Predicting and evaluating side effects of radiotherapy in cervical cancer

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Chapter 9

General discussion and future perspectives

This thesis focused on predicting and evaluating side effects of radiotherapy in cervical cancer, with particular attention to the potential benefits of proton therapy and bone marrow sparing. These techniques have the potential to decrease dose to healthy tissue and therefore reduce treatment-related side effects. In this thesis, predictors for treatment-related side effects in locally advanced cervical cancer were identified in literature and mature data from a large trial was used to develop normal tissue complication probability (NTCP) models to estimate the risk of gastrointestinal morbidities in women treated with postoperative (chemo)radiotherapy for cervical cancer. Additionally, the phase-II PROTECT study was initiated, which aimed to compare bone marrow sparing intensity modulated proton therapy (IMPT) with bone marrow sparing volumetric-modulated arc therapy (VMAT) in women with locally advanced cervical cancer. In participants undergoing bone marrow sparing VMAT, changes in bone marrow fat fraction and immune cell composition and function were evaluated.

During the course of this thesis, outcomes of large trials investigating the current standard treatment (EMBRACE-II), adjuvant chemotherapy, and adjuvant immunotherapy have been reported. In this chapter, the main findings and implications of the studies presented in this thesis, as well as the future perspectives, are discussed and considered in light of the latest developments in the field.

9.1 PREDICTING SIDE EFFECTS IN CERVICAL CANCER

Knowledge of the factors contributing to treatment-related toxicities could aid in identifying women at high risk of side effects and in developing NTCP models. However, a comprehensive overview of predictors for treatment-related toxicities in women with locally advanced cervical cancer treated with definitive chemoradiotherapy was lacking. Systematic reviews identifying predictors for hematologic toxicity, gastrointestinal, genitourinary, and vaginal toxicity, and insufficiency fractures were conducted and provided in **chapter 2** and **3**. As there was a scarcity in prediction models, multivariable NTCP models for gastrointestinal toxicities in postoperative cervical cancer were developed and presented in **chapter 4**.

9.1.1 Predictors for hematologic toxicity

The systematic review in **chapter 2** found that the volume of 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.

These findings were used as a starting point for implementing bone marrow sparing VMAT in the PROTECT study. Whole pelvic bone constraints of V_{10Gy}<90%, V_{20Gy}<65%, and V_{40Gy}<15-20% were adopted as soft planning constraints, meaning that these dose limits are preferred but not mandatory. A planning study as part of the PROTECT project showed that a reduction of 2 Gy in bone marrow mean dose (D_{mean}) was achievable with a maximum increase of 1 Gy in the D_{mean} of other organs-at-risk (OAR), such as the bladder and rectum, when using VMAT [1]. Additionally, a clinical study demonstrated that the implementation of bone marrow sparing during treatment planning for cervical cancer did not increase grade ≥2 or 3 gastrointestinal toxicity and led to only a small increase in the already low incidence of grade ≥3 genitourinary toxicity, whereas overall incidence of hematologic toxicity was reduced [2].

Notably, in planning studies using IMPT, the whole pelvic bone constraints from the PROTECT study were already met without the use of bone marrow sparing strategies during treatment planning. An additional 1 Gy reduction in bone marrow D_{mean} was again achievable with a maximum increase of 1 Gy in the D_{mean} of other OAR [3]. However, associations between bone marrow dose and hematologic toxicity might be different with proton therapy, as its dose distributions differ from photon therapy. Future studies should explore the trade-off between reducing bone marrow dose and increasing dose to other OAR for both photon and proton therapy, to better understand the clinical consequences of bone marrow sparing on other OAR and to assess the potential for further bone marrow dose reductions [4].

9.1.2 Predictors for gastrointestinal, genitourinary, and vaginal toxicity and insufficiency fractures

The systematic review in **chapter 3** identified multiple predictors of gastrointestinal, genitourinary, and vaginal toxicity, as well as insufficiency fractures. Most studies only investigated brachytherapy-related parameters, whereas the few studies evaluating EBRT parameters have found these to be associated with toxicities. Data on insufficiency fractures was limited.

The relationship between EBRT dose and toxicity of an OAR is becoming more relevant with the introduction of advanced EBRT techniques, such as proton therapy and online adaptive EBRT. Although both techniques have the potential to lower OAR dose, robust dose-toxicity relationships, alongside clinical studies, are needed to clarify their added value in improving patient outcomes.

The systematic review included only one study on insufficiency fractures. Systematic reviews of insufficiency fractures in gynecological cancers have identified patient-related factors, particularly those affecting pretreatment bone quality, as contributors, but findings regarding the impact of radiation dose were inconsistent [5, 6]. Although bone marrow sparing and advanced EBRT techniques have generally not been developed or introduced with the primary aim of preventing insufficiency fractures, they have a large potential that could be explored further. Furthermore, consensus on strategies to prevent or manage insufficiency fractures is needed so that such strategies can be started when patients at high risk are identified [5, 6].

9.1.3 Current status of NTCP models

The majority of the included studies in **chapter 2** and **3** were rated as low quality based on the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) consensus statement or Quality In Prognosis Studies (QUIPS) tool [7, 8]. Tools such as TRIPOD and QUIPS could and should be used as guidelines during the model development process to obtain high-quality models and to give insight into the methodologies applied and their limitations.

Multiple studies only reported statistically optimized dosimetric thresholds for toxicity prediction. Cut-off values are easy to comprehend and to use in the clinic, but lose more detailed information [9]. Full NTCP models that include continuous dosimetric parameters could better inform during treatment planning. For instance, for brachytherapy planning, artificial intelligence (AI) based decision-support systems such as EviGUIDE and BRIGHT can visualize the impact of various brachytherapy treatment plans on dose to OAR [10, 11]. NTCP models could be integrated in these tools or tools developed for EBRT planning to translate treatment decisions into clinical outcomes. Additionally, NTCP models combining patient and baseline characteristics could be used to select patients for advanced EBRT techniques, such as proton therapy, which has already been implemented for head-and-neck cancer [12, 13].

9.1.4 NTCP model development

As the availability of NTCP models in literature was limited, NTCP models for gastrointestinal toxicity following postoperative (chemo)radiotherapy for cervical cancer were developed with the use of least absolute shrinkage and selection operator (LASSO) regression in **chapter 4**. Higher bowel dose-volume parameters, V_{30Gy} and V_{40Gy}, were selected for models for acute diarrhea and late persistent gastrointestinal toxicity. Additional risk factors for late toxicity which were identified included the use of three-dimensional conformal radiotherapy (3DCRT), as compared to the more advanced planning technique intensity-modulated radiation therapy (IMRT), more extensive surgery before (chemo)radiotherapy, and the occurrence of acute moderate or worse diarrhea.

Figure 1 visualizes the process of NTCP model development and implementation. NTCP modeling still faces several challenges. High-quality patient data from multiple centers is needed for model development and validation. Collected risk factors, endpoints, and dosimetric parameters and delineation methods differ among prospective studies, which limits the ability to develop generalizable NTCP models. Retrospectively collected data can also be used for NTCP modeling, but is less reliable and collecting data is a labor-intensive process. Ideally, informed consent and data should be collected prospectively from every patient attending the hospital. Initiatives aiming for a standardized registration of patient data, like PROton Therapy ReseArch RegIsTry (ProTRAIT) for patients eligible for proton therapy in the Netherlands, should become part of the clinical workflow [14].

