Complications of thoracic radiotherapy

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Summary

The issue of toxicity is a primary concern for chest irradiation, because it is a dose-limiting toxicity and because in some circumstances it can alleviate the survival benefit of radiation therapy. Potential acute and delayed side effects can compromise the patients’ prognosis and generate significant morbidity. Here we review on chest complications of radiation therapy, with focus on cardiac and pulmonary radio-induced side effects. Most radiographic changes associated with thoracic irradiation are asymptomatic. However, chest irradiation generated by treatment of breast cancer, bronchopulmonary malignancies, or mediastinal lymphoma has been associated with a risk of acute radiation pneumonitis and late lung fibrosis. An increasing number of clinical studies suggest that some dosimetric factors (e.g. V20, V30, mean lung dose) should be considered for limiting the risk of lung toxicity. Improvements in radiation techniques as well as changes in indications, volumes and prescribed doses of radiation therapy should help to better spare lungs from irradiation and thus decreasing the risk of subsequent toxicity. Numerous other contributing factors should also be considered, such as chemotherapeutic agents, smoking, tumor topography, or intrinsic sensitivity. Cardiac toxicity is another clinically relevant issue in patients receiving radiation therapy for breast cancer or for lymphoma. This life threatening toxicity should be analyzed in the light of dosimetric factors (including low doses) but also associated systemic agents which almost carry a potential for additive toxicity toward myocardium or coronaries. A long-term follow-up of patients as well as an increasing knowledge of the underlying biological pathways involved in cardiac toxicity should help designing effective preventing strategies.

External beam radiotherapy is a major treatment in the management of cancer. However, exposure of healthy tissues to radiation and the toxicity it causes often limits its effectiveness. In particular, chest radiation causes a variety of acute and late complications that affect the patient’s prognosis and compromises functional outcomes. This chest irradiation can be observed under
different conditions, particularly in the treatment of breast cancer, pleuropulmonary cancer, and mediastinal lymphoma. The lungs, heart, but also the esophagus, brachial plexus and the mammary glands are among the major structures at risk that are exposed to chest radiation. In order to minimize iatrogenic radiation, it is imperative to take these complications into account when delivering radiotherapy to tumors above the diaphragm. This is a review of the main clinical and molecular mechanisms underlying acute or late toxicity associated with radiotherapy to the chest area. Radiation-induced cancers are beyond the scope of the present study.

**Pulmonary radio-induced toxicity**

**Pathophysiology and clinical presentation**

Pulmonary irradiation is observed in four main clinical situations: during radiotherapy for locally advanced non-small cell lung cancer or localized small-cell carcinoma, radiotherapy for esophageal cancer, the treatment of supra-diaphragmatic malignant lymphomas and adjuvant radiotherapy for breast cancer. The main risk of pulmonary radiation is radiation pneumonitis. There are typically two types of radiation-induced pneumonitis: acute radiation pneumonitis and late pneumonitis.

**Acute radiation pneumonitis**

Acute radiation pneumonitis occurs in the majority of cases between 6 and 12 weeks after the end of thoracic radiotherapy [1]. During the first hours of pulmonary exposure to ionizing radiation, functional and morphological changes occur in type II pneumocytes. A few hours later, some vascular alterations appear such as disjunction of the basement membrane and changes associated with congestive perivascular edema, while perfusion decreases in lung zones exposed to ionizing radiation. Then, and up to the sixth month, moderate interstitial edema, as well as inflammatory infiltrates, and moderate anergic pneumocyte proliferation occur [2]. This phase is usually asymptomatic. There are no specific clinical signs. Usually dyspnea and wheezing occur, sometimes accompanied by a non-productive cough, possibly with crackles on auscultation. A subtle change in the patient’s general condition and a low-grade fever may complete the picture. Laboratory tests may show a non-specific inflammatory syndrome. Unlike the clinical picture whose clues tend to be vague, a chest radiograph frequently shows early signs (in about half the cases). These images are reminiscent of confluent alveolar and interstitial infiltrates in the irradiated field. The chest CT scan is more sensitive, depicting the presence of linear opacities simulating fibrosis, bronchioalveolar lavage (BAL) can be useful to eliminate possible initially infectious differential diagnoses. BAL generally unveils lymphocytic alveolitis, the outcome of which is usually favorable, with or without treatment. Although the level of evidence is low, corticosteroids can accelerate symptomatic improvement after the elimination of an infectious cause. In exceptional cases, there is adverse progression to acute respiratory distress syndrome (ARDS) [3]. Rarely does one observe a picture of *bronchiolitis obliterans* with organizing pneumonia (BOOP). The clinical picture is that of non-specific pneumonitis simulating infectious pneumonia, arising immediately after radiotherapy. Imaging depicts sparse and migratory alveolar opacities. This rare entity is observed during radiotherapy for breast cancer, mainly when it is associated with concomitant tamoxifen therapy [6,7]. The clinical picture is very steroid sensitive.

