Late complications after Hodgkin's disease

M. Henry-Amar & F. Joly
Centre Francois Baclesse, Caen, France

Summary

Hodgkin's disease is considered a curable disease. The use of appropriate staging techniques and treatment methods has resulted in long-term survival rates as high as 90% in early stages, 75% or greater in advanced stages. Long-surviving Hodgkin's disease patients, however, face new problems which have become apparent as greater numbers of successfully treated patients are followed for longer periods of time. They concern mostly chronic medical as well as psychosocial complications which can interfere with survivors quality of life. Hodgkin's disease therapy may result in severe infections, thyroid, cardiovascular, pulmonary, digestive or gonadal dysfunction. It may also result in secondary malignancy which is considered the most serious complication. This review focuses on the variety of medical problems considering subsequent nonmalignant complications, secondary malignancies, long-term patient quality of life and causes of death. Because the vast majority of patients who achieve remission remain symptom-free and enjoy a normal life, an attempt is made to provide estimated risk for individuals based on available data.

Key words: causes of death, Hodgkin's disease, late complications, nonmalignant complications, quality of life, secondary cancers.

Introduction

With the careful application of appropriate staging techniques and treatment methods, the expected proportion of all patients presenting with Hodgkin's disease who should be cured of their disease is as high as 75% as of 1992 [1]. This result is already achieved in early stages because modern treatment methods (high-dose extended-field or total lymphoid radiation therapy and/or cyclical multidrug chemotherapy) are widely applied. Long-surviving Hodgkin's disease patients, however, face new problems. As greater numbers of successfully treated patients are followed for longer periods of time, medical problems associated with residua of the disease and its therapy have become more apparent [2]. Among these problems, secondary malignancies are the most serious because they are often fatal and because, in a large proportion of cases, they arise as a consequence of treatment. Hodgkin's disease therapy may also result in severe infections, thyroid, cardiovascular, pulmonary, digestive or gonadal dysfunction. Skeletal complications, mostly reported in children treated with extended-field irradiation delivering 30 Gy or more, have been dramatically lowered with the use of low-dose radiation in combination with chemotherapy or chemotherapy alone in paediatric patients. These complications will therefore not be discussed, although one might expect more complications in the skeletons years after the patients have been irradiated [3].

Nonmalignant complications

Immunologic dysfunction. The lymphoid organs are the most common sites affected by Hodgkin's disease, and it is not surprising that immune regulation disorders are observed. Functional status of the immune system is probably important in the maintenance of remission and protection against infection or secondary malignancies. Untreated Hodgkin's disease patients generally present with immunodeficiency state which was first reported by Reed in 1902 [5]. Patients exhibit lymphocytopenia mainly ascribed to a reduction of OKT4+ T-cells and to lack of T₄ cells. Their lymphocytes are poorly activated by mitogens and antigens. Patients are poor responders in the allogeneic mixed lymphocyte reaction. In contrast, B-lymphocyte functions are well preserved in these patients except in those with systemic symptoms. Therapeutic irradiation induces lymphocytopenia (which depends on target volume and dose delivered) and a profound depression.
of immune functions. While the immediate absolute B lymphocytopenia following irradiation seems to normalize within the first 1-2 years after therapy, prolonged T-cell functional impairment is often observed in long-term survivors. Aggressive combination cytotoxic drug therapy, such as the MOPP regimen (mechlorethamine, vincristine, procarbazine, prednisone) and its variants, also induce an acute reduction of T and B lymphocytes with prolonged T-cell functional impairment after cessation of chemotherapy. Spleen removal may result in persistent blood-cell abnormalities such as neutrophilia, lymphocytosis, eosinophilia and thrombocytosis. Spleenectomy also induces delayed reduction of serum IgM and potentiates the progressive fall in serum IgM secondary to irradiation and cytotoxic drug therapy. All together, in the asplenic state (either because of splenectomy or splenic irradiation), reduced IgM levels and impaired B-cell responses contribute to the persistent life-long risk of overwhelming postsplenectomy infections (OPSI).

Infectious complications. Bacteria, fungi, parasites as well as viruses are microorganisms with a predilection for individuals with Hodgkin's disease [6]. Pneumonia (37%-57%), bacteremia (25%-33%), skin infection (5%-19%) and meningitis (3%-13%) are the most common serious infections [2]. Organisms frequently isolated include Streptococcus pneumoniae (21%-32%), Staphylococcus aureus (5%-19%) and Staphylococcus epidermidis (4%-19%). Gram negative organisms are less common. A nonnegligible number of isolates, however, are polymicrobial (15%-21%). Infections are often favored by immunologic dysfunction (Herpes zoster being the most characteristic consequence). The most feared splenectomy-related infection is OPSI which can lead to death within hours of the first clinical manifestation. Patients to be submitted to splenectomy should be systematically given pneumococcal vaccine prior to surgery. Splenectomized patients and those whose spleen was irradiated should certainly be proposed for antibiotic (penicillin) prophylaxis as well as regular vaccination.