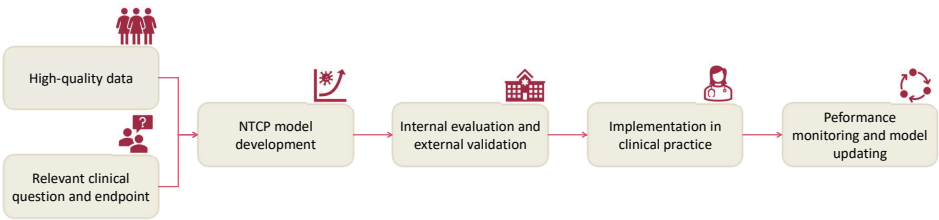

Figure 1: *Simplified flow chart of normal tissue complication probability (NTCP) model development and use in clinical practice*

There is currently no gold standard for NTCP model development. Variable selection can be performed using various statistical methods and selecting the method that best fits the data is critical. In **chapter 4** we used LASSO, which provides a simple model

with a limited number of variables. However, more complex models consisting of more variables might have a better prediction accuracy and would be useful when, for instance, the full dose-volume histogram is available. A standardized framework for NTCP model development that could be adapted to different situations would give support during model development.

The interest in AI in NTCP development is rising, as AI can use multidimensional input and detect relationships that could not be detected with conventional statistics. However, AI-based models require a lot of data, may be perceived as "black boxes" by clinicians, and raise ethical questions about accountability, data privacy, and sustainability. Therefore, AI-based modeling and models should be carefully introduced to prevent the development and use of unreliable, non-transparent or inapplicable models.

When high-quality NTCP models are available, the next challenge lies in integrating NTCP models into clinical practice. NTCP models estimate the risk of treatment-related toxicities, but interpreting the implications for individual patients and translating this to clinical decisions should be performed by physicians and eventually be incorporated into guidelines. Similar to the development of treatment planning guidelines and proton therapy indication models, the field should debate and reach consensus regarding the available evidence, acceptability of certain risks, and the use of NTCP models in clinical practice.

Lastly, when implemented in routine care, NTCP models should be continuously monitored for performance and recalibrated or updated when the clinical practice changes. As required by the medical device and AI regulations, quality assurance workflows should be established before NTCP models are implemented clinically.

9.2 EVALUATING SIDE EFFECTS IN CERVICAL CANCER

As proton therapy and additional bone marrow sparing constraints might reduce toxicities in women with locally advanced cervical cancer undergoing primary chemoradiotherapy, the phase-II PROTECT study was designed. As discussed in **chapter 5**, women were to be treated with bone marrow sparing chemoradiotherapy with VMAT or IMPT, followed by magnetic resonance imaging (MRI) based adaptive brachytherapy, to compare the two techniques in terms of dosimetric parameters, safety, oncological and quality-of-life outcomes, and immune response. Due to logistical and financial challenges, only the

recruitment, treatment, and follow-up phases of the women treated with VMAT have been completed. Nevertheless, the findings in the first phase of the PROTECT study have provided valuable insights into changes in bone marrow (**chapter 7**) and immune system function (**chapter 8**).

9.2.1 Bone marrow fat fraction changes

(Chemo)radiotherapy damages bone marrow, resulting in an increased fat content and a reduction in active bone marrow cells. As a result, patients might develop hematologic toxicity. In the PROTECT study, water-fat MRI scans were used to evaluate changes in the vertebral and pelvic bone marrow fat fraction due to chemoradiotherapy. Water-fat MRI can generate proton density fat fraction (PDFF) maps, which visualize the distribution of PDFF (the MRI-derived measure of fat fraction) throughout the body. The water-fat MRI scans used in the first phase of the PROTECT study were validated in **chapter 6**. Phantom measurements showed excellent accuracy, repeatability, and reproducibility, and volunteer measurements demonstrated acceptable repeatability and reproducibility of the PDFF measurements.

The validation study provided enough confidence to detect longitudinal changes in vertebral bone marrow PDFF greater than 10 PDFF% in the PROTECT study. Studies and clinics use various sequences, scan parameters, and reconstruction software for PDFF measurements, which are typically optimized in-house. Standardizing these protocols would make results more generalizable, encourage implementation into clinical practice, and improve the transferability of measurements between institutions [15]. In the PROTECT study, a balance had to be found between clinical feasibility and the image quality achievable with water-fat MRI protocols. The water-fat MRI protocols used were appropriate for longitudinal PDFF evaluation, but require further optimization in terms of scanning and reconstruction time for clinical use.

There are other modalities that could be used for bone marrow fat fraction imaging, including MR spectroscopy and dual-energy CT, which highly correlate with water-fat MRI measurements [16-18]. MR spectroscopy is considered the gold standard for in-vivo assessment of bone marrow fat fraction and measures the exact resonance frequencies of protons [19]. Dual-energy CT uses two x-ray photon energy spectra to characterize tissue composition [19]. However, MR spectroscopy is limited by the small voxel sampling in the heterogeneous bone marrow and the complex scanning, post-processing, and interpretation, while dual-energy CT uses ionizing radiation. In contrast, the water-fat

MRI sequence used in the PROTECT study can be added to routine MRI exams and allows for direct analysis of the PDFF map [15].

In **chapter 7**, changes in bone marrow fat fraction and immune cell counts were evaluated in the VMAT phase of 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 dose exceeded 5 Gy. Chemoradiotherapy led to immunosuppression, which was associated with mean vertebral PDFF and endured up to twelve months post-treatment. The threshold of 5 Gy could be considered while evaluating or optimizing dose-reducing techniques and should be validated in future studies.

Studies should explore whether PDFF could serve as a biomarker for monitoring bone marrow changes and predicting hematologic toxicity. It is important to note that PDFF is not the same as the mass fat fraction, as biological tissue also contains MR invisible material, but the two are closely correlated [20]. Studies identified associations between PDFF and multiple bone marrow characteristics, including bone mineral density, as measured with dual-energy X-ray absorptiometry (DXA), osteoporosis, and vertebral fractures [21]. Since PDFF is correlated with multiple bone marrow characteristics, the precise relationship between PDFF and hematopoietic function requires further investigation to enable clinical interpretation and application of PDFF.

The exact dosimetric threshold that distinguishes between reversible and irreversible increases in bone marrow fat fraction could not be determined due to the steep dose fall-off and the limited spatial resolution of the scans. However, the steep dose fall-off and the low dosimetric threshold of 5 Gy would advocate for the use of volume-based bone marrow sparing strategies to reduce the volume of bone marrow receiving a high dose. Multiple studies identified the bone marrow as a parallel organ, for which mainly the D_{mean} and low doses are important [22, 23], but as high doses are also associated with hematologic toxicity, (parts of) the bone marrow might have serial characteristics. More research is needed to clarify which doses have the greatest impact on hematologic toxicity and how bone marrow sparing can be optimized.

9.2.2 Immune cell composition and function

In **chapter 8**, immune composition and function changes in women treated with bone marrow sparing (BMS) VMAT in the PROTECT study were evaluated. BMS VMAT did not prevent reduced circulating immune cell numbers and T-cell responses to antigens,

but improved proliferative capacity of T cells and antigen-presenting capacity recovery. Chemoradiotherapy resulted in a shift from the lymphoid to the myeloid cell lineages with activation of both T cells and myeloid cells, indicating complex changes in immune regulation.