**Late fibrosis**

Late pneumonia occurs approximately 6 months after the end of thoracic radiotherapy. It is a virtually constant radiologic feature which stabilizes two years after the end of treatment. It can arise in the absence of acute pneumonia. From a pathological point of view, this phase coincides with the replacement of the inflammatory infiltrate by fibrosis and obliteration of the capillaries causing chronic ischemia. This fibrosis may lead to chronic restrictive respiratory failure, a rare occurrence, and even death (exceptional). Its most common clinical manifestation is bronchiectasis. There are several levels of late pulmonary toxicity (SOMA-LENT, CTCAE, RTOG-ERTC) with variations in therapeutic behavior from one level to another making it difficult to compare the different studies according to the rate and grade of pneumonia observed (table 1). Corticosteroids are used for the different grades of toxicity. The incidence of radiation pneumonitis after breast radiotherapy ranges between 4.5% and 63% in the literature. This variability is closely related to the definition of radiation pneumonitis, is not consistent across studies (radiological or clinical definition? requiring corticosteroids or not?). Here, most lung fibrosis and radiation-induced pneumonitis are asymptomatic due to the small irradiated lung volume and the low dose delivered.

**Dosimetric factors**

The irradiated lung volume and the radiation dose are the main factors responsible for pulmonary toxicity after thoracic radiotherapy. The use of dose-volume histograms (HDV) can accurately assess the dose delivered to the lungs and estimate the theoretical risk of radiation pneumonitis with a clinical impact.

**Lung cancer radiotherapy**

There is a direct correlation between the dosimetric parameters of lung radiotherapy (volume, dose) and the risk of developing a complication in the form of radiation pneumonitis. Most of the data available on radiation-induced
pulmonary toxicity were obtained from studies on radiotherapy for non-small cell lung cancer (NSCLC), because high doses are delivered to the lungs in this setting. Emami et al. investigated the tolerance of healthy tissues and emphasized that the risk of developing severe radiation pneumonitis at 5 years was 5% at a dose of 45 Gy delivered to one third of the healthy lung volume, 30 Gy to two-thirds of the lung volume and 17.50 Gy when the entire lung is exposed [8]. Thus there is a strong correlation between the total lung volume receiving 20 Gy (V20 Gy) and the severity of pneumonitis. When the V20 Gy is less than 8%, the risk of radiation pneumonitis is almost zero. In contrast, when the V20 Gy is between 22 and 31%, the risk of grade 2 radiation pneumonitis is 8% [9]. The volume receiving 30 Gy is another important parameter. When the V30 Gy is less than 18%, the risk of radiation-induced pneumonitis is probably marginal. However, the risk attained 24% when the V30 Gy was higher than or equal to 18% [10]. With the advent of more sophisticated radiotherapy techniques such as intensity-modulated radiation therapy (IMRT), the current problem is low doses received by total lung volume. Indeed, this technique reduces the volume receiving high doses, but significantly increases the volume receiving lower doses [11,12]. However, the lung volume exposed to doses below 20 Gy should also be taken into account because this is associated with a risk of acute or late pulmonary toxicity [13]. There is therefore, a correlation between the V5 Gy and the occurrence of radiation pneumonitis. The incidence of grade 3 or more severe pneumonia is 3% when the V5 Gy is less than or equal to 42%, and 38% when the V5 Gy exceeds the 42% threshold (P = 0.001) [14]. In the case of stereotactic lung radiation therapy, other authors showed that a V25 Gy exceeding 4.2% was a significant factor associated with radiation-induced grade 2 or more severe pneumonitis [15]. Finally, the average dose (Dav) delivered to the lungs exerts an impact on the risk of grade 2 radiation pneumonitis with a zero rate for Dav of 0–8 Gy, 11% for 8–16 Gy, 18% for 16–24 Gy and 25% for 24–36 Gy [16]. To reduce the risk of radiation-induced pneumonitis to less than 20%, the V20 Gy must be less than or equal to 30–35% and the Dav must be less than or equal to 20–23 Gy [17].