Thyroid dysfunction. Thyroid dysfunction is among the most common therapy-related complications and was recognized early and treated. Because the thyroid is directly exposed to radiation, dysfunction often concerns hypothyroidism with consequent elevation of thyroid stimulating hormone (TSH) while no consistent effect of chemotherapy alone has been demonstrated. In the European Organization for Research and Treatment of Cancer (EORTC) trials, three years after treatment completion patients expressed a 100% increase in TSH level compared with baseline whatever the treatment administered, i.e., mantle irradiation alone or combined modality with MOPP or MOPP/ABV (doxorubicin, bleomycin, vinblastine) hybrid chemotherapy [7]. Hypothyroidism develops gradually. Thyroid function was evaluated in a series of 1,787 patients treated during the period from 1961–1989 at Stanford University Medical Center [8]. Ninety-seven percent of patients were irradiated as part of their treatment and 573 patients had clinical or biological evidence of thyroid disease. The 20-year cumulative incidence rate of thyroid disease was 50%, the median time to occurrence was 4.6 years (range 0.2 to 25.6). Thyroid disease concerned hypothyroidism (20-year cumulative rate, 41%), Graves' disease (20-year cumulative rate, 3.1%), thyroiditis (20-year cumulative rate, 1.3%), thyroidectomy (including 6/26 for thyroid cancer; 20-year cumulative rate, 6.6%), and clinically benign nodule (20-year cumulative rate, 3.3%). Hypothyroidism, Graves' disease and thyroiditis occurred earlier (median 4.0, 4.8 and 5.0 years from treatment initiation, respectively) than thyroidectomy and clinically benign nodule (median 14.0 and 12.6 years, respectively). In this series, hypothyroidism was radiation dose, age and sex-dependent. The 20-year cumulative incidence was less than 5% in unirradiated patients; it was 30% if radiation dose to the thyroid was 7.5 to 30 Gy, and 45% in patients whose thyroid was irradiated at a dose exceeding 30 Gy. The proportion of patients in whom hypothyroidism developed increased with age, from 17% in those who were less than 5 years of age when treated to 39% in those who were 15 to 20 years of age when treated; it gradually declined with advancing age to 17% in patients who were over 70 years of age when treated. Risk factors analysis indicated that, in patients aged 17 years or older when irradiated, female sex (Relative risk (RR) = 1.60, P < 0.001), chemotherapy (RR = 1.42, P < 0.001) and radiation dose (RR/Gy = 1.02, P = 0.035) significantly correlated with increased risk of hypothyroidism. Hypothyroidism might not only be related to radiation to the thyroid, but also to radio-diagnostic iodine surcharge since lymphangiography and more recently abdominal CT scan are systematically performed during the initial work-up and repeated thereafter [9,10]. The literature, however, is conflicting and the question remains to be clarified in a larger series than already reported [11].

Cardiovascular dysfunction. Treatment-related cardiac complications involve the three cardiac tunicae. They have been described to be irradiation- and chemotherapy-related. Cardiac complications such as myocardial infarction and coronary artery disease, arrhythmias, myocarditis, pericarditis, pericardial effusion, and tamponade, have been well documented after radiation therapy to the mediastinum [12,13]. They are related to total radiation dose delivered, fraction size and volume irradiated. Excess of risk has been reported for total dose over 40 Gy, dose per fraction > 3 Gy, use of single anterior and anteriorly weighted radiation port and irradiation involving the whole pericardium. Pericarditis, both acute and chronic, associated or not with pericardial effusion, is the most common symptomatic complication. It has been reported to develop in 11% to 50% of patients. With the use of dose restriction to
the whole heart, addition of a subcarinal block after 25 or 35 Gy in the absence of lower mediastinal involvement or large mediastinal adenopathies, high energy linear accelerator, and dose per fraction <2 Gy, more satisfactory results are obtained with cumulative rates often less than 5%. Uncomplicated chronic pericardial effusions are frequently persistently asymptomatic and consequently often not recognized. Chronic constrictive pericarditis, with or without effusion, is a more serious consequence of radiation therapy because it requires more invasive and aggressive therapy than effusion alone; it is also associated with a higher incidence of morbidity. The use of modern irradiation techniques, however, should make it exceptional. The availability of noninvasive diagnostic procedures, such as echocardiography and radionuclide cineangioigraphy, has facilitated the recognition of myocardial damage. Complete cardiovascular work-up, however, is available in limited series only [14-17]. They generally conclude that myocardial damage is present in 25% to 50% of long survivors whose mediastinum was irradiated though a small proportion of patients who spontaneously complain of symptoms. Left ventricular ejection fraction, used as a measure of systolic function, is usually normal when measured at rest with, in a substantial number of patients, an abnormal response at exercise. Transient left ventricular ejection fraction decrease was observed even 3 years after treatment completion in both patients treated with mantle irradiation or combined modalities [7]. As Hodgkin's disease survivors age and become exposed to the risk factors of coronary artery disease, observed excess morbidity and mortality from coronary artery disease in a large series has led to the conclusion that irradiation might cause, aggravate or accelerate atherosclerosis [18-21]. In the EORTC series, the 10-year and 15-year cumulative incidence rates of myocardial infarction were 2.4% and 4.6%, respectively [22]. The role of mediastinal irradiation on myocardial infarction risk was demonstrated in the Institut Gustave Roussy series where the 10-year cumulative incidence rate was 3.9% in patients who were given irradiation to the heart while no myocardial infarction was observed in patients who had no mediastinal irradiation [20]. Doxorubicin chemotherapy has been reported to induce cardiotoxicity in Hodgkin's disease [2, 12]. In most protocols, such as ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), MOPP/ABVD or MOPP/ABV hybrid regimens, the cumulative dose of doxorubicin following six cycles of 100% standard dose is 300 mg/m² or less, with rare incidence of clinical cardiomyopathy. Whether doxorubicin potentiates irradiation-related cardiotoxicity remains unclear. In the Stanford series, no significant incidence of death from acute myocardial infarction was observed after combined therapy with MOPP compared with radiotherapy alone [23]. However, since average total mediastinal doses were lower, subcarinal blocking was more frequent and less cardiac volume may have been irradiated in patients who received combined therapy, the potential role of chemotherapy might have been underestimated.