Research in cancer immunology is challenging. Studies report contradictory observations in immune cell subset changes due to (chemo)radiotherapy. These inconsistencies could be caused by the immune cells varying in distribution, radiosensitivity, and interaction with tumor sites, as well as differences in primary tumor histology, treated site, EBRT technique, dose schedule, and timing of blood sampling [24]. Investigating each of these factors is difficult as animal studies cannot be directly translated to humans and clinical trials are often not achievable or impractical for this purpose.

Reliable biomarkers can help predict treatment outcomes or select patients for adjuvant therapies [25]. Both baseline and radiation-induced lymphopenia were suggested to be associated with reduced survival in cervical cancer [26]. However, circulating lymphocyte numbers might be cofounded by comorbidities and are not specific to antitumor immunity [24]. Circulating immune cells subpopulations and programmed death ligand (PD-L) 1 might be more specific, but they are influenced by multiple factors and various pathways may contribute to the immune response [27]. A deeper understanding of immune responses in cervical cancer is needed to identify reliable biomarkers that can be used to predict treatment response, reduce treatment-related immunosuppression, and optimize adjuvant therapies.

9.3 FUTURE PERSPECTIVES

9.3.1 Incidence of cervical cancer

In 1996, the cervical cancer population screening program was introduced in the Netherlands. Dutch women between the ages of 30 and 60 are invited to undergo a smear test every five years [28]. The current tests detect high-risk human papillomavirus (hrHPV), which may cause cervical intraepithelial neoplasia that could progress to invasive cervical cancer. In 2010, the HPV vaccine was introduced into the Dutch immunization program. Currently, all girls and boys are vaccinated at the age of 10 years. The vaccine provides approximately 95% protection against hrHPV types 16 and 18 and offers up to 87% protection against cervical cancer. The first Dutch HPV-vaccinated cohorts are gradually entering the screening program and demonstrate a high effectiveness of the vaccine [29]. Nevertheless, participation in the screening program remains important [30].

The World Health Organization (WHO) has published a global strategy to eliminate cervical cancer, defined as fewer than 4.0 cervical cancer cases per 100,000 per year (Figure 2) [31]. A Dutch modelling study from the beginning of 2022 estimated that with the current vaccination rate and screening participation rate, cervical cancer in the Netherlands could be virtually eliminated by 2042 [32]. However, participation rates remain under pressure, with approximately 50% of invited women participating in the Netherlands, and are lower in women with a lower socio-economic status, whereas this group also has the most risk factors [33, 34]. Because cervical cancer is a preventable disease, vaccination and screening programs (should) have high priority.

Only a limited number of low to middle income countries have introduced the HPV vaccine and cervical cancer screening into their healthcare programs, despite having a much higher disease burden [31, 35]. Actions are needed to scale up and maintain prevention programs in these countries. Without a higher coverage with preventive interventions, the cervical cancer incidence will (continue to) increase over the next decades in these countries as the global population is growing and ageing [35]. Nevertheless, cervical cancer will remain a significant portion of the global cancer burden for women in the upcoming century.

***Figure 2**: 90-70-90 targets that must be met by 2030 for countries to be on the path towards cervical cancer elimination as determined by the World Health Organization (WHO) [31]. HPV = human papillomavirus*

9.3.2 Advanced radiotherapy techniques to reduce toxicities

9.3.2.1 Proton therapy

9.3.2.1.1 Recently published phase-II studies evaluating proton therapy for gynecological cancers

During the course of this thesis, two other prospective, single-arm phase-II studies evaluating the role of proton therapy in gynecological cancers have published their results [36, 37]. The APROVE study from Heidelberg, Germany (NCT03184350) included 25

patients with postoperative radiotherapy for cervical or endometrial cancer between 2017 and 2020. All patients completed IMPT according to protocol. With a median follow-up of 25.1 months, 7 patients (28%) experienced progressive disease, all located outside the radiation field except for one local recurrence, and no acute or late grade 3 gastrointestinal or genitourinary toxicities. The authors compared bone marrow-related outcomes with a retrospective cohort of 25 patients treated with IMRT between 2017 and 2023 and detected a significantly lower incidence of grade ≥2 hematologic toxicity (anemia, leukopenia, and thrombopenia) with IMPT (8%, v.s. 36% for IMRT) [38]. The second study was conducted in Boston, USA (NCT01600040) and included 21 patients undergoing postoperative radiotherapy for gynecological cancers [37]. With a median follow-up of 60.6 months, 2-year and 5-year progression-free survivals were 81% and 76% and no recurrences were in-field. Acute (<4 weeks), subacute (4 weeks – 3 months) and late (>3 months after treatment) grade 3 gastrointestinal toxicities were 14%, 0% and 4.7%, whereas there were no grade 3 genitourinary toxicities. Acute, subacute, and late grade 3 hematologic toxicities were 24% (lymphopenia or neutropenia), 9.5% (lymphopenia) and 4.7% (lymphopenia).

In both studies, proton therapy was considered as safe and well-tolerated. Toxicity numbers were lower or similar to the acute and late incidence of grade ≥3 gastrointestinal toxicity (11.9% and 3.3%) and genitourinary toxicity (0% and 1.3%) in women with postoperative cervical cancer treated with IMRT in the PARCER trial [39] and the late incidence of grade ≥3 gastrointestinal toxicity (3.7%) and genitourinary toxicity (2.8%) in the EMBRACE-II study [40].

The PROTECT study will evaluate intact locally advanced cervical cancer and will overcome some of the limitations from the two abovementioned studies. The PROTECT study includes a homogeneous patient group, all receiving the same standardized treatment, as well as a control group, enabling a direct comparison between photon and proton therapy. Both arms will consist of a prespecified number of patients receiving extended-field irradiation, as proton therapy is expected to be most beneficial for these patients [4]. Additionally, the PROTECT study will combine a library-of-plans, from which for each fraction a plan is selected that best fits the anatomy, with margins and robust optimization and evaluation to better account for the sensitivity of protons to range uncertainties [41-43].

9.3.2.1.2 Currently recruiting phase-II studies evaluating proton therapy for gynecological cancers

Besides the PROTECT study, two prospective, single-arm phase-II studies are currently recruiting patients with gynecological cancers for definitive treatment with proton therapy. A study in Aarhus, Denmark (NCT06462378) aims to recruit 55 women with locally advanced cervical cancer for treatment with proton therapy, concurrent cisplatin, followed by brachytherapy to assess acute grade ≥2 hematologic toxicity. A study in Pennsylvania, USA (PROPS GYN, NCT05758688) is currently recruiting 25 women with gynecological cancers for postoperative proton therapy to evaluate acute (<6 months after end of treatment) grade ≥2 gastrointestinal toxicity.

These studies together will offer valuable insights into the feasibility of proton therapy for this patient group and may identify potential benefits that warrant further investigation in larger trials. As the PROTECT study also collects various data types to monitor the immune response, differences between photon and proton therapy that may not (yet) be detectable at a patient level could be explored.