Adjunct radiotherapy for breast cancer

Lung exposure linked to breast radiotherapy is lower and cases of radiation-induced pulmonary lesions are rare. Firstly, lung dosimetry constraints in the case of breast radiotherapy were based on the experience acquired during radiotherapy of NSCLC. More specific factors were identified. The lung distance measured between the lung limit and the central edge of the radiation beam (called the central lung distance, CLD) reflects the irradiated lung volume. The CLD is correlated with the irradiated lung volume during conventional radiotherapy using two tangential beams [18]. This volume corresponds to 0.5–0.6% per millimeter of irradiated lung depth [19]. However, the apical region of the lung is irradiated when a beam is used for the supraclavicular area. Consequently, radiation-induced pneumonitis develops in

| Table 1 |

| Late lung radiation toxicity scoring |

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RTOG criteria</strong></td>
<td>Asymptomatic or mild symptoms (dry cough)</td>
<td>Moderate symptomatic fibrosis or pneumonitis (severe cough)</td>
<td>Severe symptomatic fibrosis or pneumonitis</td>
<td>Severe respiratory insufficiency</td>
</tr>
<tr>
<td></td>
<td>Slight radiographic appearances</td>
<td>Low-grade fever Patchy radiographic appearances</td>
<td>Dense radiographic changes</td>
<td>Continuous O2</td>
</tr>
<tr>
<td><strong>SOMA-LENT scale</strong></td>
<td>Asymptomatic or mild signs (cough)</td>
<td>Symptomatic moderate fibrosis Non-radiological confluent opacities</td>
<td>Symptomatic fibrosis or severe lung disease Radiological confluent opacities</td>
<td>Severe respiratory failure Use of corticosteroids intermittently</td>
</tr>
<tr>
<td></td>
<td>Discrete radiological signs</td>
<td>O2 discontinuous</td>
<td>O2 continuous</td>
<td></td>
</tr>
<tr>
<td><strong>CTCAE (v4.03)</strong></td>
<td>Asymptomatic, radiographic findings only</td>
<td>Symptomatic, not interfering with ADL</td>
<td>Symptomatic, interfering with ADL O2 indicated</td>
<td>Life-threatening Ventilatory support indicated</td>
</tr>
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CTCAE: Common Terminology Criteria for Adverse Events; RTOG: Radiotherapy Oncology Group.
the peripheral lung during single breast radiotherapy and in the apical regions if nodal irradiation is delivered [20]. The CLD is a quick and simple indicator and the maximum lung thickness included within the tangential beams should not exceed 25 mm during conformal radiotherapy for breast cancer. The maximum length of the irradiated lung (maximum lung distance, MLD) is also often used. There is also a correlation between the risk of radiation pneumonitis and the average value of the ipsilateral lung volume receiving 20 Gy (V20 Gy) in patients treated for breast cancer. The incidence of radio-induced pneumonia is less than 1% for V20 Gy and less than 7% when two tangential beams are used. Multiplying the number of beams to treat the lymph nodes significantly increases the V20 Gy by 20–30% and the incidence of radiation-induced pneumonitis to between 7.5% and 11.5% [21–23]. It is noteworthy that there is usually no direct link between clinical symptoms and radiological changes observed in the radiation field. Patients who received radiotherapy to lymph nodes (supraclavicular and internal mammary chain) were not found to exhibit more symptomatic radiation-induced pneumonitis than patients who received breast radiotherapy alone, even though the lung volume included in the radiation field was much higher.

