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Cardiovascular mortality and morbidity following radical radiotherapy for lung cancer: is cardiovascular death under-reported?

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Abstract

Background

Lung cancer is the most common malignancy worldwide. Radical radiotherapy is an essential treatment in the management of early and locally advanced lung cancer. Cardiac events are known to occur following radical radiotherapy for lung cancer. This study examines the burden of cardiac events post radiotherapy, and estimates the accuracy of death certification in patients who received radical radiotherapy for lung cancer.

Methods

We conducted a retrospective observational cohort study for all patients receiving radical radiotherapy for non-small cell lung cancer (NSCLC) at a large cancer centre between 01/01/2010 to 31/12/2016. Baseline cardiovascular disease and cancer status and treatment data were collected, along with hospital admission data and documented cause of death from the national registry for a median follow-up period of 34 months.

Results

Of 1224 patients included in the analysis, 378 (30.9%) patients had cardiovascular disease at baseline, including 140 (11.4%) with prior myocardial infarction. In the 846 patients without known cardiovascular disease, 451 (53.3%) had a QRISK2 predicted 10-year cardiovascular risk >20% over 10 years. During follow-up, 215 hospitalisations occurred (Incidence rate 6.2 per hundred patient years) which were classified as primarily cardiac, and 622 patients died (18 per 100 patient-years). However, death certificates stated a primary cardiac cause of death in only 33 cases (5.3% of deaths). Notably, 29% of patients dying out of hospital and certified as cancer death did not have documented cancer relapse prior to death, and 61% had no community palliative care input prior to death, implying these events may have been sudden and unexpected.

Conclusion

There is a high prevalence of baseline cardiovascular disease in people undergoing radiotherapy for NSCLC, accompanied by significant rates of post-radiotherapy cardiovascular hospitalisation. However, only a small proportion of deaths are attributed to cardiovascular disease, together with the large amount of sudden deaths observed, this suggests that cardiovascular death is greatly under-reported in official statistics.

Introduction

Lung cancer is the most commonly diagnosed cancer worldwide, affecting more than 14 million people annually[1]. Every year, lung cancer causes more than 1.6 million deaths, which is greater than breast, colon and prostate cancers combined[2]. Similarly, in the UK, lung cancer is diagnosed in in excess of 46,000 people each year and is the leading cause of cancer related death[3]. Smoking is the primary cause of lung cancer in more than 80% of patients[4]. The incidence of lung cancer has fallen in the UK in the last 10 years, owing primarily to the reduction in male smoking, while the incidence of female lung cancer has risen. An increasing proportion of lung cancer patients, however, are non-smokers[1].

More than 85% of lung cancers in the UK are now diagnosed as Non-Small Cell Lung Cancer (NSCLC)[5]. Over 40% of patients with NSCLC have metastatic disease at diagnosis, often due to lack of specific early cancer symptoms[5]. Other patients are diagnosed with either early (stage I or II) or locally advanced (stage III) disease. Traditionally, surgery has been the standard treatment of early and a proportion of locally advanced NSCLC in suitable individuals. A large percentage of lung cancer, however, is diagnosed in elderly patients with multiple comorbidities and poor lung function[6]. Improvements in radiotherapy technology and delivery has led to increasing numbers of these patients, who are medically unfit for surgery, receiving fractionated radical radiotherapy, stereotactic ablative radiotherapy (SBRT), sequential or concurrent chemoradiotherapy.

It is widely acknowledged that thoracic radiotherapy can affect the heart and great vessels. Long term follow-up studies in the setting of breast cancer[7, 8] and lymphoma[9,10] have demonstrated that cardiac events are associated with radiotherapy that delivers even low doses to the heart. Interest in cardiac damage following lung cancer radiotherapy surged with the results from RTOG 0617 study[11], which showed that radiation dose to the heart, specifically cardiac V5 and V30 (volume receiving more than 5 and 30 Gray) was implicated in worse survival outcomes for patients treated with radical chemoradiotherapy.

Since then, there have been numerous other studies, and a recent meta-analysis[12] attempting to establish relationships between cardiac dose and survival. However, much of the research up to now has focused on overall survival, without examining cardiac specific episodes such as hospital admissions from cardiac events and cardiac related death. This study aims to investigate the incidence of cardiovascular specific hospital admissions and cardiac related death in the setting of radical radiotherapy for NSCLC.