9.3.2.1.3 Proton therapy in the Netherlands

It was estimated in 2016 that 5,800 patients per year (11.6% of all radiotherapy patients) in the Netherlands would be eligible for proton therapy. The three proton therapy centers in the Netherlands have the license to treat in total 2,200 patients per year, but these estimates have not yet been reached due to several barriers [44].

Proton therapy is generally more expensive than photon therapy. A Dutch cost-analysis reported a mean cost ratio of 2.00 (societal perspective) and 4.41 (healthcare perspective) for 20 fractions of proton versus photon therapy for lung cancer [45]. For most cancers, a model-based approach is used to select patients who benefit most from proton therapy compared to other techniques, such as VMAT, which have been developed in recent years and also have improved OAR sparing. Selection is based on a national indication protocol for proton therapy (NIPP), which is developed per cancer type using high-quality prediction models. As shown in this thesis, such models are lacking for locally advanced cervical cancer and the studies presented in this thesis are the first steps in this process. Generating high-quality evidence requires substantial time, effort, and financial resources. However, since indirect costs are the largest cost component of proton therapy, treatment costs could be drastically reduced when using the maximum treatment capacity [45-47]. A balance should therefore be found between identifying patients who

have the greatest advantage and increasing the number of patients treated to optimize cost-effectiveness of proton therapy.

The complex logistics of proton therapy may also limit its adoption [44]. Logistical hurdles include the increased lead time due to proton and photon treatment plans comparison and difficulties in information exchange and communication between centers [44]. For the PROTECT study, careful coordination and planning was required as proton therapy would be delivered at Holland Proton Therapy Center (HollandPTC), whereas chemotherapy and brachytherapy would be administered at the referring centers. Effective collaboration between centers is essential to overcome these challenges.

9.3.2.1.4 Global availability of proton therapy

Proton therapy facilities are resource-intensive to set up and maintain and have a lower throughput compared with photon therapy facilities. In May 2025, proton therapy facilities were only available in 24, mainly high-income, countries (Figure 3) [48, 49]. The incidence of locally advanced cervical cancer is, however, three times higher in countries with a low human development index (HDI) and mortality rates are six times higher than in very high-HDI countries [35].

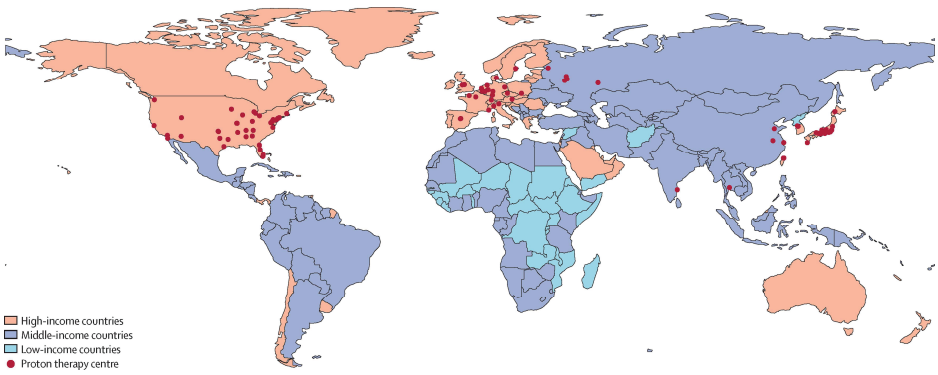

Figure 3: *Global distribution of proton therapy centers in operation (June 2023). Since the publication of this figure, Norway has also opened two centers, resulting in 24 countries with proton therapy facilities. Countries are categorized on the basis of the World Bank's world development indicators. Reprinted from The Lancet, 24, Yan et al., Global democratization of proton radiotherapy, 10, Copyright (2023), with permission from Elsevier [49]*

Even the current standard treatment is not always accessible in low-and middle-income countries [50]. For instance, these countries have a mismatch in the number of patients and brachytherapy availability [51]. Brachytherapy requires a good infrastructure and

trained healthcare professionals. Further efforts should be made to make the standard treatment more accessible to the global population. Alternatively, guidelines with recommendations for resource-limited settings, which are already available, should be extended when the advanced radiotherapy techniques considered in this thesis would be implemented and/or considered the standard in clinical practice [52].

9.3.2.2 Bone marrow sparing techniques

Besides bone marrow, other irradiated structures (Figure 4), the patient's baseline levels of blood cells, and the radiation sensitivity of blood cell populations might have influence on the hematopoietic functioning [53]. Additionally, radiation therapy can have both immune-stimulatory and immune-suppressive effects [54]. The exact interaction between chemoradiotherapy and immune system function remains unknown, but a better understanding could provide insight into factors critical for sparing the bone marrow and, more broadly, the immune system.

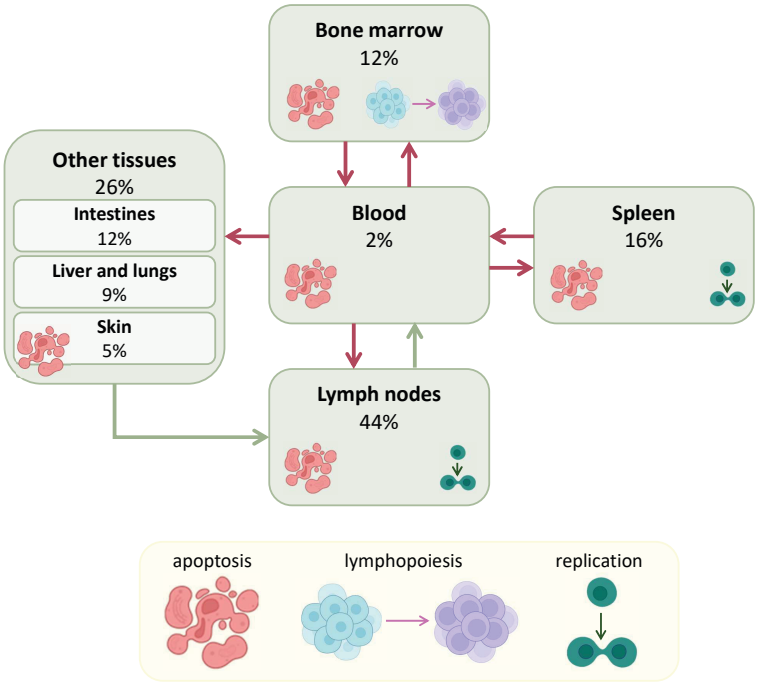

***Figure 4**: Schematic representation of the lymphatic compartment system, representing the flow of lymphocytes between lymphatic organs and tissues. Green and red arrows represent lymphatic flow in the lymph vessels and blood vessels, respectively. Adapted with permission from an image by Marianne van Tuyll van Serooskerken with icons from BioRender.com*

A study systematically comparing bone marrow sparing techniques is lacking. Functional imaging, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT), can identify active bone marrow and can also be used for bone marrow sparing [55]. However, functional imaging often requires an additional (costly) scan with radiation exposure and is not always available. Further prospective and long-term studies are necessary to determine which (combination of) imaging modalities are the most useful to implement bone marrow sparing strategies.

