Oral Oncology 46 (2010) 672–677

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Hypopharyngeal carcinoma after radiation for tuberculosis: Radiation-induced carcinoma

Lisa van der Putten [a], Remco de Bree [a,*], Dirk J. Kuik [b], Derek H.F. Rietveld [c], Johannes A. Langendijk [d], C. René Leemans [a]

[a] Department of Otolaryngology/Head and Neck Surgery, VU University Medical Center, P.O. Box 7057, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands
[b] Department of Clinical Epidemiology and Biostatistics, VU University Medical Center, P.O. Box 7057, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands
[c] Department of Radiation Oncology, VU University Medical Center, P.O. Box 7057, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands
[d] Department of Radiation Oncology, University Medical Center Groningen, P.O. Box 30.001, Hanzeplein 1, 9700 RB Groningen, The Netherlands

ARTICLE INFO

Article history:
Received 30 March 2010
Received in revised form 24 June 2010
Accepted 25 June 2010
Available online 24 July 2010

Keywords:
Head and neck cancer
Radiation-induced cancer
Hypopharynx

SUMMARY

Radiation may cause radiation-induced cancers after a long latency period. In a group of 111 patients surgically treated for hypopharyngeal carcinoma, patients previously treated with radiotherapy for tuberculosis in the neck were compared to patients without previous radiotherapy. Seven patients (7.4%) underwent radiotherapy (median age 15 years) and developed a hypopharyngeal carcinoma (median age 70 years, median latency period 54.4 year). Considering this long latency period and the localisation in the previous radiation field these tumours can be classified as potentially radiation-induced carcinomas. Patients with potentially radiation-induced carcinomas were significantly older when the hypopharyngeal carcinoma was diagnosed ($p = 0.048$), were more frequently females ($p = 0.05$) and had a worse 5-year regional control rate ($p = 0.048$). When radiotherapy is considered in young patients the risk of induction of tumours has to be kept in mind.

Introduction

Radiation has been used for diagnostics and treatment of patients since 1896, and ever since, the use of radiotherapy has been increased.[1,2] Nowadays 40% of cancer patients receive some form of radiotherapy during their treatment.[3]

Between 1940 and 1960 benign ailments such as tinea capitis, enlarged tonsils or thymus, benign breast diseases and cervical or pulmonary tuberculosis were frequently radiated with relatively high doses and great variety in radiation techniques (daily fraction doses of 60–200 röntgen (100 röntgen ≈ 1 Gy) and total doses of 600–1200 röntgen).[4]

It is generally accepted that radiation may induce development of cancer. Because of the low incidence and long latency period, demonstration that a specific radiation causes a certain cancer is difficult. Causation is assumed because cancer occurred at sites in which cancer is not common, and where radiation scars were shown.[5] Exposure of children or young adults to fractionated radiation can result in detectably increased frequencies of stable chromosome aberrations in circulating lymphocytes 30 years later.[6] Although only observed in '*in vitro*' cell culture systems, it has been shown that radiation can, by itself, induce a type of genomic instability in cells. This enhances the rate at which mutations and other genetic changes arise in the descendants of the irradiated cell after many generations of replication.[7]

In consequence of the increased use of radiotherapy, the number of radiation-induced tumours has also increased, with a relatively high risk after radiation during childhood.[3,5] For solid tumours the latency period is presumed to be at least 10 years, with a lasting high risk after 30 years.[5,8–10] After nuclear bombs in Hiroshima and Nagasaki the mean latency period was 24 years,[11] although this concerned a different type of radiation.

Tumours arising after radiation of the neck are mainly leukaemia or tumours of thyroid gland or skin.[5,12] For solid laryngeal and pharyngeal tumours a lower incidence of 1–2 per 1000 irradiated patients is reported.[13,14] Unfortunately, most studies are based on small populations and other risk factors such as alcohol and nicotine are frequently present, playing a dominant and inseparable role in the carcinogenesis of head and neck carcinomas.

Criteria described to diagnose radiation-induced tumours are: a tumour within the radiation volume, minimal 3 years after the last irradiation, absence of a maximum latency period, administered dose more than 2 Gy, and exclusion of a metastatic tumour process, a recurrence or development of a second primary tumour.[15–17]

With these criteria in hand seven cases of hypopharyngeal squamous cell carcinoma after previous radiation on the neck for

* Corresponding author. Tel.: +31 204443689; fax: +31 204443688.
E-mail address: r.bree@vumc.nl (R. de Bree).

1368-8375/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.oraloncology.2010.06.013

tuberculosis were identified in our institute and compared with patients without radiotherapy in their history.

Patients and methods

Patients

Between January 1978 and November 2004, 111 patients were surgically treated for a hypopharyngeal squamous cell carcinoma in the VU University Medical Center. Of these, seven patients were previously radiated for tuberculosis in the neck and 89 patients did not receive radiotherapy in the past. Fourteen patients with previous radiotherapy for a cause other than tuberculosis (other primary head and neck cancer) were excluded. One patient with a hypopharyngeal carcinoma on the contralateral side (which could have been outside the radiation field) was excluded.