Methods

All patients diagnosed with NSCLC and who received radical radiotherapy at the Leeds Cancer Centre, UK, from 01/01/2010 to 31/12/2016 were included in the study. Radical radiotherapy is defined as radiotherapy given with intention of cure and consists of stereotactic body radiotherapy (SBRT), fractionated radical radiotherapy (FRRT) or chemoradiotherapy (given either concurrently or sequentially). Electronic health records containing primary care and secondary care information for each patient were reviewed. Patient demographics, tumour diagnosis and treatment information were collected. Hospitalisation episodes with cardiac events were collected by reviewing local secondary care records and discharge summaries. Information regarding cardiovascular disease (CVD) related medications at diagnosis of lung cancer was also collected. These included statins, antiplatelet agents (aspirin, ticagrelor, clopidogrel and dipyridamole), angiotensin converting enzyme inhibitors/angiotensin II receptor blockers (ACE-I) and beta receptor blockers (BB). For patients under the age of 80 with no previous history of CVD, QRISK2 score was calculated[13]. QRISK2 is a clinically validated tool which estimates 10-year risk of cardiovascular disease.

Official mortality and morbidity data were acquired from Public Health England, in particular to define the causes of death (from the Office of National Statistics database) and hospital admission (from Hospital Episodes Statistics). Cause of death data includes the primary cause of death and place of death according to the certifying physician. Hospital admissions data include primary and secondary diagnosis for each hospital admission episode, coded according to ICD-10 (International statistical classification of diseases and related health problems – version 10) criteria. The primary

diagnosis was used to define the main diagnosis of each hospital admission episode. Cardiac hospitalisation and cardiac death are defined by ICD 10 codes for myocardial infarction/angina/ischaemic heart disease (I20-I25), heart failure (I50), arrhythmias (I47-I49), non-rheumatic valve disease(I34-I37) and atypical chest pain (R07). A cardiac death is defined by primary cause of death (part 1a) on death certificates, which includes myocardial infarction/angina/ischaemic heart disease (I20-I25), heart failure (I50), arrhythmias (I47-I49), non-rheumatic valve disease(I34-I37). A lung cancer death is defined by ICD 10 code C34. A respiratory related death is defined by ICD 10 codes for pneumonia(J09-J18), COPD(J44) and lower respiratory tract infection(J20-22). Death from other cancers is defined by ICD10 codes for cancers other than lung cancer.

This study has received NHS Regional Ethics Committee (REC) approval. Permission from the REC and the national Confidentiality Advisory Group (CAG) was gained for usage of data from local and national databases.

Statistics:

IBM SPSS statistics version 25 was used for statistical analysis. Descriptive statistics were performed. Statistical significance was defined as $P<0.05$. Categorical data was analysed using Chi squared tests. Unpaired T test was used for continuous data.

Results

1224 patients were included, with a median follow-up period of 34 months. 378 patients were diagnosed with cardiovascular disease at baseline, of which 140 had previous myocardial infarction (MI), 124 had prior angina or ischaemic heart disease, 45 patients had heart failure, 91 had arrythmias and 15 had valvular disease. Cancer and radiotherapy treatment demographics are summarised in table 1. Of patients with no previous CVD, 53.5% had QRISK2 of more than 20, which predicts a 20% or more risk of cardiovascular events in 10 years. Patients with CVD at baseline were significantly older, had earlier stage disease and more radiologically diagnosed tumours than patients without CVD.

There were 215 hospitalisation events due to cardiac cause following radiotherapy in 179 patients. More than one cardiac hospitalisation occurred in 26 patients. Of all cardiac hospitalisation events, there were 68 related to myocardial infarction, 15 to angina, 14 to ischaemic heart disease, 5 to valve disease (all aortic stenosis), 65 to heart failure, 26 to arrythmias, 2 to myocarditis and 20 to atypical chest pain. Demographics of patients who had a cardiac event are summarised in table 2, compared to patients who did not have cardiac hospitalisations. Patients who experienced cardiac hospitalisations, were more likely to have CVD at baseline, as well as radiologically diagnosed tumours.