9.3.2.3 Other potential radiotherapy techniques to reduce toxicities

Other radiotherapy techniques with the potential to reduce toxicities in locally advanced cervical cancer are online daily adaptive radiotherapy with MR or cone beam CT (CBCT) imaging. The current library-of-plans approach, in which the plan that best fits the anatomy of that day is selected, could be replaced by daily treatment plan optimization, potentially resulting in reduced margins and improved OAR sparing. The first studies evaluating CBCT- or MR-guided EBRT for gynecological cancers have been performed and concluded that these techniques were feasible in simulated doses [56, 57] and could be used safely in clinical practice [56, 58, 59]. Challenges the overcome include the limited longitudinal field size of MR-guided linear accelerators [60], which means that patients requiring extended-field irradiation cannot yet be treated with this technique, and the prolonged on-couch time. Future studies should further investigate the potential added value and cost-effectiveness of online adaptive radiotherapy in this patient population.

Another approach to reducing hematologic toxicity is to shorten the treatment course through hypofractionation. Two clinical studies in a breast cancer and a palliative cohort respectively, found a reduction in hematologic toxicity with hypofractionation [61, 62]. Other advantages are fewer visits for the patients and the reduction in resources needed. First phase-II studies in cervical cancer are ongoing to assess the feasibility of hypofractionation in this patient group [63-65].

9.3.3 Adjuvant treatments for locally advanced cervical cancer

9.3.3.1 Results from the EMBRACE-II study

The large international EMBRACE-II study aimed to establish, systematically implement, and evaluate the internationally standard treatment for locally advanced cervical cancer and recently reported an improved 5-year disease-free survival compared to the LUMC

cohort and EMBRACE-I study (Table 1) [40, 66, 67]. EMBRACE-II included radiotherapy to the para-aortic region in women at high risk due to pelvic lymph node metastases, reducing the risk of para-aortic nodal relapse and further optimizing locoregional control. Additionally, EMBRACE-II showed a better 5-year overall survival and a reduced incidence of late grade ≥3 toxicities. Other outcomes, such as grade ≥2 toxicities and quality-of-life, have not yet been reported.

In the past years, studies have evaluated adding chemotherapy or immunotherapy, mainly immune checkpoint inhibitors, to the standard chemoradiotherapy to possibly reduce the risk of disseminated disease and improve overall survival. The potential of immunotherapy is one of the reasons to focus on reducing hematologic toxicity in this thesis. However, in the light of the results from EMBRACE-II, the field should debate if and for which patients adjuvant therapies might be beneficial.

9.3.3.2 Adjuvant chemotherapy

A meta-analysis evaluating the addition of adjuvant systemic therapy to chemoradiotherapy and brachytherapy for locally advanced cervical cancer found that adjuvant systemic therapy did not significantly improve overall survival, whereas acute toxicity significantly increased [68, 69]. In the largest study, the randomized, phase-III OUTBACK trial (NCT01414608), 22% of the patients in the adjuvant chemotherapy group did not receive any chemotherapy, most commonly due to patient preference.

The phase-III INTERLACE trial (NCT01566240) showed contrasting results (Table 1) [70]. In this trial, neo-adjuvant chemotherapy followed by chemoradiotherapy was feasible and significantly improved oncological outcomes. Despite the higher incidence of grade ≥3 toxicities in the neo-adjuvant chemotherapy group, mainly due to hematologic toxicity, quality of life was comparable among the two arms [71].

Several points in the INTERLACE trial, however, raise concerns about the applicability of the results. Brachytherapy and EBRT were according to older techniques and compliance to brachytherapy and EBRT differed between the two arms [72]. Since INTERLACE included a more favorable patient group, outcomes from its standard arm are inferior when compared with a matched EMBRACE-I cohort and even more so when compared with EMBRACE-II. A small subgroup of patients might benefit from neoadjuvant chemotherapy, but more understanding is needed to draw conclusions regarding this benefit and to identify these patients [72].

9.3.3.3 Adjuvant immune checkpoint inhibition

Adding checkpoint inhibitor therapy to the treatment of locally advanced cervical cancer is also a field of interest. The hypothesis is that immunotherapy will improve the systemic T-cell response to tumor antigens that can detect and kill micrometastatic tumors and are presented to more tumor-specific circulating T cells. Since programmed death ligand (PD-L) 1 is expressed in the majority of cervical cancer tumors, it is suggested that immune checkpoint inhibitors targeting PD-1 or PD-L1 could be effective (Figure 5) [73].

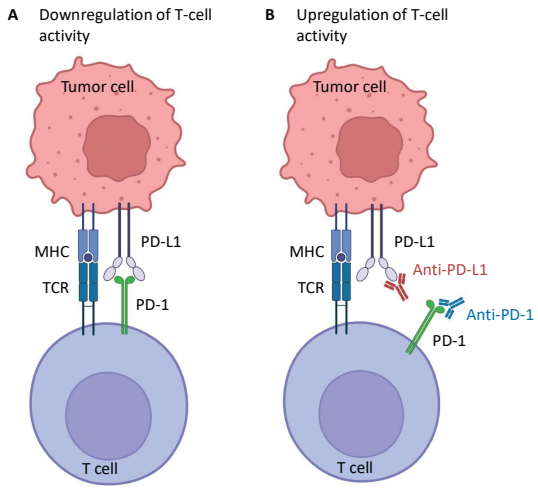

Figure 5: *Schematic representation of checkpoint proteins, such as programmed death (PD)-1 on T cells and programmed death ligand (PD-L)1 on tumor cells, and the binding between an antigen presented by major histocompatibility complex (MHC) and the T-cell receptor (TCR). A) Binding of PD-L1 to PD-1 inhibits T cell killing of the tumor cell. B) By blocking the binding with an immune checkpoint inhibitor T cells can kill the tumor cell. Adapted from Cancers, 7, Alard et al., Advances in Anti-Cancer Immunotherapy: Car-T Cell, Checkpoint Inhibitors, Dendritic Cell Vaccines, and Oncolytic Viruses, and Emerging Cellular and Molecular Targets, 1826, Copyright (2020), licensed under CC BY 4.0 [74] with icons from BioRender.com*

Two randomized phase-III trials and one randomized phase-II trial evaluating adjuvant immunotherapy have published their results during the course of this thesis (Table 2) [75-77]. The CALLA trial did not demonstrate a beneficial effect of durvalumab [78]. In contrast, the ENGOT-cx11/GOG-3047/KEYNOTE-A18 trial showed an improved outcomes with pembrolizumab [79, 80]. Even though grade ≥3 adverse events and immune-related adverse events were higher in the pembrolizumab-chemoradiotherapy group, quality-of-life analyses showed no differences between the groups [81]. Lastly, the phase-II ATEZOLACC study evaluated adjuvant atezolizumab in locally advanced cervical cancer but did not detect an improvement in overall or progression-free survival [77].