**Pulmonary dysfunction.** Radiation pneumonitis and pulmonary fibrosis represent the most common complications following mantle irradiation. Almost 20% of patients develop X-ray changes which are characteristic of acute radiation pneumonitis within 1 to 3 months after irradiation although it may be delayed as long as 6 months [24]. These changes are generally asymptomatic. When present, common symptoms include dyspnea on mild exertion, non productive cough and low-grade fever which, in most patients, do not require therapy or additional diagnostic evaluation. The incidence of radiation pneumonitis mainly depends on total dose delivered to the mediastinum, irradiated volume and technique [25, 26]. It also depends on the fraction size for a given dose; the larger the fraction size, the higher the probability of lung damage [27]. The use of lung blocks and the administration of chemotherapy before irradiation in patients with large mediastinal masses limit the dose and reduce incidence to less than 5%. Pulmonary fibrosis begins to appear 6 months after treatment; it usually stabilizes after 12 to 18 months. The volume irradiated appears to be the most important factor for pulmonary fibrosis, although the risk can vary according to the type of combined modality therapy. After MOPP plus irradiation, the incidence of pulmonary changes were 49% compared with 15% after ABVD plus irradiation in a randomized study [28]. The incidence of radiation-induced lung damage, as determined by computed tomography changes (increase in lung density within the irradiated volume) was prospectively evaluated in patients treated with combined modality treatment with radiation therapy (35 Gy in 20 fractions) together with either MOPP (12 patients), ABVD (16 patients), or MOPP/ABVD (12 patients) [29]. The actuarial risk of developing pneumonitis was 71% in patients treated with ABVD and irradiation, 49% in patients treated with MOPP and irradiation, and 52% in patients treated with MOPP/ABVD and irradiation. Minor restrictive ventilatory defects (decreased vital capacity and total lung compliance) are seen after mediastinal irradiation [30]. They are increased with combined modality treatment, in particular after ABVD and irradiation [22, 31]. ABVD-related pulmonary toxicity may be a consequence of bleomycin-induced pulmonary fibrosis and of doxorubicin-induced 'radiation recall' pneumonitis [32]. In contrast, the risk of pulmonary dysfunction is low after chemotherapy alone but may have been underestimated, since the series of patients initially treated with chemotherapy alone and carefully followed thereafter for late complications are limited.

**Digestive complications.** Most late digestive complications of Hodgkin's disease therapy concern infections, ulcers, gastritis and small bowel obstructions or perforations. They are mainly related to staging laparot-
omy and/or abdominal irradiation. Among laparotomy-related complications, splenectomy-related OPSI is probably the most serious. In a series of 133 patients followed 2.5 to 28 years after laparotomy, 6.8% developed OPSI from which one patient died [33]. The role of pneumococcal vaccine was clearly demonstrated. None of the 25 patients who received pneumococcal vaccine before splenectomy developed OPSI, while 5 of 44 (11%) patients who were vaccinated after splenectomy and 4 of 64 (6%) patients who were not vaccinated developed OPSI. The influence of radiation dose was studied in a series of 855 patients (478 with Hodgkin's disease and 377 with seminoma) who were treated with infradiaphragmatic irradiation but with no whole abdominal irradiation. The incidence of major bowel complications (requiring hospitalization for management or surgery) significantly correlated with the radiation dose delivered to the paraaortic region; for doses <35 Gy, the 3-year cumulative rate was 1% compared with 3% for dose \( \geq 35 \) Gy \((P = 0.03)\) [34]. The role of infradiaphragmatic irradiation technique as well as that of staging laparotomy was assessed in the EORTC trials. In these protocols, irradiation usually delivered 39 to 41 Gy to the paraaortic region; the proportion of late complications did not vary with radiation dose [35]. Late digestive complications did not relate to staging laparotomy in patients whose abdomen was not irradiated. In contrast, both staging laparotomy and fraction \( > 2 \) Gy increased the risk which was maximum in laparotomized patients treated with fractions of 3.3 Gy (5-year cumulative rate, 28%) [22]. With modern irradiation technique and withdrawal of staging laparotomy from most treatment strategies, these complications should no longer be observed.

