Towards better quality of life after radiation therapy by improved response modeling

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Radiumhemmets föreläsningssal, Karolinska Universitetssjukhuset, Solna.

Fredagen den 14 juni kl. 10.00

av
Eleftheria Alevronta
M.Sc

Huvudhandledare:
Docent Bengt Lind
Karolinska Institutet
Institutionen för onkologi-patologi
Medicinsk strålningsfysik

Bihandledare:
Professor Gunnar Steineck
Karolinska Institutet
Institutionen för onkologi-patologi
Klinisk cancerepidemiologi

Dr. Massoud al-Abany
Karolinska Institutet
Institutionen för onkologi-patologi
Klinisk cancerepidemiologi

Fakultetsopponent:
Professor Joseph O. Deasy
Washington University
Department of Radiation Oncology
Bioinformatics and Outcomes Research

Betygsnämnd:
Docent Alexandru Dasu
Linköpings universitet
Institutionen för medicin och hälsa
Medicinsk radiofysik

Docent Silvia Johansson
Uppsala universitet
Institutionen för radiologi, onkologi och strålningsvetenskap
Onkologi

Professor Karen Belkic
Karolinska Institutet
Institutionen för onkologi-patologi
Medical Radiation Physics

Stockholm 2013

ABSTRACT

Background: To improve the quality of life of radiotherapy cancer survivors we need to improve our knowledge of the dose, volume and time-response relations of radiotherapy induced late effects.

Aims: The aim of the thesis was to investigate predictors for normal-tissue complications of head and neck, and gynecological radiotherapy using response modeling. We aimed to study this effect by using existing and new normal-tissue complication models.

Methods: In this thesis, we included 72 patients, who had received external beam radiation therapy (EBRT) for head and neck cancer in Stockholm. Of those, 33 developed esophageal stricture to the proximal esophagus. Gynecological-cancer survivors were treated with pelvic-radiation therapy only or in combination with other treatments in the Stockholm and Gothenburg regions during 1991 to 2003 were also investigated. Dose-volume histograms (DVHs) of 519 gynecological cancer survivors and 73 head and neck cancer survivors were extracted from the treatment planning systems. The dose-effect relations between the symptom 'emptying of all stools into clothing without forewarning' and bowel organs and the anal-sphincter were investigated, considering additional possible risk factors. The dose-volume response relations for these organs at risk (OAR) were also investigated for 77 gynecological cancer survivors, who were treated with EBRT only. Moreover, the dose, volume and time-effect of the dose to the vagina and 'absence of vaginal elasticity' were investigated for 78 survivors treated with EBRT only. A novel model is proposed, describing the influence of follow-up time on the dose-response relations. To explore the dose-volume effect of the late complications the Relative Seriality, the Lyman and the gEUD models were fitted to the dose volume data. To investigate the dose-effects and the dose-time effects the Probit and the proposed Probit-time models were also used.

Results: The best estimates of the dose–response parameters indicated a steep dose-response relation for the radiation induced esophageal strictures for the period of 2001–2005. Mean doses higher than 50 Gy to the anal-sphincter and bowel organs were related with the occurrence of 'emptying all stools into clothing without fore-warning'. Dose to the anal-sphincter region and sigmoid seemed to be most relevant, but all OARs were found to have steep dose-responses for this symptom. According to the estimated volume parameters the investigated OARs do not show any volume effect for this endpoint. All the studied models had the same predictive power for the symptom as a function of the dose for all investigated OARs. The Probit-time model fit our data better than the pure Probit for 'absence of vaginal elasticity'. According to the volume parameter from the relative seriality, the vagina has shown a pronounced volume effect for this endpoint.

Findings: Dose-response relations and volume dependence were found for the radiation induced esophageal strictures. The EBRT dose to the bowel organs and the anal-sphincter were related to the occurrence of 'empty-ing of all stools into clothing without forewarning'. The mean dose to the vagina was related to the occurrence of 'absence of vaginal elasticity'. The steepness of the dose-response relation for the mean dose to the vagina and the symptom increased with time.

Implications: The risk of 'emptying of all stools into clothing without forewarning' might be lowered by delineating the anal-sphincter region and the sigmoid as well as the rectum and the small intestines during the treatment planning process. This thesis suggests radiobiological parameters for the proximal esophagus, the anal-sphincter region, the bowel organs and the vagina. Those parameters could be used in terms of avoiding the studied normal-tissue complications in the future. Finally, our findings suggest that the effect of time be considered at the time of treatment and communication with the patient.