Table 1: *Results from studies in locally advanced cervical cancer (LACC). FIGO = The International Federation of Gynecology and Obstetrics, LN = lymph nodes, CRT = chemoradiotherapy, IQR = interquartile range, OS = overall survival, PFS = progression-free survival, AEs = adverse events, AUC = area-under-the-curve, * = outcomes shown as intervention arm v.s. standard arm.*

Trial	Study design	Enrollment period	No. of patients included	Eligibility	Randomisation	Treatment	Median follow-up (IQR) [months]	OS	PFS	AEs
EMBRACE-I (NCT00920920)	Prospective observational	2008-2015	1,341	Untreated LACC (FIGO 2009 stage IB-IVA, IVB with LN+ to the level of L2)	NA	CRT followed by MR-based adaptive brachytherapy	51 (20-64)	5Y: 75%	5Y: 68%	Late grade ≥3: 14.6%
LUMC cohort	Retrospective	2008-2016	155	Untreated LACC (FIGO 2009 stage IB-IVA)	NA	CRT followed by MR-based adaptive brachytherapy	57 (27.8-79.3)	5Y: 65.9%	5Y: 65.2%	Late grade ≥3: 13.1%
EMBRACE-II (NCT03617133)	Phase III	2016-2021	1,376	Untreated LACC (FIGO 2009 stage IB-IVA, IVB with LN to the level of L2)	NA	CRT followed by MR-based adaptive brachytherapy according to EMBRACE-II protocol	39	5Y: 82%	5Y: 73%	Late grade ≥3: 8.9%
INTERLACE (NCT01566240)	Phase III	2012-2022	500	Untreated LACC (FIGO 2008 stage IB1 with LN+ or IB2, IIA, IIB, IIIB, or IVA)	1:1 neo-adjuvant carboplatin and paclitaxel or placebo before CRT	Weekly carboplatin (AUC 2) and paclitaxel (80 mg/m^2) up to 6 weeks before CRT followed by MR-based adaptive brachytherapy	67	5Y*: 80% v.s. 72%	5Y*: 72% v.s. 64%	Acute grade ≥3*: 59% and 48%

Table 2: *Results from randomized studies in adjuvant immunotherapy for locally advanced cervical cancer (LACC). FIGO = The International Federation of Gynecology and Obstetrics, LN = lymph nodes, CRT = chemoradiotherapy, IQR = interquartile range, OS = overall survival, PFS = progression-free survival, AEs = adverse events, * = outcomes shown as intervention arm v.s. standard arm.*

Trial	Phase	Enrollment period	No. of patients included	Eligibility	Randomisation	Immunotherapy details	Median follow-up (IQR) [months]	OS*	PFS*	Acute AEs*
CALLA (NCT03830866)	III	2019-2020	770	Untreated high-risk LACC (FIGO stage 2009 IB2-IIB LN positive, stage ≥III any LN status)	1:1 durvalumab or placebo with and following CRT	Every 4 weeks (1,500 mg) with and after CRT up to 24 cycles	18.5 (IQR 13.2-23.7)	Not yet mature	1Y: 76.0% v.s. 73.3%	Grade ≥3: 52% v.s. 51%
ENGOT-cx11/ GOG-3047/ KEYNOTE-A18 (NCT04221945)	III	2020-2022	1,060	Untreated high-risk LACC (FIGO 2014 stage IB2-IIB with LN+ or III-IVA, any LN status)	1:1 pembrolizumab or placebo with and following CRT	Every 3 weeks with CRT (200 mg) up to 5 cycles, followed by every 6 weeks (400 mg) up to 15 cycles	29.9 (IQR 23.3-34.3)	3Y: 82.6% v.s. 74.8%	2Y: 67.8% v.s. 57.3%	Grade ≥3: 78% v.s. 70% Immune-related any grade: 39% v.s. 17%
ATEZOLACC (NCT03612791)	II	2018-2024	189	Untreated LACC (FIGO 2009 IB1-IIA with LN+, IIB-IVA, and any stage with PLN+)	1:1 atezolizumab or placebo with and following CRT	Every 3 weeks (1,200 mg) up to 20 cycles	33.6	2Y: 83% v.s. 82%	2Y: 70% v.s. 64%	Grade ≥3: 65% v.s. 53%

Based on the positive KEYNOTE-A18, the Food and Drug Administration (FDA) approved pembrolizumab with chemoradiotherapy for patients with FIGO 2014 stage III-IVA cervical cancer in January 2024. However, similar to adjuvant chemotherapy, there is quite some discussion in the field about the added value of adjuvant immunotherapy. The oncological outcomes in both arms of the KEYNOTE-A18 trial were inferior or similar to the 3-year outcomes of a selected, high-risk cohort in EMBRACE-II. Additionally, adding pembrolizumab as prescribed in the KEYNOTE-A18 results in a cost of $183,400 per quality-adjusted life-year (QALY), which is above the generally accepted threshold of $100,000 per QALY [82]. Lastly, treatment duration is significantly prolonged with adjuvant immunotherapy, which may cause additional burden for patients.

EMBRACE-II will be followed by EMBRACE high-risk, which is a phase-II study to evaluate the effect of adjuvant pembrolizumab and lenvatinib (anti vascular endothelial growth factor (anti-VEGF)) in high-risk patients. These and other trials will further explore the role of immune checkpoint inhibitors for (locally advanced) cervical cancer. Next steps would be to optimize the timing of immunotherapy regarding chemotherapy and radiotherapy, as the optimal scheduling and dosing may vary between cancer types and the immunotherapy used [83], to identify patients that potentially benefit, and to evaluate cost-effectiveness of adjuvant treatment. The added value compared to the standard chemoradiotherapy will be an ongoing debate.

9.4 CONCLUSION

The adoption of chemoradiotherapy with image-guided adaptive brachytherapy as the standard treatment for locally advanced cervical cancer has improved oncological outcomes over the last decades. However, treatment-related toxicities continue to affect patients' quality of life and limit opportunities for treatment intensification. These toxicities are associated with multiple patient, treatment, and dose-related factors. In this thesis, multivariable normal tissue complication probability (NTCP) models were developed to estimate the risk of gastrointestinal toxicities due to postoperative (chemo)radiotherapy for cervical cancer. Such prediction models might become valuable tools for treatment planning and for identifying patients at high risk of toxicity. The studies presented here also demonstrated that bone marrow is highly sensitive to radiation, as bone marrow fat fraction increased at low doses. 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. The findings of this thesis 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 the treatment of locally advanced cervical cancer.

