for doses below a certain threshold, there is little or no risk, while others[22] have even proposed a mechanism of hormesis by which the risk of a second malignancy actually decreases at very low radiation doses and only starts to increase above a threshold dose. Radiobiological theory and experiments do not support the existence of a threshold or of hormesis. Rather they suggest that at low doses the risk is directly proportional to dose with zero risk when the dose is zero and no threshold. Even very low radiation doses (1 mGy) may induce cell death due to lack of repair of DNA double-strand breaks.[23] At slightly higher doses (5–20 mGy), DNA repair is activated,[24], and at mid-level doses (~200 mGy) DNA repair starts to be counteracted by apoptosis. However, differ-

ent radiation doses can activate multiple genetic activities, making the process of DNA repair rather complex.[25–27]

The 15 country IARC study[28] analysed the risk of solid cancer after low radiation doses in workers in the nuclear industry, and showed that the excess relative risk per Sievert for all solid tumours combined was around 1 (0.97, CI: 0.14–1.97), while for leukaemia the excess relative risk was 1.93 (<0–8.47) per Sievert. On this basis, 1–2% of deaths from cancer in this population may be attributed to low dose radiation.

Darby et al.[29] carried out a pooled analysis of 13 European case-control studies of indoor radon and lung cancer, and showed that lung cancer risk increased with radon concentration by about 16% per 100 Bq/m^3 for never smokers, ex-smokers, and current smokers alike, suggesting that in Europe about 9% of lung cancers may be due to indoor radon in the homes, most of them in conjunction with smoking.

Although there is a considerable amount of knowledge about the dose-response relationship for radiation-induced cancer in some situations, recent data suggest that mammalian cells react differently at different dose levels and dose rates as regards DNA damage signalling, gene induction, DNA repair and apoptosis. This complex situation means that direct extrapolations from high exposure data to low doses or from one situation to another may be misleading.

3. Long-term hazards of radiotherapy in breast cancer

Since the mid 1980s the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has collated and analysed data on late-effects in trials evaluating adjuvant radiotherapy after breast cancer surgery[11] in more than 40,000 patients.

3.1. *Incidence of second primary cancers after radiotherapy*

The ratio of annual event rates in irradiated compared with unirradiated patients is significantly increased for contralateral breast cancer (1.18, standard error (se): 0.06) and for cancer of sites other than breast cancer (1.20, se: 0.06), with significant increases for lung cancer, soft tissue sarcoma and leukaemia. The absolute excesses risk in the irradiated group is about 1.8% at 15 years. These excesses appear after a follow-up of ~10 years, and increase with time since irradiation and they explain in part an increased mortality of 1.3% at 15 years in the irradiated group from causes other than breast cancer.

3.2. *Mortality from circulatory disease after radiotherapy*

The risk of death from circulatory disease is also significantly increased in the irradiated compared with the unirradiated group, with relative risk 1.25 (se: 0.06). Reconstruction of the techniques used in the trials enabled confirmation that the dose to the heart was appreciably higher for left-sided than for right-sided tumours.[30] It is therefore of note that the radiation-related increase in circulatory disease is higher for left-sided breast cancer (1.44) than for right-sided breast cancer (1.18).

Cardiac doses from radiotherapy for breast cancer have decreased recently, and the cardiac risk that will arise from current treatments is uncertain. Major efforts are therefore needed to establish the likely risk of heart disease at current cardiac doses, in order to inform those formulating guidelines on the indications for loco-regional irradiation.

