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Oncology in Focus

Radiation-induced tumours of the head and neck

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Abstract
In order to study the induction of malignancy in normal tissues due to ionizing radiation, we reviewed the files of 2500 patients with a tumour of the head and neck treated at the Netherlands Cancer Institute (Antoni van Leeuwenhoek Ziekenhuis), Amsterdam, from 1977 to 1993. We then checked whether or not these patients had been previously irradiated. Patients with a thyroid carcinoma or skin cancer were excluded from the study, since it is generally known that previous irradiation is a risk factor in these tumours. Eighteen patients were found to have a malignancy within a previously irradiated area (0.70 per cent). The mean interval between radiation and diagnosis of the head and neck tumour was 36.5 years. There were five soft tissue sarcomas, nine squamous cell carcinomas and four salivary gland tumours. Fourteen patients were operated upon whereas four received palliative treatment only. The median survival of the total group was 3.5 years. Particularly, in young patients because of the better cancer therapy and prolonged survival one must be aware of the increased risk of radiation-induced tumours.

Key words: Head and neck neoplasms; Radiotherapy; Neoplasms, radiation-induced

Introduction

Although radiotherapy is known to be an effective treatment modality in the management of malignant disease, ionizing radiation can also induce malignant tumour formation. This has been shown by studies on the sequelae of human exposure to atomic bombs. Practically all types of carcinoma can be induced by irradiation. For most radiation-induced malignancies a dose-response relationship between exposure to moderate or high doses and tumour risk has been observed (United Nations Scientific Committee, 1988). Little is known, however, about the cancer risk in previously irradiated head and neck areas with low doses of ionizing radiation.

In certain circumstances, the determination of ionizing radiation as an aetiological factor is uncertain if the patient already has an increased risk for cancer formation. This occurs in patients with a history of heavy smoking and drinking, for example (Parker, 1990). The study of carcinogenic effects of low dose radiation levels thus requires a large, well defined study with a long follow-up period (Hall, 1991). Because of the difficulty of such a study, publication of case reports on this subject remain important. Recently, a few patients were seen by us with a tumour arising within a previously irradiated area of the head and neck. These patients were the stimulus for a retrospective analysis of radiation-induced tumours of the head and neck in our Institute.

Patients and methods

In order to study the late effects of ionizing radiation on normal tissues, we analysed the records of all patients presenting with a tumour of the head and neck at the Netherlands Cancer Institute between January 1977 and June 1993. It is generally known that irradiation can lead to thyroid tumours and skin cancer and these malignancies were not included in the study. A computer database containing clinical details of patients treated in our Institute was consulted and 35 out of a total group of 2500 patients treated for head and neck tumours were found to have a malignancy within a previously irradiated area.

The medical records of these 35 patients were carefully reviewed and checked for criteria of radiation-induced tumours which were defined as follows: (1) documented history of irradiation; (2) long latency period of greater than five years, (3) histologically proven malignant tumour arising within the irradiation field; and (4) different histology of the new tumour, if the radiation was given for malignancy. Ten patients were excluded from the study due to histopathological findings, since it was impossible to distinguish between a radiation-induced tumour, a possible recurrence of the primary tumour, or a new primary, despite a long latency period (four to 36 years). Three other patients had a squamous cell carcinoma of the aerodigestive tract 14–55 years after irradiation of the neck, but these patients were also heavy smokers and drinkers. In addition, after careful examination of the radiation data, three more patients appeared to have a tumour outside the original irradiation field. After revision of the histopathology a previously diagnosed malignant fibrous histiocytoma was found to be a benign tumour.