REFERENCES

1. Kuipers S, Godart J, Corbeau A, Sharfo AW, Breedveld S, Mens JW, et al. The impact of bone marrow sparing on organs at risk dose for cervical cancer: a Pareto front analysis. Frontiers in Oncology. 2023;13.
2. Miszczyk M, Wu T, Kuna K, Stankiewicz M, Staniewska E, Nowicka Z, et al. Clinical outcomes of pelvic bone marrow sparing radiotherapy for cervical cancer: A systematic review and meta-analysis of randomised controlled trials. Clinical and Translational Radiation Oncology. 2024;47:100801.
3. Kuipers SC, Godart J, Corbeau A, Breedveld S, Mens JWM, de Boer SM, et al. Dosimetric impact of bone marrow sparing for robustly optimized IMPT for locally advanced cervical cancer. Radiotherapy and Oncology. 2024;195:110222.
4. van de Sande MAE, Creutzberg CL, van de Water S, Sharfo AW, Hoogeman MS. Which cervical and endometrial cancer patients will benefit most from intensity-modulated proton therapy? Radiotherapy and Oncology. 2016;120(3):397-403.
5. Razavian N, Laucis A, Sun Y, Spratt DE, Owen D, Schonewolf C, et al. Radiation-Induced Insufficiency Fractures After Pelvic Irradiation for Gynecologic Malignancies: A Systematic Review. International Journal of Radiation Oncology*Biology*Physics. 2020;108(3):620-34.
6. Sapienza LG, Salcedo MP, Ning MS, Jhingran A, Klopp AH, Calsavara VF, et al. Pelvic Insufficiency Fractures After External Beam Radiation Therapy for Gynecologic Cancers: A Meta-analysis and Meta-regression of 3929 Patients. International Journal of Radiation Oncology*Biology*Physics. 2020;106(3):475-84.
7. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD). Circulation. 2015;131(2):211-9.
8. Assessing Bias in Studies of Prognostic Factors. Annals of Internal Medicine. 2013;158(4):280-6.
9. Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ. 2006;332(7549):1080.
10. Ecker S, Kirisits C, Schmid M, Knoth J, Heilemann G, De Leeuw A, et al. EviGUIDE - a tool for evidence-based decision making in image-guided adaptive brachytherapy for cervical cancer. Radiotherapy and Oncology. 2023;186:109748.
11. Dickhoff LRM, Scholman RJ, Barten DLJ, Kerkhof EM, Roorda JJ, Velema LA, et al. Keeping your best options open with AI-based treatment planning in prostate and cervix brachytherapy. Brachytherapy. 2024;23(2):188-98.
12. Stieb S, Lee A, van Dijk LV, Frank S, Fuller CD, Blanchard P. NTCP Modeling of Late Effects for Head and Neck Cancer: A Systematic Review. International Journal of Particle Therapy. 2021;8(1):95-107.
13. Gan Y, Langendijk JA, van der Schaaf A, van den Bosch L, Oldehinkel E, Lin Z, et al. An efficient strategy to select head and neck cancer patients for adaptive radiotherapy. Radiotherapy and Oncology. 2023;186:109763.
14. Kalendralis P, Sloep M, Choudhury A, Seyben L, Snel J, George NM, et al. Technical note: A knowledge graph approach to registering tumour specific data of patient-candidates for proton therapy in the Netherlands. Medical Physics. 2023;50(2):1044-50.

15. Reeder SB, Hu HH, Sirlin CB. Proton density fat-fraction: a standardized MR-based biomarker of tissue fat concentration. J Magn Reson Imaging. 2012;36(5):1011-4.
16. Karampinos DC, Melkus G, Baum T, Bauer JS, Rummeny EJ, Krug R. Bone marrow fat quantification in the presence of trabecular bone: Initial comparison between water-fat imaging and single-voxel MRS. Magnetic Resonance in Medicine. 2014;71(3):1158-65.
17. Arentsen L, Yagi M, Takahashi Y, Bolan PJ, White M, Yee D, et al. Validation of marrow fat assessment using noninvasive imaging with histologic examination of human bone samples. Bone. 2015;72:118-22.
18. Li G, Xu Z, Gu H, Li X, Yuan W, Chang S, et al. Comparison of chemical shift-encoded water–fat MRI and MR spectroscopy in quantification of marrow fat in postmenopausal females. Journal of Magnetic Resonance Imaging. 2017;45(1):66-73.
19. Jarraya M, Bredella MA. Clinical imaging of marrow adiposity. Best Practice & Research Clinical Endocrinology & Metabolism. 2021;35(4):101511.
20. MacEwan IJ, Glembotski NE, D'Lima D, Bae W, Masuda K, Rashidi HH, et al. Proton density water fraction as a biomarker of bone marrow cellularity: Validation in ex vivo spine specimens. Magnetic Resonance Imaging. 2014;32(9):1097-101.
21. Karampinos DC, Ruschke S, Dieckmeyer M, Diefenbach M, Franz D, Gersing AS, et al. Quantitative MRI and spectroscopy of bone marrow. Journal of Magnetic Resonance Imaging. 2018;47(2):332-53.
22. Bazan JG, Luxton G, Mok EC, Koong AC, Chang DT. Normal Tissue Complication Probability Modeling of Acute Hematologic Toxicity in Patients Treated With Intensity-Modulated Radiation Therapy for Squamous Cell Carcinoma of the Anal Canal. International Journal of Radiation Oncology*Biology*Physics. 2012;84(3):700-6.
23. Lee AY, Golden DW, Bazan JG, Kopec M, Pelizzari CA, Aggarwal S, et al. Hematologic Nadirs During Chemoradiation for Anal Cancer: Temporal Characterization and Dosimetric Predictors. International Journal of Radiation Oncology*Biology*Physics. 2017;97(2):306-12.
24. Grassberger C, Ellsworth SG, Wilks MQ, Keane FK, Loeffler JS. Assessing the interactions between radiotherapy and antitumour immunity. Nature Reviews Clinical Oncology. 2019;16(12):729-45.
25. Ludwig JA, Weinstein JN. Biomarkers in Cancer Staging, Prognosis and Treatment Selection. Nature Reviews Cancer. 2005;5(11):845-56.
26. Onal C, Yildirim BA, Guler OC, Mertsoylu H. The Utility of Pretreatment and Posttreatment Lymphopenia in Cervical Squamous Cell Carcinoma Patients Treated With Definitive Chemoradiotherapy. International Journal of Gynecological Cancer. 2018;28(8):1553-9.
27. Santoro A, Angelico G, Inzani F, Arciuolo D, d'Amati A, Addante F, et al. The emerging and challenging role of PD-L1 in patients with gynecological cancers: An updating review with clinico-pathological considerations. Gynecologic Oncology. 2024;184:57-66.
28. Aitken C, Olthof E, Kaljouw S, Jansen E, de Koning H, de Kok I. Landelijke evaluatie van het bevolkingsonderzoek baarmoederhalskanker in Nederland 2017-20202022.
29. van Lonkhuijzen L, Mom C, van der Aa M. Cervical Cancer in the HPV-Vaccination Cohort in the Netherlands. 2025.
30. World Health Organization. Human papillomavirus vaccines: WHO position paper (2022 update). Wkly Epidemiol Rec. 2022;97(50):645-72.