3.3. *Late effects of hypo-fractionated radiotherapy in breast cancer patients*

The study of a large Swedish cohort treated by hypo-fractionated radiotherapy in the 1960s has enabled analysis of very late treatment effects [Friberg S and Rudén B-I, personal communication]. The definition of hypo-fractionation for this study was a dose per fraction higher than 2 Gy and with a late effect equivalent total dose over 53 Gy.[31] The main reasons for proposing this regimen were the introduction of megavoltage machines in the 1950s (with a better depth dose distribution), the shortage of treatment machines and the desire to make treatment easier for patients and personnel by decreasing the number of fractions. At the time, calculations of equivalent dose were carried out using models based on acute skin reaction, such as those proposed by Strandqvist[32] and Ellis.[33] Only patients developing injuries were analysed: some injuries appeared after a lag of more than 20 years. For each of the patients studied the dose plan was individually reconstructed. From 600 patients treated, 200 are still alive, weekly doses varied from 2.5 Gy for five times to 6 Gy twice a week with a NTD (nominal tumour dose) from 53 to 80 Gy. The most frequent complications were paresis, important pain, arm oedema and/or stiff shoulder, and cardiac events mainly for patients with left-sided tumours. These complications had major consequences for the patients, such as physical handicap, excruciating pain, involuntary retirement and sick pension, lowered income, increased expenses (special clothes and need for help), and broken marriages. Other similar experiences have been reported in 17 centres in the UK..[34,35] At the present time, randomised trials on less extreme hypo-fractionated regimens are conducted with acceptable results,[36,37] even though long-term follow-up is still lacking.[38]

3.4. *Fat necrosis incidence in a randomised trial*

The National Institute of Oncology in Budapest conducted a randomised trial,[39] comparing whole breast irradiation to partial breast irradiation (with hypofractionated high-dose rate brachytherapy or conventionally fractionated electron beam). With a median follow-up of 66 months, the total 4-year actuarial rate of fat necrosis, including asymptomatic cases, was lower in the electron beam group (18% versus >30% for the other two groups). However, the rate of symptomatic fat necrosis was similar, around 10%, for all groups, and only symptomatic fat necrosis was predictive of poor cosmetic results.

4. Late effects of treatments in paediatric cancers

Children who have already developed one cancer may be genetically predisposed to cancer and therefore represent a special population. In addition, they are more sensitive to iat-

rogenic effects of radiotherapy and chemotherapy than adults. Also, because of their small body size, there is a higher proportion of healthy tissue receiving moderate (1–10 Gy) radiation doses during radiotherapy. Finally, if their initial cancer is cured, they have a longer life expectancy than adults and so a longer time at risk of developing a second cancer.

In a France–UK cohort,[40,41] the incidence of second cancers in the absence of chemotherapy and radiotherapy was about 1% at 25 years, rising to about 3% following either chemotherapy or radiotherapy, and rising further to over 8% following both chemotherapy and radiotherapy; the latter percentage is ~20 times higher than that of the general population. It has been observed that patterns of second cancer are similar for radiotherapy and chemotherapy. Treatment by high dose chemotherapy and bone marrow transplantation increases the already elevated risk by a factor between 2 and 4.

Dose-response relationships differ for different types of second cancer. For leukaemia, melanoma, and soft tissue and bone sarcoma, the data suggest a quadratic or linear-quadratic dose-response and a clear excess appears only after doses above 10 Gy. Conversely, for thyroid, breast and brain tumours the dose-response appears linear and an excess has been observed even for relatively low radiation doses.

The timing of combined radiotherapy–chemotherapy may also be important. In the France–UK cohort, the odds ratio (OR) for second malignancy is 1.8 (0.6–5.2) for sequential chemo-radiotherapy and 3.4 (1.2–9.2) for concomitant regimens[42] after adjustment for the chemotherapy doses and radiation dose to the site of the second cancer.

In the same cohort, it was also possible to demonstrate a dose-dependent risk of cardiovascular complications for children treated with radiotherapy or chemotherapy. The cardiovascular risk was certainly increased with the use of anthracyclines whose effect was dose dependent, but also was increased by other chemotherapy regimens.

To investigate dose-responses in radiotherapy, the IGR has developed specific software to estimate radiation doses delivered outside the treatment fields during radiotherapy, including secondary irradiation coming from machine scattering and leakage.[43] These estimations will contribute toward improved knowledge of the dose-response relationship for radiation in these circumstances.

Finally, several subjects need further investigation: a) genetic susceptibility; b) role of concomitant versus sequential radio-chemotherapy combinations; c) effect of new drugs and new radiotherapy modalities such as IMRT; d) finding of short term complication markers; e) evaluation of very (more than 20 years) long-term risks; f) analysis of interactions between anthracycline and radiotherapy doses.

5. Leukaemia and cancers following ^{131}I administration for thyroid cancer treatment

There have been several cohort studies on this topic. For instance, Sandeep et al.[44] studied 2821 second cancers occurring in an international database of 39,000 patients treated for thyroid cancer. The SMR (standardised mortality ratio) for all second cancers was significantly increased: 1.6 (1.3–2.0), and included malignancies of the salivary glands, bone, leukaemia, bowel, kidney and soft tissues.