Mediastinal radiotherapy for hematological malignancies
Early-stage Hodgkin’s lymphoma is treated with combined radiotherapy and chemotherapy with excellent response and overall survival achieving approximately 90% [24]. However, the occurrence of late complications may significantly alter the quality of life of survivors [25]. Late pulmonary complications of radiation therapy mainly depend on the dose and the size of the radiation beam [26]. Extensive supradiaphragmatic mantle field irradiation delivered for Hodgkin’s lymphoma is associated with radiation pneumonitis rates ranging from 3–31% depending on the radiotherapy techniques used. The risk factors for the development of radiation pneumonitis are total lung irradiation, prior chemotherapy and the radiation dose [27–29]. New radiotherapy techniques using more conformal radiotherapy and smaller beams and also lower doses reduce the risk of radiation pneumonitis [29]. Moreover, combining chemotherapy such as ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) and mediastinal radiotherapy leads to an increased risk of pulmonary toxicity [30–32]. Thus, the risk of all grades of radiation pneumonitis is about 10% in patients treated for Hodgkin’s disease with ABVD-based chemotherapy followed by conformal mediastinal radiotherapy. The main dosimetric risk factors are an average dose delivered to the total lung volume (mean lung dose MLD) ≥ 13.5 Gy and the V20 Gy ≥ 33.5% or more [33]. The risk of symptomatic radiation pneumonitis (grade 2 and above), however, is lower with modern radiotherapy techniques and does not exceed 3%. The MLD and a V20 Gy exceeding 36% and 13.5 Gy appear to be threshold values to be considered in the context of “involved-field” mediastinal radiotherapy, i.e. treating initially invaded lymph nodes area [29]. Using the “involved node” technique, which exclusively irradiates initially invaded lymph nodes, reduces the irradiation volume, and thus the dose to the lungs. The PET scan needs to be incorporated but treatment planning has not yet been validated as a standard of care [34,35]. Standard “involved-field” radiotherapy at a dose of 30 Gy for localized Hodgkin’s disease achieves complete remissions after three to four cycles of chemotherapy [36].

Other contributing factors
In addition to dosimetric risk factors, other factors may add to the risk of developing radiation-induced pulmonary toxicity, such as the use of concomitant chemotherapy or factors inherent in the patient such as the presence of pre-existing lung disease, impaired lung function, smoking and a genetic predisposition.

Concomitant radio-chemotherapy
Concomitant systemic treatments in the context of radio-chemotherapy are risk factors for radiation-induced pneumonitis. There are no specific recommendations for lung dose constraints for concomitant radio-chemotherapy. The only recommendations apply exclusively to radiation therapy alone without concomitant chemotherapy. Taking into account the ipsilateral lung volume receiving 20 Gy and 30 Gy also seems relevant in the context of concomitant radio-chemotherapy, which is now the standard of care for locally advanced inoperable lung cancer [37,38]. However, some drugs significantly increase the risk of complications because they increase normal tissue radiosensitivity. Thus, a combination of thoracic radiotherapy and chemotherapy with gemcitabine in a phase I trial was associated with a 30% incidence of grade 3 pneumonitis in patients treated for stage III non-small cell lung cancer [39]. The use of gemcitabine is therefore forbidden in combination with thoracic radiotherapy.

“Recall pneumonitis” phenomena have rarely been reported in the literature. They correspond to pneumonia in a previously irradiated territory following subsequent chemotherapy (anthracyclines, gemcitabine, etoposide, vinorelbine, taxanes) [40]. They may also be observed after exposure to targeted therapies such as sunitinib [41,42].