830 patients had died at the time of the study, of whom 622 had causes of death available. Only 33 patients had death certification based upon post mortem examination. 260 patients died at home or in nursing home (HN), and 322 patients died in hospital or hospice (HH). For 40 patients, the death location was unknown. Documented cause of death data is summarised in table 3, for HN and HH patients. Whilst 71% of deaths in the HN group were documented as cancer related, only 40% of patients who died in HH were recorded as having cancer-related death. 34% of deaths in the HH group were attributed to respiratory related death, although only 11% in the HN group has a documented respiratory related death. Of these patients, those who died at HN had higher rate of post radiotherapy cardiac hospitalisations and lower rate of documented disease relapse, including relapsed disease outside the chest. For patients who died at HN and certified as cancer death, 29% did not have documented disease relapse, and only 39% had community palliative care input prior to death, suggesting in the majority, death was unexpected and sudden.

Discussion

The study population is typical of the patient group diagnosed with non metastatic, NSCLC in the UK, with respect to age, sex, smoking habits and performance status[14]. Over 30% of patients in this study had prior diagnosis of CVD, and over 10% had prior MI. This is greater than the prevalence of CVD in the general population, which is less than 10%[15]. However, in comparison to patient groups with known diagnosis of COPD and similar age demonstrate, similar rates of ischaemic heart disease are

observed[16]. It is likely that this still represents an underestimate of the real burden of CVD in the population, especially amongst females[17]Indeed, patients without a history of CVD exhibited high predicted risk of developing CVD in the future, as more than half had a predicted 10-year event rate >20% according to a clinically applied UK-validated prediction model. Together, these demonstrate that the study population is one with high existing CVD burden and would be expected to be prone to future cardiac events.

There has been a high number of cardiac hospitalisations following radiotherapy treatment. Most cardiac hospitalisations occurred within the first two years of radiotherapy, and this is consistent with reports from recent literature[12]. Cardiac hospitalisations took place mainly in patients with pre-existing CVD, however over 40% occurred in patients without pre-existing CVD. This further highlights the increased risk of cardiac events after thoracic radiotherapy in this population.

Only 5.3% of deaths in the study cohort were certified as primarily cardiac, which is substantially lower than the 25% of deaths in the general population that are believed to be caused by cardiovascular disease[15]. Unsurprisingly, most deaths are classified as cancer related, especially for patients who died at home. In this group of patients many had no diagnosed disease relapse following radiotherapy and very few received community palliative care input prior to death. This raises the suspicion that many who died at home could have died from causes other than cancer. Just 3.9% of deaths in the cohort were assessed with a post mortem examination and defining the likely cause of death in cancer patients can be complex. However, studies have shown that up to a third of death certificates could be incorrect and half of post mortems produce findings unsuspected

before death[18]. Lung cancer and its treatments predispose patients to CVD[19]. Interaction between radiotherapy and the heart in lung cancer is an area of current research and there are ongoing studies investigating potential mechanisms. A recently published study[20] found an association between mean cardiac radiotherapy dose and cardiac events as well as all-cause mortality in patients without pre-existing CVD. Future work in this area should take into account baseline CVD, cardiac specific hospitalisation and cardiac specific death.

Our data suggest the need for increased awareness of CVD in lung cancer patients. In our cohort, even established CVD was not well managed with evidence-based preventative medications at the time of lung cancer diagnosis, and many people continued to smoke. Furthermore, many people without known CVD had high predicted-cardiovascular risk, and so may benefit from consideration of CVD prevention strategies. Given than lung cancer radiotherapy may increase the risk of cardiovascular death, it is imperative that cardiovascular health is considered prior to starting radiotherapy treatment. Although evidence is lacking, this could take the form of a physician led assessment of CVD risk at time of lung cancer diagnosis. Our data should also prompt increased suspicion of cardiac related death in people dying without evidence of recent cancer progression, particularly if the death was sudden and unexpected. It is imperative that certifying physicians consider recording non-cancer causes of death in these circumstances, given the role of certification data in guiding future strategies to improve survival in people with cancer.

Major limitations of this study include the retrospective nature of data collection and patients from a single cancer centre. Death certificate information was also missing for a proportion of patients. A

major strength of this study is the inclusion of data from national database which complement local datasets. The data is strengthened by the fact that the study population had a long follow up period close to 3 years.

Conclusion

There is a high prevalence of baseline cardiovascular disease in people undergoing radiotherapy for NSCLC, accompanied by significant rates of post-radiotherapy cardiovascular hospitalisation. However, only a small proportion of deaths are attributed to cardiovascular disease, suggesting cardiovascular death is under-reported in official statistics.

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