**Gonadal dysfunction.** With the increasing use of chemotherapy in the treatment of Hodgkin's disease, lasting effects on gonadal function have been reported. The magnitude of the effect can vary with drug class or combination used in treatment, the total dose administered, and the age and pubertal status of the patient at the time of therapy [36]. After 6 to 10 cycles of COPP (cyclophosphamide, vincristine, procarbazine, prednisone) chemotherapy given as sole treatment, 100% \((n = 92)\) of males were azoospermic 1 to 17 years after treatment completion, 97% had testicular atrophy, and germinal aplasia was shown in 100% of the 19 patients submitted to testicular biopsy [37]. Serum FSH level was increased three-fold while serum LH level increase was moderate. Similar findings were reported in a series of 50 male patients treated with either MVPP (mechlorethamine, vinblastine, procarbazine, prednisone) or CHVPP/EVA (chlorambucil, vinblastine, procarbazine, prednisone, doxorubicin, vincristine, etoposide) chemotherapy for 5 to 8 cycles, with no difference between the two chemotherapy regimens [38]. In female patients \((n = 39)\), chemotherapy resulted in 76% amenorrhea; of these, 60% had persistent amenorrhea. In men, there were no significant differences in the incidence of amenorrhea, or mean of serum FSH and LH levels between MVPP- and CHVPP/EVA-treated women. These results were confirmed in the EORTC trials in which patients were successfully treated with irradiation alone or a combination of irradiation and MOPP, MOPP/ABV hybrid or ABVD, and in the Istituto Nazionale Tumori (Milan) series [7, 39]. Other chemotherapy regimens have been used in order to reduce the risk of long-term sequelae. VEEP (vincristine, epirubicin, etoposide, prednisone) chemotherapy alone (3 to 10 courses) was associated with 6% \((2/33)\) abnormal sperm count; in females, none of the 22 patients tested had posttreatment gonadal toxicity [40]. In a series of 75 boys treated with OPPA (vincristine, procarbazine, prednisone, doxorubicin, 2 courses) and COPP (0 to 6 courses) chemotherapy, all had normal pubertal development but 24% and 88% expressed elevated basal and stimulated LH, respectively, indicating chemotherapy-induced Leydig cell damage; in addition, there was 41% and 53% incidence of elevated basal and stimulated serum FSH levels, respectively, indicating severe spermatogenesis impairment [41]. In this series, testicular dysfunction was observed in boys treated before as well as during puberty. However, increased basal serum FSH and LH levels were dose-dependent: the higher the number of COPP courses, the higher the incidence rate. These results were confirmed in the Stanford series where 83% \((10/12)\) of boys who were treated with six cycles of MOPP with or without pelvic irradiation were azoospermic with no evidence of recovery as long as 11 years of follow-up [42]. The Stanford series also included gonadal evaluation of 86 girls. Seventy-five \((87\%)\) had normal menstrual function but none of the girls who underwent pelvic irradiation without prior oophorexy has maintained ovarian function. Therefore, the chance of maintaining gonadal function following combined modality treatment appears to be much greater among girls than boys. After treatment completion, most patients of reproductive age who desire children came to the following questions: Will my child have an increased risk of developing Hodgkin's disease? How long should I wait before becoming pregnant? Will the treatment I have had cause congenital defects in my child? The available data do not bring absolute answers since large studies with long-term follow-up have been infrequent. The outcome of pregnancies in patients (or their partners) who were successfully treated for Hodgkin's disease was recently addressed in a series of 104 adult females and 117 adult males [43]. After treatment, 43 females and 51 males actively attempted conception; 35 \((81\%)\) females and 25 \((49\%)\) partners of male patients had 84 pregnancies, which resulted in 68 living children for a median of 11 years \((minimum > 4.5\) years). Among the 84 pregnancies, there was one premature birth at 29 weeks, three spontaneous abortions, 11 elective abortions and two stillborn. There was no apparent increase in complications of pregnancies, spontaneous abortions, or con-
genital abnormalities. The partners of male patients who were treated with combined modality treatment, however, had a lower frequency of pregnancy than did the female patients who attempted conception. There is no convincing evidence that the risk of Hodgkin's disease in offspring is genetically increased although a large number of families have been reported to have multiple occurrences of Hodgkin's disease [44]. Similarly, there is no evidence of significant increase in congenital defects in the offspring of these patients. Therefore, information from studies of progeny in Hodgkin's disease should not discourage patients in remission after treatment of their disease from childbearing.

Secondary malignancies

Several years after therapy, Hodgkin's disease patients have an increased risk of developing acute leukaemia, mostly acute nonlymphoblastic leukaemia (ANLL), non-Hodgkin's lymphoma (NHL), and second solid tumours [45-47]. Since large series with sufficient follow-up have become available, more accurate risk assessments can be made. They concern patients who were treated during childhood as well as those who were adults when the disease developed.