Combined chemo-radiotherapy in locally advanced breast cancer does not appear to significantly increase the risk of radiation pneumonitis. A phase I–II trial evaluated the administration of bi-weekly and concomitant paclitaxel with radiotherapy for locally advanced breast cancer. No radiation pneumonitis was reported after a median follow-up of 32 months [43]. Caution should however be exercised as other teams have reported radiation pneumonitis in 19% of patients treated with concomitant paclitaxel. However, the rate was 16% in patients receiving the combination in a sequential manner [44].
Hormone therapy can also increase this risk, since co-administration of tamoxifen and adjuvant breast radiotherapy is associated with a doubling of the risk of pulmonary fibrosis in the axillary and supraclavicular fields. Indeed, tamoxifen could stimulate the secretion of transforming growth factor beta (TGFβ), which accelerates chemotaxis and the activation of neutrophils, T lymphocytes, monocytes and fibroblasts caused by radiotherapy [45]. This excess risk of radiation pneumonitis was not observed during synchronous administration of aromatase inhibitors [46].

**Smoking**

The impact of smoking on the risk of radiation pneumonitis has been extensively discussed. Traditionally, smoking was considered a risk factor for radiation pneumonitis [47]. However, relatively recent data in the literature report conflicting data and suggest that smoking may play an independent protective role [48]. Takeda et al. reported a protective effect of tobacco when tobacco consumption was relatively low, but the inverse relationship was observed for heavy smoking, the latter increasing the risk of severe radiation pneumonitis in patients treated with stereotactic radiotherapy for stage III NSCLC [49]. However, the impact of smoking is primarily in terms of comorbidities, such as chronic obstructive pulmonary disease (COPD) and associated ventilatory disorders, which may increase the symptoms associated with lung irradiation and the risk of symptomatic radiation pneumonitis. Pulmonary function tests with measurement of the DLCO should be included before radiotherapy [50].

**Topography of lung cancer**

Topographical factors can have an impact on the risk of radiation-induced pneumonitis. The risk appears to be increased when the tumor is located in the lower lobe [51]. This could be explained by better functionality with better ventilation and thus better oxygenation of the lower part of the lungs. Radiation of the lower lobes will therefore exert a greater clinical impact. It also appears that tumors of the lower lobes are more susceptible to respiratory movements, and therefore require larger beams for adequate dosimetric coverage [52].

**Intrinsic radiosensitivity**

Individual susceptibility to ionizing radiation exists because some patients develop pulmonary toxicity despite compliance with dose constraints. Cytokine (IL-6 and IL-10) and growth factor (TGFβ1) involvement are among the phenomena implicated in radiation-induced fibrosis and the destruction of lung parenchymal architecture [53,54]. Several studies have attempted to correlate the levels of these circulating molecules and the risk of pulmonary toxicity in order to select patients for possible escalated or de-escalated doses of radiotherapy. In a prospective study of 96 patients treated for stage IIA-IIIB NSCLC and evaluating predictive molecular factors of pulmonary fibrosis with bioassays (IL-6, TNF alpha, TGFβ1 and IL-10) performed before and at 6 months of therapy, only dosimetric factors were significantly correlated with late pulmonary fibrosis in the multivariate analysis [55]. More conclusive results have been reported regarding the association between these molecular factors and the risk of acute radiation pneumonitis [56]. These assays were still in the field of research and failed to demonstrate a clinical impact. However, radiological opacities corresponding to radiation pneumonitis outside the radiation fields suggest that there are immunological factors involved in the onset of radiation pneumonitis [20,57].

**Cardiac toxicity**

Late cardiotoxicity due to chest irradiation occurs in two contexts: radiation therapy for breast cancer and lymphoma. These two malignancies carry a relatively better prognosis than lung cancer, and prolonged survival is achieved.