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TABLE I
PATIENT CHARACTERISTICS, SURVIVAL AND PATHOLOGY FINDINGS

Case	Sex	Age	Reason for radiotherapy (RT)	Lat. prd	RI-tumour	Histology	RT dose	Treatment	Radical surgery	Survival	Status
1[1]	F	70	Mammary carcinoma	18 yr	Supraclavicular	MFH	50 Gy	S	Yes	2 yr+ 6 mo	NED
2	M	43	Tuberculosis (neck)	35 yr	Supraclavicular	Fibrosarcoma	≤1000 R[5]	S + C	No	8 yr+ 10 mo	DOD
3[1]	M	43	M. Hodgkin	11 yr	Supraclavicular	MFH	36 Gy	C	–	8 mo	DOD
4[1]	M	69	Laryngeal ca. T_2N_0	16 yr	Larynx	MFH	70 Gy	S	Yes	11 yr+ 10 mo	NED
5	M	53	Tuberculosis (neck)	44 yr	Supraglottic ca.	SCC	≤1000 R[5]	S + RT[2]	Yes	3 yr	DOD
6	F	80	Cerv. lymphadenopath	65 yr	Supraglottic ca.[3]	SCC	≤1000 R[5]	–	–	8 mo	DOD
7	F	82	Cerv. lymphadenopath	64 yr	Parotid gland	muco-epidemoid ca.	≤1000 R[5]	S + RT	No	7 yr+ 6 mo	DOD
8	F	61	Cerv. lymphadenopath	47 yr	Hypopharynx T_3N_3	SCC	≤1000 R[5]	S + RT	Yes	9 yr+ 10 mo	DND
9	F	70	Goitre	51 yr	Cervical oesoph.	SCC	≤1000 R[5]	S	Yes	16 dy	NED
10	F	62	tuberculosis (neck)	41 yr	Tonsil ca.[3,4]	SCC	≤1000 R[5]	S + RT	Yes	3 yr+ 7 mo	DOD
11	F	79	Hirsutism	57 yr	Submand. gland	Ad. cyst. ca.	≤1000 R[5]	S + RT	No	3 yr+ 2 mo	DOD
12	F	65	Goitre	40 yr	Hypopharynx T_xN_3	SCC	≤1000 R[5]	–	–	2 yr+ 3 mo	DOD
13	F	66	Tuberculosis (neck)	46 yr	Hypopharynx T_1N_3	SCC	≤1000 R[5]	S + RT	Yes	5 yr	NED
14	F	73	Cerv. lymphadenopath	64 yr	Hypopharynx T_4N_3	SCC	≤1000 R[5]	S + RT	Yes	6 yr	NED
15	F	80	Goitre	25 yr	Submand. gland	Ad.cyst.ca.	≤1000 R[5]	S	Yes	2 yr+ 6 mo (LFU)	AWD
16[1]	M	53	Nasopharynx carcinoma	18 yr	Dorsum nose	Spindle cell sa.	70 Gy	S + C	Yes	5 mo	AWD
17[1]	F	38	M. Hodgkin	14 yr	Submand. gland	Adeno ca.	38 Gy	S	No	3 mo	AWD
18[1]	F	39	Ad.cyst.ca.parotid	9 yr	Nasal septum	SCC	60 Gy	S	No	8 mo	DOD

Ad.cyst.ca: adenoid cystic carcinoma. AWD: alive with disease. C: chemotherapy. ca.: carcinoma. Cerv lymphadenopath: cervical lymphadenopathy. DOD: dead of disease. Lat.prd: latency period. LFU: lost to follow-up. MFH: malignant fibrous histiocytoma. mo: months. NED: no evidence of disease. Rad. surg.: radical surgery. RI: radiation-induced. RT: radiotherapy. S: surgery. sa.: sarcoma. SCC: squamous cell carcinoma. Submand: submandibular. Surv.: survival.

[1]RT was performed in Netherlands Cancer Institute. [2]Overlying RT damaged skin was surgically removed. [3]Basal cell carcinoma in irradiated skin as well. [4]Papillary thyroid cancer as well. [5]No radiation data available. Dose ≤ 1000 R as suggested in old textbooks.

These seven patients were also excluded from the study. Therefore, 18 patients met our criteria for a radiation-induced tumour.

Results

The 18 patients who met the criteria of a radiation-induced tumour (Table I) comprised 0.70 per cent of all head and neck tumours treated in our Institute over the study period. Seven of them were male and 11 were female, with a mean age of 63 years. Six patients were treated with a well-documented high radiation dose, ranging from 36 to 70 Gy. The remaining 12 patients were treated by ionizing radiation for various benign disorders. Since no detailed data on radiation doses were known in these cases, we relied on the information retrieved from old radiotherapy textbooks (Glaumer, 1949; Van der Plaats, 1953). Generally, chronic infections such as tuberculosis or cervical lymphadenopathy were irradiated with 300–800 Röntgen (R) in four to six fractions. Hyperplasia or hyperfunction of the thyroid gland were treated by irradiation with up to 1000 R in a daily dose of 300–400 R, whereas hirsutism was irradiated to a total dose of 500 R. The indications for radiotherapy are summarized in Table I. The mean time interval between radiation and the diagnosis of a radiation-induced tumour of the total group was 36.5 years (nine to 65 years).

The following histopathological diagnoses were made: five soft tissue sarcomas, nine squamous cell carcinomas of the upper aerodigestive tract and four salivary gland tumours. In the group of squamous cell carcinomas, the heavy smokers and drinkers were excluded for the purposes of this study, as mentioned earlier. The preferred treatment for patients with a radiation-induced tumour was surgery. Eleven patients underwent radical excision of their radiation-induced tumour, of which four tumours (36 per cent) recurred (*Cases* 5, 10, 15 and 16) . Five (*Cases* 2, 7, 11, 17 and 18) had non-radically removed tumours and all died of, or are still alive with, disease. Four patients (*Cases* 3, 6, 12 and 18) received palliative treatment only because of the extent of disease and all these patients died of their disease, within three to eight months. One patient (*Case* 15) had recurrent disease nine months post-operatively, but was lost to follow-up, another patient (*Case* 9) died 16 days post-operatively due to massive bleeding of a calcified innominate artery, and two patients (*Cases* 16 and 17) are still alive (with disease) but these are only two to four months post-operation. The median survival of the overall patient group was 3.5 years (16 days–11 years). The disease-free specific survival of the patient group is shown in Figure 1.