A France–Sweden–Italy cohort analysis,[45] showed an increased risk when the dose exceeded 7.4 GBq, especially for bone and soft tissue sarcomas, colorectal cancer and leukaemia. However, as the events are rare, the shape of the dose-response is still unknown, and there is a need for a large pooled analysis with information on radiation doses.

6. Late side-effects after treatment of testis cancer

Several reports have been published by the Norwegian Radium Hospital in Oslo.[2,3] There is a wide spectrum of effects, including: second malignancies, gonadal morbidity, neurotoxicity, gastro-intestinal and cardiovascular morbidity, and a subclinical decrease in renal function.

In an international database of almost 40,000 1-year testicular cancer survivors,[4] it was shown that, for patients who had a testicular cancer at 20 years of age, the risk of second malignancy at 70 years was around 40% as compared with 20% for the normal population; the corresponding figures for patients who had testicular cancer at 35 years were 30% and 15%. In other series,[5] a multivariate analysis showed that the relative risk of cardiovascular disease was 2.8 (1.9–4.2) for patients treated with sub-diaphragmatic and mediastinal radiotherapy compared with surgery alone, and 1.7 (1.2–2.4) for patients treated with PVB or BEP chemotherapy and 2.1 (1.7–2.7) for smokers. These data are in agreement with another Norwegian study conducted in 1289 patients that showed that the age-adjusted relative risk of hypertension was 1.29 for those receiving radiotherapy compared with surgery alone, and 1.63 for those treated with a total dose of cisplatin $\leqslant$ 850 mg, and 2.32 for with a total dose > 850 mg..[46]

In the study by Travis et al.[4], the relative risk for treated patients compared with the general population was 1.43 for all cancers combined, with significant increases for a wide variety of tumours, including all digestive cancers, bladder cancer, thyroid cancer, lymphoma and leukaemia. More recently, Fosså et al.[3] showed that all non-cancer deaths were significantly increased with an SMR of 1.06 due to increases in infections (1.28), hypertension (1.39), and lung diseases (1.94).

7. Discussion and recommendations

The study of late side-effects after cancer treatment has been possible largely thanks to the existence of cancer registries, especially those in which the patients have been cross-matched with population death registries, so that it has been possible to obtain the certified cause of death for those who have died from causes other than cancer, as well as information on second cancers.[1,47,48] Large randomised trials and meta-analyses have also played a role.[11] However, these efforts represent a small proportion of all cancer patients and, to date, few registries or trials are able to carry out long-term follow-up for endpoints other than cause of death, such as episodes in hospital.

By its nature the investigation of long-term effects after cancer is retrospective, thus assessing toxicity and morbidity after treatment modalities that may be 'outdated' today. One

major concern is therefore that recently introduced drugs in clinical practice, such as aromatase inhibitors, taxanes, herceptin, and others, have only been evaluated in randomised trials that have a relative short follow-up to date. There is a clear need for prolonged follow-up of these trials but, nevertheless, sponsors often plan for only 5–10 years of follow-up.

Long-term understanding of the late-side effects of treatment for cancer can only be gained if sufficient resources are made available to carry the necessary research, including not only follow-up for date and cause of death, but also consideration of disease episodes and possible markers of disease, so that our understanding of late side-effects can be increased.[15]

For cancers where patients are already known to be at risk of specific long-term effects, there is also a lack of agreed guidelines for long-term clinical follow-up of the individual patient at risk.

New facilities for long-term follow-up such as nurse-cared and/or shared-cared models and/or the creation of follow-up clinics at cancer centres need designing, and then piloting and evaluation. For example, one possibility might be that cancer survivors be followed for 3–10 years in the cancer centre (depending on recurrence risks, participation in clinical trials, etc). They would then be transferred to a carefully detailed programme in which the oncologic nurse may have a major role in ensuring patient inclusion for as long as necessary.

The field of long-term cancer survivorship is a new field of clinical oncology where understanding of the physiopathology, prevention, diagnosis and the general treatment of late effects are major issues.

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Conflict of interest statement

None declared.

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