**Pathophysiology and clinical presentation**

Early cardiotoxicity resulting from radiation-induced cell damage is directly related to the activation of apoptosis, necrotic phenomena, and to damage inflicted on the vascular endothelium, leading to an increase in vascular permeability and stromal edema. In some rare cases, early pericarditis can be observed. Delayed cardiac lesions are irreversible and multifactorial. They are associated with the occurrence of epithelial nuclear atypia and the development of multinucleated fibroblasts in the stroma, resulting in changes in the intima of vessels, fibrinoid necrosis, hyalinization of the tunica media, multiple micro-thrombi and finally, parenchymal atrophy. Thus, irradiation can cause cardiac fibrosis and thinning of the pericardium, which may in some cases generate constrictive pericarditis, myocardial fibrosis, or endothelial fibrosis causing valvular heart disease, coronary artery disease with fibrosis of the coronary arteries, or accelerated atherosclerosis [58–61]. The clinical presentation is not specific, and depends on the irradiation site and location of fibrotic rearrangements. There are numerous common pathways between radiation-induced vasculopathy and the fibrotic process, which are both characterized by an inappropriate secretion of components of the extracellular matrix. Irradiation activates the transcription factor nuclear factor kappa-B (NF-kB), which triggers vascular inflammation through regulation of proinflammatory factors such as tumor necrosis factor (TNF)-α or IL-6 [62]. At the same time, production of reactive oxygen species by irradiation also activates production of transforming growth factor beta1 (TGFβ1) in various mesenchymal or epithelial cells. In turns, TGFβ1 converts fibroblasts into myofibroblasts, which activate inappropriate collagen deposit [63]. Although cardiomyopathy induced by radiation occur only with high doses or if it is given in combination with anthracyclines, radiation can cause cardiovascular complications with an
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increased risk of cardiac mortality by heart doses of less than 5 Gy for patients treated for breast cancer and childhood cancer. In the myocardium, complications are mainly due to interstitial fibrosis characterized by proliferation of bands of collagen separating and/or replacing cardiomyocytes. As cardiomyocytes are much less radiosensitive than endothelial cells, little is known about myocytes damage induced by radiation which appears to be a consequence of microvascular damage, ischemia and fibrosis [64].

Cardiotoxicity after breast radiotherapy

Adjuvant radiotherapy is a standard therapy for the treatment of breast cancer after conservative surgery and mastectomy with a reduced risk of death from breast cancer at 15 years of 3.8%, RR = 0.82, 95% CI = (0.75–0.90), P = 0.00005 [65]. However, this benefit in local control and survival can be offset by the occurrence of cardiac complications. Numerous studies have evaluated the impact of dosimetric criteria (dose per fraction, total dose and dose distribution) in the occurrence of cardiovascular toxicity after breast radiotherapy. With a median follow-up of 15 years, the EBCTCG (Early Breast Cancer Trialists’ Collaborative Group) collaborative group showed a significant 27% increase in cardiac mortality (OR = 1.27, 95% CI = 13–41%) after breast radiotherapy in 23,500 patients [66]. This excess cardiovascular mortality offsets the benefit of radiotherapy in terms of overall survival, especially in the lower risk group for which the expected benefit of radiotherapy is marginal in terms of overall survival. Other large studies conducted in women who received radiotherapy from 1970 to 1980 (with older radiotherapy techniques) showed that the mortality rate was higher when patients were irradiated for cancer of the left breast, compared to the right breast. The ratio of cardiac mortality was 1.58 in 115,165 patients, 15 years or more after the initial diagnosis of cancer (95% CI = 1.11 to 1.82, P < 0.0001) [67]. A Swedish study confirmed greater cardiac mortality following left breast irradiation in 89,407 patients (OR = 1.10, 95% CI = 1.03 to 1.18, P = 0.004) [68].