Patient 1 was radiated on the right neck at 2 years of age because of tuberculosis. Forty-six years later a pT4N2bM0 piriform sinus carcinoma on the right side was diagnosed. His family history was positive for cancer: father had prostate carcinoma. He smoked five cigarettes per day for an unknown period and consumed alcohol incidentally. He underwent a total laryngectomy with partial pharyngectomy (primary closure) with R0 resection margins, a radical neck dissection ipsilateral and, because of extracapsular spread, postoperative radiotherapy with a cumulative dose of 56 Gy. Two years later he developed distant metastases, which eventually was the cause of his death.

Patient 2 was radiated on both sides of the neck for a period of 3 years because of tuberculosis when she was 9 years old. Sixty-eight years after radiotherapy a pT3N3M0 piriform sinus carcinoma was diagnosed. Her family history was negative for cancer, she did not use alcohol, but has smoked (25 pack years) in the past. A total laryngopharyngectomy (R0) with jejunum free flap reconstruction and anterolateral neck dissection on both sides was performed. Because of extracapsular spread, postoperative radiotherapy was given with a total dose of 65 Gy. She died 2 years later, free of tumour.

Patient 3 was radiated on the right neck because of tuberculosis when he was 15 years old. Sixty-four years later he developed a pT3N0M0 piriform sinus carcinoma on the right side, for which a total laryngectomy with partial pharyngectomy (primary closure) and ipsilateral radical neck dissection was performed, with R0 resection margins and no lymph node metastases. Postoperative radiotherapy with a cumulative dose of 63 Gy was given. He did not have other risk factors except smoking 2–3 cigars per week for an unknown period. Four years after surgery he died of distant metastases.

Patient 4 was radiated on the right side of the neck with three fractions of unknown dose per week during 3 weeks because of tuberculosis when he was 21 years old. Fifty-five years later he developed a pT3N2cM0 piriform sinus carcinoma on the right side. His father had liver cancer. He did not smoke and used no alcohol. A total laryngopharyngectomy with deltopectoralis flap reconstruction was performed (with R1 resection margins), with postoperative radiotherapy of 40 Gy. Three months after surgery lymph node metastases with extracapsular spread were diagnosed for which he underwent a bilateral lymph node dissection. He died of tumour-related problems.

Patient 5 was radiated for tuberculosis on the right side of the neck when he was 25 years old. After 36 years he developed a pT4N2bM0 piriform sinus carcinoma on the right side. He smoked 20 cigarettes per day for an unknown period and used no alcohol. His history and his family history were uneventful. After a total laryngopharyngectomy with jejunum reconstruction (R1 resection margins) and ipsilateral radical lymph node dissection for lymph node metastases with extracapsular spread, he was radiated with a cumulative dose of 59.6 Gy. Eight months after surgery contralateral lymph node metastases were found, and he died within in short period.

Patient 6 was radiated during three periods (1929–1938) on the right side of the neck and right lung top with a total dose of 11,500 röntgen because of tuberculosis when she was 7 years old. Sixty-two years later she developed a pT2N0M0 posterior hypopharyngeal wall carcinoma on the right side. The initial treatment consisted of radiotherapy, followed by a total laryngopharyngectomy with gastric pull-up and pectoralis major flap reconstruction for a recurrence (R1 resection margins). Her family history was negative for cancer. She did not smoke and used alcohol only incidentally. Some years before the hypopharyngeal carcinoma a basalioma was excised from the radiated area. A year after laryngectomy she developed a local recurrence of the hypopharyngeal carcinoma, of which she died.

Patient 7 was radiated for tuberculosis on both sides of the neck, when she was 18 years old. She never smoked and used no alcohol. Her family history was negative for cancer. Twenty years after radiation she underwent a strumectomy for thyroid cancer, with suspicion of a radiation-induced tumour. Forty-seven years after radiotherapy she presented with a posterior pharyngeal wall carcinoma. A total laryngopharyngectomy with neck dissections was performed (R0 resection margins and no extracapsular spread). Until now she is free of disease.

Methods

Patient, tumour and treatment characteristics were scored and compared between the two groups. Complications were scored as: no complication, minor complication and major complication. A complication was classified as major when surgery and/or intensive care was needed. The seven patients described above were classified as radiation-induced carcinomas. See Table 1 for summary of characteristics.

Statistics

Chi-square tests were used to test the unadjusted association between categorical variables. For continuous variables the two patient groups were compared with Student's *t*-test or Mann–Whitney, where appropriate. Survival curves were constructed with the Kaplan–Meier method from the day of surgery, and compared with the log rank test. To analyze the effect of preoperative radiotherapy on the disease specific survival controlled for confounding by treatment for the hypopharyngeal cancer (postoperative radiotherapy, surgical margins of the primary tumour and lymph node dissection, and type of lymph node dissection ipsi- and contralateral), Cox regression was used. SPSS 15.0 was used.

Results

The group of seven patients (group A) with potentially radiation-induced carcinomas, was compared with the group of 89 patients (group B). Results are summarized in Table 2.

Patients from group A were radiated for tuberculosis at a median age of 15 years, with a median latency period of 54 years until diagnosis of the hypopharyngeal carcinoma (range 36–69 years). Surgery was performed between 1977 and 1994.

When compared to group B, the median age at the time of diagnosis was (marginally) higher in group A (70 vs. 60 years; $p = 0.048$). Also, group A tended to consist of more females ($p = 0.053$).