**Secondary ANLL and myelodysplastic syndrome.** Hodgkin's disease patients have a cumulative risk of developing secondary ANLL which has been reported as high as 10% at 10 years [48]. The risk, however, greatly depends on the type of therapy the patients received. It is much higher in patients treated with chemotherapy or with combined modality therapy than in patients treated with radiation therapy alone. The risk depends on the type of chemotherapy given, the higher risk being associated with MOPP and MOPP-like regimens; it depends on the amount of chemotherapy administered and might be associated with the extent of radiation therapy [45, 49]. After irradiation alone, the 15-year probability of developing an ANLL was 0.2%; it was null in patients treated with localized (involved- or mantle-field) irradiation compared with 3.4% in patients treated with extended-field (sub-total or total lymphoid) irradiation [50]. In this series, patients treated with chemotherapy alone had a 15-year probability of secondary ANLL of 11.1% while those treated with combined modality therapy had a 15-year probability of 4.3%. Among the latter, the risk was not increased in patients treated with chemotherapy and extended-field irradiation compared with those treated with chemotherapy and localized irradiation (4.4% versus 4.2%, respectively). These results confirm previous findings concerning the small impact of irradiation when associated with chemotherapy [51-56] while opposite results have been reported [57, 58]. In all studies, however, the cumulative risk of secondary ANLL tends to plateau 10 to 15 years after treatment completion. An attempt to quantify the risk of developing a secondary ANLL or a myelodysplastic syndrome in relation to the type and/or the amount of chemotherapy delivered has been made in several studies. The risk increased with the number of cycles, the dose or the alkylating score [51, 55-59-62]. The risk of chemotherapy-related secondary ANLL was shown to significantly correlate with various drugs such as nitrogen mustard (alone or associated with procarbazine and/or vincristine), cyclophosphamide and procarbazine, vincristine and procarbazine, lomustine, chlorambucil, vinblastine [51, 53, 55, 60, 62-64]. Other risk factors reported to correlate with an increased risk of secondary ANLL are age at which Hodgkin's disease developed, clinical stage and splenic treatment (splenectomy and splenic irradiation). The effect of age remains controversial. In many studies, an increase in cumulative probability as well as in relative risk have been found in patients aged above 40 or 50 [45, 58, 65-67] while in others the risk was not increased [68] or decreased with older age [51, 54, 69]. Advanced clinical stage was associated with an increased risk, even after confounding factors have been considered in the analysis, which might suggest that the risk of developing a secondary ANLL is related to greater functional defect of the immune system in these patients compared with that of patients with early stage disease [51, 52, 65, 69]. Van Leeuwen and coworkers have first pointed out that splenectomy is a risk factor for secondary ANLL [70]. This finding was later confirmed in some studies [51, 61-63, 67] while in others no significant increased risk was associated with previous splenectomy [50, 52, 54, 58, 65, 68, 69]. When increased, the risk is always limited in magnitude and cannot be compared with that associated with the use of alkylating agents. In a recent study, splenectomy was associated with an increased risk of leukaemia (RR = 13.3), NHL (RR = 16.6) or Hodgkin's disease (RR = 18.2) in patients treated for benign haematologic disorders [71]. These findings together with the infection risk and other splenectomy-related morbidity have been considered by some investigators to exclude splenectomy from staging and treatment strategy in Hodgkin's disease.

**Secondary non-Hodgkin's lymphoma.** NHL was first described as possibly treatment-related in 1979 [72]. Significantly increased risk was confirmed in all further studies [52-54, 58, 59, 65, 66, 73, 74]. NHL generally develops 5 to 15 years posttreatment; its cumulative incidence rate ranges from less than 1% to 4%-5% at that time but might increase with longer follow-up [66]. Increase in risk was associated with various factors such as older age, male gender, lymphocytic predominant Hodgkin's disease histologic subtype, and combined modality therapy [52, 54, 58, 65, 66, 69, 75]. In a recent study involving 10,472 patients treated at 14 cancer centres in the United States and Canada, only mechloatrethamine was associated with an increased risk (RR = 2.4; 95% CI, 1.2-4.8) of secondary NHL [62]. Immunodeficiency induced by the therapy or immuno-
logic defects of the Hodgkin’s disease itself as well as virus, such as Epstein–Barr virus or more recently HIV, might be co-factors for the subsequent development of NHL but their respective role remains unclear [75].

