Early mortality after radical radiotherapy

Project description

Unsurprisingly, death is a feared complication of any intensive therapy. This includes antineoplastic treatment. In recent decades, a stringent focus on death as a complication to surgery has resulted in a significant reduction in perioperative mortality rates [1]. An important step in this development has been the mutual understanding and definition of the risk period, i.e. the 30-day perioperative period. This indicator of quality has constituted a metric for interventions and has allowed comparison between centers.

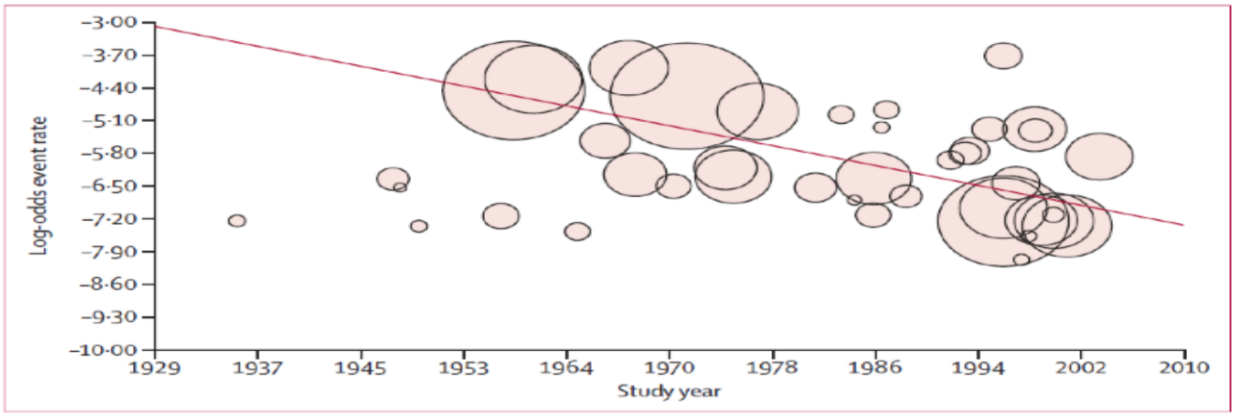

Figure 1. Development in perioperative mortality worldwide, every circle represents a single study. [1]

Radiotherapy is central in the treatment of most cancers and is associated with significant toxicity. Depending on the treatment site, radiotherapy may give rise to severe pain, infections, fatigue and weight loss, all of which contribute to an increased risk of treatment-associated death [2]. Despite a considerable technological development in radiation delivery, there is a substantial lack of studies addressing short-term mortality following definitive radiotherapy. In addition, there is no consensus on the metrics used to quantify this parameter. This hampers local and international comparison, complicating efforts to reduce early mortality rates.

The most intensive treatment regiments are radical radiotherapy with or without chemotherapy for head-neck and lung cancer, both of which are associated with significant acute morbidity and considerable rates of short-term mortality [3]. Treatment of these two cancers therefore serve as excellent models for developing systematic quality metrics for short-term mortality following radiotherapy with curative intent. In Denmark, approximately 900 patients with head-neck cancer and 600 patients with lung cancer (excluding stereotactic radiotherapy) receive radiotherapy with curative intent per year.

Cancer of the head-neck region is a common malignancy and overall rates in Denmark and worldwide are increasing [4,5]. Until the 1980s, the treatment in Denmark consisted of 33-34 dosage fractions with five fractions each week. However, based on successive randomized clinical trials, the intensity has increased with a higher number of weekly treatments, the addition of a radio sensitizer, and finally with the introduction of chemotherapy administered concurrent with radiotherapy [6]. While local control rates are approaching 75%, there are substantial short- and long-term side effects including mucositis, dysphagia, weight loss and fatigue [5]. Clinical trials only include patients in decent general condition, and this selection rarely reflects the

diversity of patients seen in normal clinical practice. Consequently, there is reason to be concerned that the toxicity effects observed in clinical trials are amplified on a population level.

In Denmark, approximately one in four head-neck cancer patients die within the first 12 months of curatively intended radiotherapy. Less than half of these deaths can be ascribed to cancer-specific causes and this discrepancy is most conspicuous the first year after treatment [7]. It is evident that malnutrition before, during, and after treatment is associated with an increased risk of complications and mortality [8,9]. A vast number of biomarkers have been studied in cancer patients and albumin levels before and after treatment appear to be associated with both cancer-specific and non-specific mortality [10]. However, so far studies have typically been hospital-based series limited by a low number of patients and without consensus on which biomarkers to use. In Denmark, serial measurements of albumin, hemoglobin and body weight have been prospectively registered along with other clinically relevant parameters in all head-neck cancer patients undergoing curative radiotherapy for the past 20 years and represent a unique source of information [11].