A cohort of 27,283 patients treated in the 1970s demonstrated that mortality from ischemic heart disease at 15 years was significantly increased at 13.1% (95% CI = 11.6 to 14.6) for women treated for cancer of the left breast versus 10.2% (95% CI = 8.9 to 11.5) for women treated for cancer of the right breast (P = 0.02) [69]. This excess cardiac mortality has not been found in more recent studies using modern radiotherapy techniques, but the incidence of cardiac events is higher for tumors of the left breast. Thus, a study of 35,825 patients treated between 1976 and 2006 showed that the relative risk of myocardial infarction was increased (RR = 1.22, 95% CI = 1.06 to 1.42), as was that of angina (RR = 1.25, 95% CI = 1.05 to 1.49), pericarditis (RR = 1.61, 95% CI = 1.06 to 2.43), and valvular heart disease (RR = 1.54, 95% CI = 1.11 to 2.13). A history of heart disease was instrumental in the occurrence of a cardiac event (RR = 1.58, 95% CI = 1.19 to 2.10) [70]. The advent of new radiotherapy technologies should help reduce this excessive cardiac mortality and significantly lower cardiac exposure compared to these long-term results with older radiation techniques. In addition, the indications for radiotherapy have evolved over the last decades. For example, indications for irradiation of the internal mammary chain, which increases the rate of cardiac exposure, are now challenged and therefore less frequently used. In parallel, the delineation of organs-at-risk and the analysis of dose distribution to identify new dosimetric constraints are likely to limit the likelihood that these side effects will occur later. Thus, a British prospective study analyzed the doses delivered to the heart and coronary arteries based on lateralization of the radiation delivered by two tangential beams (n = 50 patients). The average dose delivered to the heart was 2.3 Gy to the left breast versus 1.5 Gy to the right breast, and similarly the average dose received by the anterior interventricular artery (IVA) was 7.6 Gy for the left versus 1.6 Gy for the right breast [71].

A recent study published by Darby et al. provided further insights on the risk of ischemic coronary heart disease in a large cohort of breast cancer patients receiving radiotherapy [72]. They incorporated systemic agents or individual risk factors at time of radiotherapy and tried to establish correlations between dose to the heart and the risk of coronary disease. Authors reported that there was a linear correlation between the mean dose to the heart and the risk of coronary event. This risk increased by 7.4% per Gray. The estimated dose to the whole heart was only 4.9 Gy (range, 0.03–27.72), but the authors did not evidence a threshold for cardiac toxicity, suggesting that even low doses can generate cardiovascular morbidity. The increase in coronary events began within the first 5 years after radiation therapy. Then, it continued into the third decade after completion of the radiotherapy course. Some chemotherapeutic agents such as anthracyclines, 5-fluorouracil, taxanes or more recently, HER2 signaling pathway inhibitors, such as trastuzumab or lapatinib, are widely recognized risk factors for cardiovascular toxicity. Some of these agents have been validated in the adjuvant setting for the treatment of breast cancer, and they increase the potential cardiac risk associated with radiotherapy [61]. Radiotherapy-induced cardiotoxicity should be part of a multifactorial approach. Adjuvant chemotherapy significantly increases the risk of developing cardiovascular toxicity. Fumoleau et al. compared the incidence and risk factors for left ventricular dysfunction in patients receiving epirubicin-based adjuvant chemotherapy for breast carcinoma [69]. The frequency of ventricular dysfunction at 7 years was 1.36% (95% CI = 0.85 to 1.87) when patients received an anthracycline versus 0.21% (95% CI = 0.00 to 0.52) otherwise (P = 0.004) and the two significant risk factors for toxicity were age ≥ 65 years and a body mass index > 27 kg/m2. Pinder et al. examined the
toxicity of adjuvant anthracyclines in approximately 43,000 patients followed up for breast carcinoma aged 65 and over [73]. The adjusted hazard ratio for congestive cardiac dysfunction was 1.26 (95% CI = 1.12 to 1.42) for patients aged 66 to 70 years treated with anthracyclines compared to patients treated with other drugs. The highlighted risk factors for cardiotoxicity included the existence of cardiovascular risk factors (hypertension, dyslipidemia, coronary artery disease). Left versus right breast irradiation was not considered significant [70]. However, patients may develop subclinical cardiomyopathy which exerts a significant impact with a more prolonged follow-up. Potential patient-related risk factors should be more accurately identified when evaluating the cardiotoxicity induced by breast cancer treatments. However, chemotherapy and radiotherapy are not normally combined (except for very locally advanced tumors treated with concomitant radio-chemotherapy) and one of the main topics addressed these recent years concerned breast radiotherapy and systemic treatments such as trastuzumab. This monoclonal antibody targets HER2, which is overexpressed in approximately 15–20% of breast cancers and activates several intracellular signaling pathways involved in the proliferation and survival of tumor cells [74]. Trastuzumab proved beneficial in the metastatic and adjuvant settings for patients with tumors overexpressing the HER2 receptor [75,76]. Cardiac events are frequently reported in patients receiving trastuzumab. The toxicity of trastuzumab differs from that induced by radiotherapy because it is reversible (type II toxicity), whereas radiation-induced damage is irreversible (type I toxicity) [61]. The HER2 receptor is involved in the survival of cardiomyocytes and the development of embryonic heart cells. This pathway is also involved in the sympathetic-vagal balance [77–79]. The cumulative incidence of heart failure was 2.9% in the N9813 adjuvant trial and 4.1% in the B-31 adjuvant trial [78,79]. In the HERA trial, the rate of cardiovascular toxicity was lower [77]. Only 4% of patients permanently discontinued treatment because of cardiovascular toxicity, including decreases in asymptomatic ventricular ejection function. The main difference between this study and the two previous ones was that trastuzumab was administered in a sequential manner and not concomitantly with radiation therapy [77]. There are no data regarding the long-term risk of cardiac deaths after targeted therapies (trastuzumab or bevacizumab) associated with breast irradiation. However, although it has not been demonstrated that radiotherapy combined with trastuzumab significantly increases the incidence of symptomatic cardiac events, one should be very careful when delivering such adjuvant radiotherapy, for example, by using modern techniques to reduce the dose to the heart or by avoiding if possible radiotherapy of the internal mammary chain which is currently being debated [80].