**Secondary solid tumours.** While the excess of secondary ANLL and NHL is generally significant over the 1–14-year period after the start of initial therapy, that of secondary solid tumours becomes apparent after the fifth year, increasing with time. In large series, the 15-year cumulative incidence rate of secondary solid tumours varies from 10 to 15% [50, 52–54, 58, 65, 66, 68]. In all series with sufficient follow-up, solid tumours represent two to three times as many ANLL and NHL indicating that secondary solid tumours have become the most serious complication in long-term survivors of Hodgkin’s disease. In general population comparisons, however, relative risks are generally comprised between 1.5 and 2.5 while that of ANLL or NHL often exceed 10. This apparent discrepancy comes from the difference between the natural incidence of ANLL and NHL, which are low (less than 10 cases per 100,000 inhabitants per year), and that of solid tumours which is much greater [76]. Not all localizations have been found in excess; it generally concerns lung (RR = 1.9 to 7.7), female breast (RR = 1.4 to 4.1), stomach (RR = 1.2 to 10), thyroid (RR = 2.4 to 68), bone (RR = 4.5 to 106) and melanoma (RR = 1.6 to 16), although other specific sites (such as salivary glands, head and neck, small intestine and colon in males, pleura, cervix and ovary) have been associated with an increased risk [8, 47, 52, 66, 73, 78]. The relative risk increase is almost inversely proportional to the natural incidence rate of a given site; it generally concerns few numbers leading to absolute risks always less than one case per hundred person-years at risk. Search for risk factors for developing a second solid tumour often ended to demonstrate that besides host factors (such as gender, age or cigarette smoking) radiation therapy is the main risk factor. This finding is not surprising since almost all sites associated with a significantly increased risk concern sites which might have been included in the radiation fields. Of the 23 second solid tumours which occurred in the EORTC series, 16 developed within an irradiated area; thirteen of these 16 tumours occurred in patients initially treated with extended-field irradiation [74]. In this series, the cumulative risk of second solid tumours was significantly higher in patients initially treated with extended-field irradiation compared with those treated with mantle irradiation when either all solid tumours (P = 0.01) or solid tumours which developed within an irradiated area (P = 0.009) were considered. A similar observation was made at the Institut Gustave Roussy concerning secondary gastric carcinomas. Six of nine patients referred to this institution for gastric carcinoma presented with limited plastic; all patients were previously treated with extended-field irradiation (including stomach within irradiation volume) and large fraction size (≥2.5 Gy) [79]. Chemotherapy given in combination to radiation therapy as part of initial treatment was shown to add to the risk of irradiation alone in one study [50]. In a case-control study, chemotherapy was associated with a risk of lung cancer which was twice that of irradiation alone or combined modality treatment [80]. These findings must be discussed together with the results of a recent study in which chemotherapy as a whole or individual drugs were associated with second cancer risk [62]. Irradiation to thorax was associated with an increased risk (RR = 2.7) of solid tumours of respiratory system and intrathoracic organs developing 10 years or more after exposure while chemotherapy was associated with an increased risk (RR = 2.2) of these tumours developing early (within the 0–4-year period after exposure). Tumours of bones, joints, articular cartilage and soft tissues preferentially developed after chemotherapy (RR = 6.0) whatever the period considered; drugs associated with an increase in risk were procarbazine (RR = 3.7), vincristine (RR = 2.8), doxorubicin (RR = 4.2) and bleomycin (RR = 3.0). Irradiation to the abdomen (RR = 2.4) was associated with tumours of the female genital system developing late (over 10 years after exposure) while chemotherapy (RR = 3.5) was associated with these tumours developing 5 years or more after exposure; vincristine was associated with an increased risk (RR = 4.7) while hormones were associated with a decreased risk (RR = 0.2). Finally, an increased risk (RR = 8.3) of thyroid cancer was observed after chemotherapy for the 0–4-year period after exposure, principally after exposure to lomustine (RR = 7.3). These results, however, must be confirmed from an independent series of patients with sufficient follow-up and treated with modern standards. If confirmed, they should encourage oncologists to more carefully use chemotherapy in the treatment of Hodgkin’s disease patients. Spleen treatment as risk factor for second solid tumour was recently reported for the first time [58]. An assumption was made that splenic irradiation should induce similar spleen function loss as does splenectomy. In a series of 1,003 adult patients continuously disease-free, 56 second tumours developed (37 solid tumours, 11 ANLLs and 8 NHLs), 17 in patients whose spleen was not treated, 22 in splenectomized patients and 17 in patients whose spleen was irradiated. Splenectomy (RR = 2.95, P = 0.023) and splenic irradiation (RR = 5.35, P = 0.002) were found independent risk factors for solid tumours. No correlation between splenectomy and an increased risk of second cancer was found in two previous studies performed on a large series of male American servicemen splenectomized for external trauma during World War II [81] and Danish people splenectomized for traumatic splenic rupture or other noncarcinologic reasons [71]. These findings raise an argument for a secondary cancer risk more likely related to underlying patient conditions than to splenectomy itself. Spleen treatment (spleen removal or splenic irradiation), however, might have a limited but significant impact in particular pa-
tient subgroups, possibly those with pronounced persistent immunodeficiency. In these subgroups, treatment strategies should therefore be carefully adapted to initial clinical presentation and patient's ab initio prognosis.

Secondary malignancies in childhood. Most knowledge on second cancer risk in patients treated for childhood Hodgkin's disease comes from the Late Effect Study Group. Updated results from 1,380 patients treated from 1955 to 1986, with a median follow-up of 10.7 years, have been recently reported [82]. In this series, 104 second cancers developed (73 solid tumours including 46 tumours within radiation fields, 26 ANLL and 5 NHLs) leading to an overall 15-year cumulative incidence rate of 9%. The rates were 6% and 4% for solid tumours and ANLL, respectively. The median time to second cancer was shorter for ANLL (4.4 years) than for solid tumours (13.8 years). In this series, most solid tumours developed within radiation fields. The most common were localized to the female breast (14 cases; RR = 66) and thyroid (12 cases). The cumulative incidence of secondary breast cancer at 40 years of age was 32%, confirming that the risk for breast cancer is higher in patients irradiated as children or adolescents than in patients irradiated over age 40 years [78, 83]. Children and adolescents are also at higher risk than adults for developing secondary bone sarcoma, connective tissue sarcoma or thyroid cancer [84]. Since the treatment of Hodgkin's disease is similar in children and adults, it can be concluded that, for these localizations, children are more sensitive to ionizing radiation effects than are adults. A significant association between secondary ANLLs and previous administration of alkylating agents has been reported with higher doses inducing higher risks; the risk of ANLL and that of NHL also correlated with splenectomy [46, 56, 82]. Host factors such as age and gender might also influence the risk for secondary cancer. In a series of 191 children of whom 109 were initially treated with radiation alone, 15 patients subsequently developed a second tumour 6–20 years after the diagnosis of Hodgkin's disease for a 15-year cumulative incidence rate of 12%. The rates were 24% in females (10 cases) and 5% in males (5 cases) with a relative risk for female compared with male patients of 4.5 (P = 0.013) [85]. The 15 patients who developed a second tumour were all irradiated and 4/10 second tumours in females developed in breast emphasizing the role played by irradiation in the genesis of second cancers.

In the last two decades, most if not all studies focused on the potential risk for occurrence of a second tumour in relation to initial Hodgkin's disease treatment or to a specific agent. Recently, other factors (such as alterations in the retinoblastoma locus, germ-line mutations in p53, congenital or acquired immunodeficiency states) have emerged as predisposing factors on the risk for developing a second tumour [84]. Though not yet related to solid tumours secondary to Hodgkin's disease, the impact of host factors should certainly be considered in the future beyond that of the treatment itself.