The overall 5-year survival of lung cancer patients is around 10%. Combined chemo- and radiotherapy delivered with curative intent is recommended to patients with locally advanced lung cancer. However, like in head-neck cancer patients, the intensive treatment comes at the cost of increased toxicity and early mortality rates are significant [12]. 90-day mortality rates above 10% have been reported and poor performance status, low BMI and increasing dose to the lungs have been associated with an early detrimental outcome [12,13].

Another possibly avoidable cause of early mortality following radiotherapy of both cancers is infectious complications, facilitated by immunosuppression, weight loss, and comorbidities. Neutropenia and infection are well-known risks following systemic antineoplastic treatment with chemotherapy [14], but knowledge on the frequency, timing and bacteriological spectrum of infections following radiotherapy is limited. Determining these factors is a necessary step to introduce interventions aimed towards reducing the risk of infectious complications following radiotherapy.

Research strategy

Aim 1: Characterization of incidence and causes of short-term mortality in Danish patients referred to radical radiotherapy for head-neck and lung cancer

Danish registries will be used to extract lists of patients dying within 90 and 180 days following first curatively intended radiotherapy fraction for head-neck and lung cancer. These two distinct periods are chosen, as it is not *a priori* known at which point cancer-related deaths begin to significantly outnumber non-specific deaths.

Date of first treatment for all patients treated with curative intent in Denmark between 1st of January 1992 and 31st of December 2017 will be extracted from the Danish Head and Neck Cancer Group (DAHANCA) database along with the central person registry identifier of the corresponding patient [11]. Thus, vital status at 90 and 180 days following first treatment can be determined through the central person registry. This will form the *Head-neck cancer early mortality database* foundation.

The multidisciplinary database covering Danish lung cancer patients does not contain radiotherapy treatment and outcome data in sufficient detail to constitute a starting point for a

short-term mortality database with meaningful radiotherapy treatment stratification. Consequently, the lung cancer patients treated with radical radiotherapy between 1st of January 2008 and 31st of December 2017 will be identified from institutional databases from the collaborating centers (Rigshospitalet, Herlev, Næstved, Odense, Aarhus, Vejle, and Aalborg) and form the *Lung cancer early mortality database* [15].

Using the databases, standardized mortality ratios (SMRs) are to be calculated as the relation between observed deaths in the cohorts and expected numbers obtained by multiplying survival time in the study cohort and mortality rates in the Danish population matched by age, gender and calendar period. As the exact cause of death in patients with a preceding cancer diagnosis is prone to misclassification, SMRs will also be estimated according to whether patients are considered recurrence-free or have known recurrence or residual disease. This information is available from the DAHANCA database and can be used in the head-neck cancer patients. This analysis will identify the period where excess mortality is most significant. For lung cancer patients the primary analysis will be on overall death, combining treatment-associated and cancer-associated death.

Subsequently, manual extraction of 20 consecutive patient charts in each cohort in the early mortality data will form a pilot study with qualitative review of the course of deterioration of the patient health. This qualitative pilot study will allow definition of a limited set of categories of non-cancer death causes. Following the pilot study, all patients treated in recent years in the early mortality databases are to be reviewed manually. This will be done by extracting charts from electronic patient records. Time to death and cause of death in the predefined categories will then be determined.

Aim 2: Identification of factors associated with increased risk of non-cancer mortality in the early phase after radical radiotherapy

In Danish head-neck cancer patients, hemoglobin, albumin and body weight are measured prior to radiotherapy treatment, at bi-weekly intervals during radiotherapy and at two months following treatment. Values are generally stored in the DAHANCA database, and will otherwise be available from patient files. It is hypothesized that data on hemoglobin, albumin and weight loss allows identification of head-neck cancer patients at high risk of early, non-cancer death. This hypothesis will be investigated in a nested case-control study using patients dying within the time interval previously chosen without prior disease progression as cases and patients alive at one year following treatment as controls. [11].

Prior to treatment, all lung cancer patients receiving radiotherapy with curative intent undergo a pulmonary function assessment. Based on these results, the individual patient's ability to tolerate radical radiotherapy is assessed. The main objective has been to ensure an adequate physical ability following radiotherapy. Pulmonary function assessment results of 30% of expected values are generally considered as the cut-off point for radical treatment. Given the intensity of the acute side effects with fatigue, risk of infections and loss of pulmonary function, it is plausible lower pre-treatment pulmonary function may influence the risk of early, non-cancer death [12]. To test the hypothesis, a nested case-control study will be conducted, using patients dying within the time interval previously chosen without prior disease progression as cases, and patients alive at one year following radiotherapy as controls.

