Predicting and evaluating side effects of radiotherapy in cervical cancer

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Appendices

Summary

Nederlandse samenvatting

List of publications
and conference proceedings

Curriculum Vitae

Dankwoord

SUMMARY

Introduction

Each year, more than 900 women in the Netherlands are diagnosed with cervical cancer. Approximately one-third of these diagnoses is locally advanced cervical cancer, which is defined as having a tumor larger than 4 cm, invasion into nearby tissues or adjacent organs, and/or regional lymph node involvement. The standard treatment for women with locally advanced cervical cancer consists of external beam radiation therapy (EBRT) combined with concurrent chemotherapy, followed by image-guided adaptive brachytherapy. Recent data report favorable outcomes with this treatment, with 5-year locoregional control of 92%, overall survival of 82%, and disease-free survival of 73%. However, since healthy tissue in the pelvic area is unavoidably exposed to part of the radiation, the majority of the women develop short-term and/or long-term side effects, which could have a profound impact on quality of life. Additionally, bone marrow damage due to chemoradiotherapy could lead to hematologic toxicity, which is defined as a reduced number of circulating blood cells. Hematologic toxicity may negatively affect clinical outcomes of both the current standard treatment and promising therapies such as adjuvant immunotherapy.

Proton therapy offers highly localized dose deposition and can therefore more effectively reduce the dose to healthy tissue during EBRT as compared to the standard intensity-modulated photon therapy. Additionally, bone marrow sparing strategies in photon therapy planning allow for reduction of the bone marrow dose. Both techniques might reduce the risk of treatment-related toxicities.

The aim of this thesis was to investigate side effects in locally advanced cervical cancer treatment, with a particular attention to the potential benefits of proton therapy and bone marrow sparing.

Predicting side effects

This thesis started with two systematic literature reviews to identify variables that contribute to side effects in locally advanced cervical cancer. The whole pelvic bones receiving 10 Gy (V_{10Gy}) >95-75%, 20 Gy (V_{20Gy}) >80-65%, and 40 Gy (V_{40Gy}) >37-28% were associated with moderate or worse (grade ≥2) hematologic toxicity (**chapter 2**). Regarding gastrointestinal, genitourinary, and vaginal toxicity as well as insufficiency fractures (**chapter 3**), most studies have only investigated brachytherapy-related parameters, whereas the few studies evaluating EBRT parameters have found these to be associated with toxicities. While more research is needed, the observed relationships between EBRT dose and side effects suggest a role for proton therapy in reducing such toxicities.

Ideally, models predicting toxicity risk are used to optimize the radiation dose distribution during treatment planning or to identify patients that might benefit from advanced EBRT techniques such as proton therapy. However, such normal tissue complication probability (NTCP) models were not identified within the literature reviews. Data from the large, prospective PARCER study was used to develop NTCP models for gastrointestinal toxicity following postoperative (chemo)radiotherapy for cervical cancer (**chapter 4**). Higher bowel dose-volume parameters, namely V_{30Gy} and V_{40Gy}, were identified as risk factors for acute diarrhea and late persistent gastrointestinal toxicity. Other variables associated with late toxicity included the use of a less advanced EBRT technique, more extensive surgery, and the occurrence of acute diarrhea. These NTCP models should be further extended, validated with external data, and carefully implemented in routine care before these can be used clinically to predict side effects.

Evaluating side effects

An important aim of this thesis was to compare proton therapy with photon therapy for locally advanced cervical cancer treatment in the PROTECT study (**chapter 5**). Fifteen women were to be treated with bone marrow sparing chemoradiotherapy with volumetric-modulated arc photon therapy (VMAT) or intensity-modulated proton therapy (IMPT), followed by brachytherapy. The identified associations between pelvic bone dose and hematologic toxicity from the literature review in **chapter 2** were used as a starting point to implement bone marrow sparing strategies. Due to financial and logistical challenges, only the recruitment, treatment, and follow-up phases of the women treated with VMAT photon therapy have been completed up to now. Nevertheless, the findings in this first phase of the PROTECT study have provided valuable insights into changes in bone marrow and immune system function.

(Chemo)radiotherapy leads to bone marrow cell depletion, resulting in an increased fat content and a reduced production of immune cells. As a result, patients may develop hematologic toxicity. Water-fat MRI scans were used in the PROTECT study to measure changes in bone marrow fat fraction. These scans generate proton density fat fraction (PDFF) maps, which indicate the distribution of fat content throughout the body.

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Phantom and volunteer measurements were performed in **chapter 6** to validate the water-fat MRI scans. Phantom measurements showed excellent accuracy, repeatability, and reproducibility; and volunteer measurements demonstrated acceptable repeatability and reproducibility of the bone marrow PDFF measurements. This study demonstrated that longitudinal changes of more than 10 PDFF% can be detected with water-fat MRI. In **chapter 7**, changes in the vertebral and pelvic bone marrow PDFF due to chemoradiotherapy were evaluated for women treated with bone marrow sparing VMAT photon therapy in the PROTECT study. A mean vertebral dose greater than 1 Gy resulted in an increase in bone marrow PDFF, without post-treatment recovery when the vertebral dose exceeded 5 Gy. Despite the use of bone marrow sparing, immunosuppression occurred in all women, persisting up to twelve months post-treatment. These findings suggest that a threshold of 5 Gy should be considered while optimizing or evaluating dose-reducing techniques.

The immune cell composition and function of the bone marrow was evaluated using blood samples collected during the PROTECT study. These findings were exploratively compared with a historical cohort of women that were treated with older EBRT techniques without bone marrow sparing (**chapter 8**). Bone marrow sparing VMAT was not found to prevent immunosuppression, as it reduced the number of circulating immune cells and T-cell reactivity to antigens, but improved antigen-presenting capacity and proliferative capacity of T cells. Chemoradiotherapy changed immune cell composition by shifting focus from the lymphoid to the myeloid lineage, activating immune cells, and both increasing and decreasing immunosuppressive cell subsets.

Both **chapter 7** and **8** indicate that bone marrow sparing techniques should be optimized to minimize immunosuppression. Likewise, proton therapy holds potential for reducing bone marrow toxicity, but this should be evaluated in the ongoing PROTECT study.

Conclusion

Multiple factors contribute to side effects in the treatment of locally advanced cervical cancer. Models predicting toxicities, such as the NTCP models developed in this thesis, could play an important role in the future, particularly as support tools during treatment planning to optimize therapy and to identify patients at high risk of toxicity. Studies in this thesis showed that bone marrow is very sensitive to radiation dose and that the current chemoradiotherapy reduced the number and function of circulating immune cells up

to twelve months post-treatment, despite the use of bone marrow sparing strategies. These findings could be used to evaluate, improve, and implement bone marrow sparing strategies and proton therapy to gain more insight into the added value of these techniques in locally advanced cervical cancer treatment.