Quality of life in long-term survivors

Treatment-related acute and chronic medical as well as psychosocial complications can interfere with Hodgkin's disease survivors' quality of life [86–88]. The range and magnitude of psychosocial problems (physical impairments, social and familial morbidity, sexual, discrimination in employment and in obtaining insurance) observed in Hodgkin's disease survivors have been only recently explored [89, 90]. Psychological and social disturbances are usually reported during and after treatment [89–92]. The actual problem of the quality of life in long-term survivors has been addressed in only a few studies, most of them being not comparative. In 1995, a study was conducted to compare the type and frequency of psychosocial difficulties among 93 French adult Hodgkin's disease survivors (4 to 17 years since treatment) with that of 186 healthy controls using a population-based case-control design [4]. Hodgkin's disease survivors expressed more limitation in physical activities than controls because of residual physical (P < 0.001) and role-functioning (P < 0.001) impairments, persistence of dyspnea (P < 0.001) and chronic fatigue (P = 0.025) as measured by the EORTC QLQ-C30 core questionnaire [93]. These results were in agreement with those previously reported in hospital series [89, 90, 94]. Hodgkin's disease survivors also more often expressed difficulties (P = 0.015) in concentration or in remembering things than controls as previously reported [95, 96]. Global health status was equally scored as good by patients and controls while data in the literature are conflicting [89, 94, 96]. In the Joly et al. study, just as in a majority of cancer quality of life studies, no major late psychological or psychiatric distress were observed in both survivors and controls [94, 97, 98], while psychologically vulnerable cancer patient groups who remain distressed over time have been described [99].

Familial disturbances are of great concern among long survivors of cancer. Data on interpersonal relationships and sexual activities are conflicting. In the Joly et al. study, patients experienced less separations or divorces but similar sexual activity compared with controls, and changes in relationships with friends were less frequent in cases than in controls who also reported to have lost more friends [4]. Whereas married status at the time of diagnosis can influence survival, altered marriage practices were very limited among survivors from childhood and adolescent cancers as were changes in relationships with close friends as a result of the illness [87, 89, 100, 101]. Other studies demonstrated that long-term Hodgkin's disease survivors might experience more frequent separations and divorces than in the general population [89, 92]. Gen-
eral satisfaction with sex life or more changes in interest in sex and attractiveness have been reported [87, 90]. Although children were less frequent in cases than in controls, often related to chemotherapy-induced sterility, French patients expressed familial projects at the same magnitude as controls; familial relationships appeared to be satisfactory and did not influence the level of the quality of life, in contrast to what was observed in studies focusing on adolescent long-term survivors [92, 102].

Of the French newly diagnosed cancer patients who were working at the time of disease, 64% reported returning to work after treatment [103]; however, work post changes were mentioned by 38% of patients which is in agreement with the Joly et al. study [4]. In the latter study, Hodgkin's disease survivors more frequently reported less professional ambition as if, preferring to have more modest goals giving more time to enjoy life, they chose not to run after success as described by Siegel and Christ [87]. In contrast, compared with their situation before the disease developed, patients enrolled in the Stanford series reported having an increased professional ambition [90]. These conflicting results must be tempered since, in the Stanford series, no control group was available; the study was performed in 1985 in patients treated 1 to 21 years beforehand and involved people of different education. Most Hodgkin's disease survivors associate work-related problems with their illness [87, 94]. Work-related problems are reported in long-term cancer survivors concerning promotional and income prospects, closely related with problems getting bank loans or difficulties with insurance companies [89, 94, 96]. Even in patients cured from their disease, problems regarding insurance and bank loans remain a major difficulty for long-term survivors along daily life as well as in professional life, in particular in those who wish to treat their own firm [89, 90, 104]. Although society remains slow to integrate the improved prognosis of Hodgkin's disease patients into its perception of them and into its employment and insurance policies, Hodgkin's disease survivors seem to have learned to cope with problems related to their disease and its treatment.

Causes of death

The risk of dying from specific causes after Hodgkin's disease has been reported in limited studies. In 1986, Rubin et al. reported no significant difference between overall survival and survival corrected for second cancer mortality in a series of 320 clinical stage I–IV patients, while the EORTC reported a 5% difference in the 15-year survival rates between crude and corrected survival in a series of 1,501 clinical stage I–II patients [74, 105]. Similar findings were reported by the Stanford University group, the International Database on Hodgkin's Disease (IDHD) and the British National Lymphoma Investigation (BNLI) [23, 86, 106]. In patients cured of Hodgkin's disease, intercurrent deaths represented the first cause, followed by secondary cancer- and treatment-related deaths [23, 106, 107]. Intercurrent deaths were mainly caused from cardiovascular and infective complications.