Aim 3: Bacteremia in the early phase after radical radiotherapy

It is hypothesized that bacteremia is more frequent during or shortly after radical radiotherapy and that its presence contributes to the risk of early, non-cancer mortality. As part of the PERSIMUNE data warehouse (www.persimune.dk), microbiological data from all labs in

Denmark since 2010 can be assessed. In addition, the data warehouse contains nationwide information on biochemical analyses ranging back to 2014. Microbiological and biochemical data from the capitol region ranging back to 2005 and 2009, respectively, are available to some extent. Head-neck and lung cancer patients undergoing radical radiotherapy will be identified as previously described and the prevalence of bacteremia during and after treatment in the cohorts will be investigated. This will allow for an investigation of factors possibly associated with the development of bacteremia, among these chemotherapy treatment, performance status, smoking, and body-mass index. The prevalence and microbiological spectrum will be analyzed according to treatment characteristics and presence of leukopenia.

Collaborators

The Danish Head and Neck Cancer Group (DAHANCA)
Danish Oncology Lung Cancer Group (DOLG). The protocol was presented at the DOLG radiotherapy meeting Nov 23, 2018 at Rigshospitalet and supported by the group.
DCCC radiotherapy WP 14 (Biostatistics and modelling core).

National and international perspectives

The existence of population-based databases in Denmark represents a unique opportunity to investigate the incidence of early mortality following definitive radiotherapy. Identification of factors associated with this outcome would be relevant both nationally and internationally and enable interventions to improve survival. The project may also facilitate the establishment of systematic metrics for early mortality following definitive radiotherapy, which would have broad implications.

References

1. Bainbridge D, Martin J, Arango M, Cheng D. Perioperative and anaesthetic-related mortality in developed and developing countries: A systematic review and meta-analysis. Lancet 2012;
2. Citrin DE, Mitchell JB. Mechanisms of Normal Tissue Injury From Irradiation. Semin. Radiat. Oncol. 2017;
3. Spencer K, Ellis R, Birch R, et al. Caution is required in the implementation of 90-day mortality indicators for radiotherapy in a curative setting: A retrospective population-based analysis of over 16,000 episodes. Radiother Oncol 2017;
4. Carlander ALF, Grønhøj Larsen C, Jensen DH, et al. Continuing rise in oropharyngeal cancer in a high HPV prevalence area: A Danish population-based study from 2011 to 2014. Eur J Cancer 2017;
5. Corry J, Peters LJ, Rischin D. Optimising the therapeutic ratio in head and neck cancer. Lancet Oncol. 2010;
6. Baumann M, Krause M, Overgaard J, et al. Radiation oncology in the era of precision medicine. Nat. Rev. Cancer. 2016;
7. Boje CR, Dalton SO, Gronborg TK, et al. The impact of comorbidity on outcome in 12 623 Danish Head and Neck Cancer Patients: A population based study from the DAHANCA database. Acta Oncol (Madr) 2013;52(2):285–93.
8. Datema FR, Ferrier MB, Baatenburg De Jong RJ. Impact of severe malnutrition on short-term mortality and overall survival in head and neck cancer. Oral Oncol 2011;
9. Langius JAE, Zandbergen MC, Eerenstein SEJ, et al. Effect of nutritional interventions on nutritional status, quality of life and mortality in patients with head and neck cancer receiving (chemo)radiotherapy: a systematic review. Clin Nutr [Internet] 2013;32(5):671–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23845384
10. Moon H, Roh JL, Lee SW, et al. Prognostic value of nutritional and hematologic markers in head and neck squamous cell carcinoma treated by chemoradiotherapy. Radiother Oncol [Internet] 2016;118(2):330–4. Available from: http://dx.doi.org/10.1016/j.radonc.2015.10.029
11. Overgaard J, Jovanovic A, Godballe C, Grau Eriksen J. The Danish head and neck cancer database. Clin. Epidemiol. 2016;
12. Warner A, Dahele M, Hu B, et al. Factors Associated with Early Mortality in Patients Treated with Concurrent Chemoradiation Therapy for Locally Advanced Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2016;94(3):612–20.
13. Bowden JCS, Williams LJ, Simms A, et al. Prediction of 90 Day and Overall Survival after Chemoradiotherapy for Lung Cancer: Role of Performance Status and Body Composition. Clin Oncol [Internet] 2017;29(9):576–84. Available from: http://dx.doi.org/10.1016/j.clon.2017.06.005
14. Vento S, Cainelli F, Temesgen Z. Lung infections after cancer chemotherapy. Lancet Oncol. 2008;
15. Barthelemy-Brichant N, Sabatier J, Dewé W, Albert A, Deneufbourg JM. Evaluation of frequency and type of errors detected by a computerized record and verify system during radiation treatment. Radiother Oncol 1999;
16. Rasmussen JH, Vogelius IR, Fischer BM, et al. Prognostic value of 18F-fludeoxyglucose uptake in 287 patients with head and neck squamous cell carcinoma. Head Neck 2015;