Discussion

In general, individuals with a malignant neoplasm have been reported to have a relatively increased risk of developing a second primary cancer i.e. 1.29 times higher

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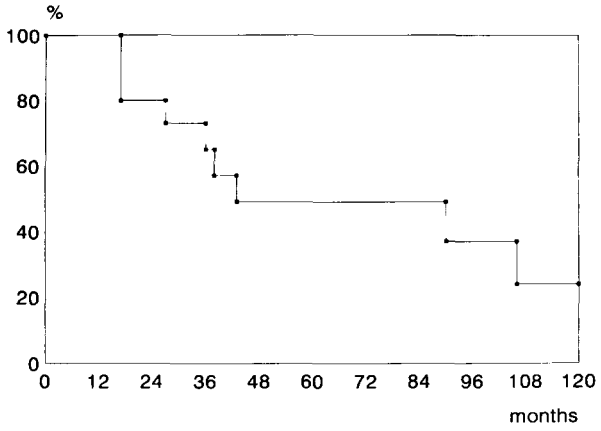

FIG. 1

Survival curve of 18 patients with radiation-induced tumours of the head and neck.

than that of the population with no history of malignancy (Stein *et al.*, 1991). A higher relative risk can be due to carcinogenic effects of tumour treatment like ionizing radiation, which is a weak carcinogen compared to carcinogenic substances such as some cytostatic drugs (Coleman, 1982). In the head and neck region, the detection of radiation-induced cancers is difficult because of the risk of multiple primary tumours in certain groups of patients. Clinical data on this issue are scarce in the head and neck literature. So far, 36 cases of radiation-induced sarcomas (Donohue *et al.*, 1967; Gane *et al.*, 1970; Coia *et al.*, 1980; Steeves and Bataini, 1981; Eisenbud *et al.*, 1982; Rennie *et al.*, 1983; Spiegel and Bogdasarian, 1985; Narula *et al.*, 1986; Griem *et al.*, 1989; Maisel *et al.*, 1989; Glaubiger *et al.*, 1991; Liddington *et al.*, 1992) and squamous cell carcinomas (Schindel and Castoriano, 1972; Kumar and Newland, 1980; Strauss and Hershey, 1983; Weshler *et al.*, 1983; Amendola *et al.*, 1985; Maisel and Case, 1992) have been described. Radiation-induced salivary gland tumours and thyroid carcinomas are more common and have been reviewed by others (Fleming *et al.*, 1985; Watkin and Hobsley, 1986; Robinson and Neugut, 1990).

The induction period for solid tumours after therapeutic radiation is usually considered to be 10 years on average (Hall, 1991). This is in accordance with our findings of a mean of 14.3 years for patients treated with high dose radiation. Interestingly, however, the mean interval of low dose radiation-induced tumours was 48.3 years in our study, which is almost three times longer. In patients irradiated for Hodgkin's disease, a high risk for radiation-induced tumours may already be noticed within five years after completion of therapy, with an increased risk at ten years after therapy (Van Leeuwen *et al.*, 1989; Van Leeuwen *et al.*, 1994). No more details on low dose radiation are available in those cases treated before 1959, but from the literature we know that for most irradiated benign lesions a minimum dose of 1000 R was applied (Glaumer, 1949; Van der Plaats, 1953). Although more radiation-induced tumours were seen in our series due to low dose rather than high dose radiotherapy (12 *versus* 6 years), it is generally assumed that the cancer risk increases at higher doses, particularly when radiation is used therapeutically (Tucker, 1993). It seems that squamous cell carcinomas display a longer latency period than radiation-induced sarcomas (mean latency: 45 *versus* 20 years). In addition, most squamous cell carcinomas were induced by low dose radiation, whereas most soft tissue sarcomas were induced by a high radiation dose. This may indicate that the histology and the latency period of the tumour is dependent on the radiation dose.

We did not find any histological characteristics typical for a radiation-induced tumour. Particularly for squamous cell carcinomas of the upper aerodigestive tract, it remains difficult to decide whether these tumours are caused by previous irradiation or not. The absence of smoking and drinking habits, and a tumour presenting in the irradiation field, we took as suggestive of radiation-induction. Three patients with a new malignancy within the irradiation field in our series were excluded because of the assumption that heavy smoking and drinking contributed to their cancer formation, although it cannot be excluded that irradiation acted as a cofactor in these cases. From an epidemiological point of view, the survival data after treatment for the new tumour are not that different from the non-radiation-induced tumours in the head and neck. This may indicate that the biological behaviour of these malignancies is not determined by characteristics specific for radiation-induction.

Irradiation for benign lesions in the head and neck is no longer used. Indications today are limited and apply to the following: non-radical removal of pleomorphic adenomas, aggressive fibromatosis and chemodectomas. In these cases radiation-induced tumours must still be considered. It may be advisable for prolonged follow-up to allow for early detection of an induced tumour in these patients.

There is a low incidence of radiation-induced tumours in the head and neck, although it is likely to increase due to several factors. These include increased effectiveness of cancer therapy, with prolonged survival and increased life expectancy with progressive aging of the population. One must therefore be aware of the increasing risk of radiation-induced tumours in patients treated with radiotherapy for head and neck tumours, especially in young patients.

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