### Cardiotoxicity after radiotherapy for mediastinal lymphoma

Mediastinal radiotherapy plays an important role in the management of malignant lymphomas above the diaphragm. However, this cardiac exposure to ionizing radiation is a cause of toxicity and mortality. Cardiovascular diseases are the third leading cause of death among survivors of Hodgkin’s lymphoma. In three large studies totaling 4553 survivors treated between 1960 and 1990 who received mediastinal radiotherapy, cardiovascular disease were observed in 9.4% to 16% of deaths [81–83]. Mortality of cardiac origin can be explained by the occurrence of coronary artery disease, heart failure, myocardial fibrosis and valvular disease [82]. Similarly, among 1,474 patients treated between 1965 and 1995, the survivors were found to have an increased incidence of cardiovascular disease by a factor of three to five compared to the general population, and a cumulative incidence of 24% after a median follow-up of 18.7 years [84]. Several studies have shown that the rate of death from myocardial infarction was 2.2 to 7.6-fold higher in patients who received mediastinal radiotherapy for supradiaphragmatic lymphoma compared to the general population [85]. Stanford University recently recommended routine screening for coronary heart disease in surviving patients who had previously received radiotherapy [86]. As described earlier in the chapter on pulmonary toxicity, the development of therapeutic modalities and in particular, the abandonment of extensive prophylactic nodal radiotherapy above the diaphragm, as well as modern radiotherapy techniques have allowed us to significantly reduce the dose to cardiac structures, including the coronary arteries, and should reduce the incidence of cardiac toxicities. It is noteworthy that adding mediastinal radiotherapy to first-line anthracycline-based chemotherapy, most likely contributes to the incidence of cardiovascular side effects. The causes of cardiotoxicity after treatment of lymphoma are multifactorial (radiotherapy and chemotherapy). Radiation-induced myocardial fibrosis leads to restrictive cardiomyopathy with impaired diastolic function in 12–83% of cases after 15 to 17 years of follow-up [87,88]. Indeed, anthracyclines result in impaired systolic function. In a cohort of Dutch patients followed up for Hodgkin’s disease, the cumulative incidence of heart failure at 25 years was 7.5% after radiotherapy alone and 10.7% when patients received a combination of anthracycline-containing chemotherapy and radiotherapy [84].

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