The risk of dying from cardiac failure was investigated in four series. In a cohort of 957 patients diagnosed with Hodgkin's disease between 1942–1975, 25 coronary heart disease deaths were observed, giving a death rate relative to the general population rate of 0.91, not significantly different from 1 [18]. In contrast, the RRs of death were 1.97 (P < 0.001) in the Dutch series [108], 3.2 (P < 0.01) in the Stanford series [23], 2.8 (P < 0.001) in the IDHD series [personal communication], and 8.63 (P < 0.001) in the EORTC series [107]. Factors affecting death from cardiac failure were heart irradiation as part of the mantle-field irradiation in almost all series, and male gender. In the Stanford series, a mediastinal radiation dose above 30 Gy was associated with an increased risk (RR = 3.5) and patients treated with radiation therapy alone had a higher risk than those treated with combined modality therapy; the cumulative probability of dying from cardiac failure was 15.5% in males and 3.5% in females [21]. In this series, the risk of dying from acute myocardial infarction or from other cardiac disease was much greater when patients were treated before the age of 20 (RR = 44.1 and 21.5, respectively); that of acute myocardial infarction decreased thereafter (from 7.3 in patients aged 20–29 to 1.8 in patients aged 50 or above) but remained significantly increased at all ages, whereas the risk of dying from other cardiac disease remained increased in patients younger than 40 only (RR = 8.8 and 4.8 in patients aged 20–29 and 30–39, respectively). The risk of both myocardial infarction and other cardiac disease-related death also significantly increased with time from initial Hodgkin's disease treatment.

In the Stanford series, infective deaths concerned opportunistic infection, pneumonia and chronic disease, and asplenic sepsis [23]. They were as frequent as cardiac deaths and were not influenced by the administration of previous MOPP chemotherapy. They might, however, have been a consequence of mediastinal and lung irradiation, splenectomy, or both. In patients treated with a combination of irradiation and MOPP, total nodal irradiation was shown to significantly increase the risk of dying from other causes (4 ANLL and 5 infections in 74 patients) than disease progression compared with mantle and paraaortic irradiation (1 infection in 121 patients) [109]. Infective deaths represented 35% of all intercurrent deaths which occurred in 774 patients aged 15–29, who remained disease-free in the BNLI series [106]. In the IDHD series, infective deaths represented 34% of all intercurrent deaths, corresponding to a RR of 9.0 (P < 0.001) (personal communication).

Overall, the risk of dying from causes other than Hodgkin's disease progression was analyzed relative to
that of the general population (matched for sex, age and country) in the IDHD series on all stages, and in the EORTC series on early stages. In the IDHD series, the risk was 2.01 in males and 2.30 in females; it was 2.07 in early stage patients and 2.13 in advanced stage patients [86]. The risk increased with time from initial treatment, from 1.79 in the 0-4-year period to 3.08 in the 15-19 year period; in contrast, the risk decreased with age at Hodgkin's disease diagnosis, from 4.13 in patients aged 15-19 to 1.42 in patients aged 60 or above. In this series, the 20-year cumulative probability of dying from intercurrent disease was above that of dying from Hodgkin's disease progression. In the EORTC series, patients cured from Hodgkin's disease had a risk of dying from causes unrelated to the disease itself multiplied by 3.11 (P < 0.001) compared to that of the general population [107]. The risk was higher in females than in males (RR = 3.28 and 3.06, respectively); it was higher in patients aged 15-39 at diagnosis than in patients aged 40 and above (RR = 3.46 and 2.85, respectively). The risk increased with time from initial treatment, from 1.91 in the 0-2-year period to 3.85 in the 15-17-year period with a peak (RR = 5.79) during the 9-11-year period. Similar findings were observed in males and in females; they were also observed in patients aged 15-39 and in older patients.

Finally, in the Stanford series, the loss in the 20-year survival rate was 7% due to death from a malignancy other than Hodgkin's disease; it was 7% due to death from acute myocardial infarction [23]. In the EORTC series, second cancer and cardiac failure (sudden deaths of unspecified cause excluded) were responsible for a difference in the 20-year survival rate of 7.3% and 5.7%, respectively [107]. The BNLI reported a 5.5% difference (deaths from all causes included) at 20 years between observed and expected survival rates in patients aged 15-29 [106]. In the IDHD series, deaths unrelated to Hodgkin's disease and its treatment were responsible for a decrease in the 15-year survival rate of 7% [86].

Conclusion

Long-term nonmalignant as well as malignant complications are seen because the treatment of Hodgkin's disease is successful. Nonmalignant complications are likely to be treatment-related, though some problems might be associated with the disease itself. Modern irradiation techniques, new combination chemotherapies and new strategies should concur to decrease incidence rates. Even malignant complications are mostly treatment-induced; the exact role of radiation therapy (dose and volume) as risk factor for solid tumours remains to be assessed. Oncologists who nowadays tend to propose chemotherapy as the unique treatment in all stages Hodgkin's disease should carefully balance between the risk of radiation- and chemotherapy-related malignant (leukaemias and solid tumours) and nonmalignant complications. Treatment duration should also be considered because the longer the treatment, the higher the probability of psychological distress. Most patients who achieve remission remain disease-free as well as free of serious complications. Nonetheless, Hodgkin's disease survivors should be carefully followed at regular intervals to help prevent or early diagnose complications which can occur long after the patient has been cured. An attempt should also be made by the medical community to convince society, life insurance companies and banks that they can help Hodgkin's disease survivors enjoy a normal life.

Dedication

This paper is dedicated to patients who daily face problems with courage. Their voluntary participation in treatment and follow-up protocols have helped the medical community to better understand the aetiology of these complications.

References


Correspondence to:
Dr. Michel Henry-Amar
Centre François Baclesse
Service de Recherche Clinique
Route de Lion-sur-Mer, B.P. 5026
F-14021 Caen cedex, France