31. World Health Organization. Global strategy to accelerate the elimination of cervical cancer as a public health problem: World Health Organization; 2020.
32. Jansen EEL, de Kok IMCM, Kaljouw S, Demirel E, de Koning HJ, Hontelez JAC. Rapid elimination of cervical cancer while maintaining the harms and benefits ratio of cervical cancer screening: a modelling study. BMC Medicine. 2022;20(1):433.
33. Aitken CA, Kaljouw S, Siebers AG, Bron M, Morssink A, van Kemenade FJ, et al. Investigating the decrease in participation in the Dutch cervical cancer screening programme: The role of personal and organisational characteristics. Prev Med Rep. 2021;22:101328.
34. van der Aa MA, Siesling S, Louwman MW, Visser O, Pukkala E, Coebergh JWW. Geographical relationships between sociodemographic factors and incidence of cervical cancer in the Netherlands 1989–2003. European Journal of Cancer Prevention. 2008;17(5):453-9.
35. Singh D, Vignat J, Lorenzoni V, Eslahi M, Ginsburg O, Lauby-Secretan B, et al. Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative. The Lancet Global Health. 2023;11(2):e197-e206.
36. Arians N, Lindel K, Krisam J, Oelmann-Avendano JT, Meixner E, König L, et al. Treatment Tolerability and Toxicity of Postoperative Proton Beam Therapy for Gynecologic Malignancies: Results of the Prospective Phase 2 APROVE Trial. International Journal of Radiation Oncology*Biology*Physics. 2023;116(4):825-36.
37. Russo AL, Depauw N, Horick NK, Wo JY, Nyamwanda JA, Giap F, et al. Long-Term Results of a Phase 2 Study of Adjuvant Proton Radiation Therapy for Node-Positive Cancer of the Uterus and Cervix. International Journal of Radiation Oncology*Biology*Physics. 2025.
38. Wark A, Gupta A, Meixner E, König L, Hörner-Rieber J, Forster T, et al. Bone Marrow Sparing by Intensity Modulated Proton Beam Therapy in Postoperative Irradiation of Gynecologic Malignancies. Technology in Cancer Research & Treatment. 2024;23:15330338241252622.
39. Chopra S, Gupta S, Kannan S, Dora T, Engineer R, Mangaj A, et al. Late Toxicity After Adjuvant Conventional Radiation Versus Image-Guided Intensity-Modulated Radiotherapy for Cervical Cancer (PARCER): A Randomized Controlled Trial. Journal of Clinical Oncology. 2021;39(33):3682-92.
40. Pötter R, Tanderup K, Schmid MP, Ecker S, Kroon P, Lindegaard J, et al. 2638 EMBRACE II-a multicenter prospective interventional cohort study on IGRT-IMRT+ cisplatin+ MR-IGABT in locally advanced cervix cancer: overall results. Radiotherapy and Oncology. 2025;206:S837-S40.
41. Korevaar EW, Habraken SJM, Scandurra D, Kierkels RGJ, Unipan M, Eenink MGC, et al. Practical robustness evaluation in radiotherapy – A photon and proton-proof alternative to PTV-based plan evaluation. Radiotherapy and Oncology. 2019;141:267-74.
42. Unkelbach J, Chan TCY, Bortfeld T. Accounting for range uncertainties in the optimization of intensity modulated proton therapy. Physics in Medicine & Biology. 2007;52(10):2755.
43. Kuipers SC, Godart J, Negenman EM, Corbeau A, Zolnay AG, Deuzeman HH, et al. Margin and robustness settings for a library-of-plans IMPT strategy for locally advanced cervical cancer. Physics in Medicine & Biology. 2024;69(24):245016.
44. Thijssen SV, Boersma LJ, Heising L, Swart RR, X. J. Ou C, Roumen C, et al. Clues to address barriers for access to proton therapy in the Netherlands. Radiotherapy and Oncology. 2023;178:109432.

45. Sugden BM, Witlox WJA, Ramaekers BLT, Hattu D, Vluggen B, van Loon J, et al. Adaptable framework for cost-analyses in radiotherapy: Application to the cost of proton versus photon therapy for lung cancer in The Netherlands. Radiotherapy and Oncology. 2025;206:110832.
46. Chen S, Cao Z, Prettner K, Kuhn M, Yang J, Jiao L, et al. Estimates and Projections of the Global Economic Cost of 29 Cancers in 204 Countries and Territories From 2020 to 2050. JAMA Oncology. 2023;9(4):465-72.
47. Chen YH, Blommestein HM, Klazenga R, Uyl-de Groot C, van Vulpen M. Costs of Newly Funded Proton Therapy Using Time-Driven Activity-Based Costing in The Netherlands. Cancers. 2023;15(2):516.
48. Particle Therapy Co-Operative Group (PTCOG). Particle therapy facilities in clinical operation 2025 [Available from: https://www.ptcog.site/index.php/facilities-in-operation-public.
49. Yan S, Ngoma TA, Ngwa W, Bortfeld TR. Global democratisation of proton radiotherapy. The Lancet Oncology. 2023;24(6):e245-e54.
50. Lichter K, Anakwenze Akinfenwa C, MacDuffie E, Bhatia R, Small C, Croke J, et al. Treatment of cervical cancer: overcoming challenges in access to brachytherapy. Expert Review of Anticancer Therapy. 2022;22(4):353-9.
51. Gurram L, Kalra B, Mahantshetty U. Meeting the Global Need for Radiation Therapy in Cervical Cancer—An Overview. Seminars in Radiation Oncology. 2020;30(4):348-54.
52. Chuang LT, Temin S, Camacho R, Dueñas-Gonzalez A, Feldman S, Gultekin M, et al. Management and Care of Women With Invasive Cervical Cancer: American Society of Clinical Oncology Resource-Stratified Clinical Practice Guideline. Journal of Global Oncology. 2016;2(5):311-40.
53. Paganetti H. A review on lymphocyte radiosensitivity and its impact on radiotherapy. Frontiers in Oncology. 2023;Volume 13 - 2023.
54. Rodríguez-Ruiz ME, Vanpouille-Box C, Melero I, Formenti SC, Demaria S. Immunological Mechanisms Responsible for Radiation-Induced Abscopal Effect. Trends in Immunology. 2018;39(8):644-55.
55. Konnerth D, Gaasch A, Zinn A, Rogowski P, Rottler M, Walter F, et al. Hematologic Toxicity and Bone Marrow-Sparing Strategies in Chemoradiation for Locally Advanced Cervical Cancer: A Systematic Review. Cancers. 2024;16(10):1842.
56. Shelley CE, Bolt MA, Hollingdale R, Chadwick SJ, Barnard AP, Rashid M, et al. Implementing cone-beam computed tomography-guided online adaptive radiotherapy in cervical cancer. Clinical and Translational Radiation Oncology. 2023;40:100596.
57. Branco D, Mayadev J, Moore K, Ray X. Dosimetric and feasibility evaluation of a CBCT-based daily adaptive radiotherapy protocol for locally advanced cervical cancer. Journal of Applied Clinical Medical Physics. 2023;24(1):e13783.
58. Boldrini L, Piras A, Chiloiro G, Autorino R, Cellini F, Cusumano D, et al. Low Tesla magnetic resonance guided radiotherapy for locally advanced cervical cancer: first clinical experience. Tumori Journal. 2020;106(6):497-505.
59. Lakomy DS, Yang J, Vedam S, Wang J, Lee B, Sobremonte A, et al. Clinical Implementation and Initial Experience With a 1.5 Tesla MR-Linac for MR-Guided Radiation Therapy for Gynecologic Cancer: An R-IDEAL Stage 1 and 2a First in Humans Feasibility Study of New Technology Implementation. Practical Radiation Oncology. 2022;12(4):e296-e305.

60. Chuter RW, Whitehurst P, Choudhury A, van Herk M, McWilliam A. Technical Note: Investigating the impact of field size on patient selection for the 1.5T MR-Linac. Medical Physics. 2017;44(11):5667-71.

61. Sun G-Y, Wang S-L, Song Y-W, Jin J, Wang W-H, Liu Y-P, et al. Radiation-Induced Lymphopenia Predicts Poorer Prognosis in Patients With Breast Cancer: A Post Hoc Analysis of a Randomized Controlled Trial of Postmastectomy Hypofractionated Radiation Therapy. International Journal of Radiation Oncology*Biology*Physics. 2020;108(1):277-85.

62. Saito T. Dosimetric predictors of treatment-related lymphopenia induced by palliative radiotherapy: predictive ability of dose-volume parameters based on body surface contour. Radiology and Oncology. 2017;51(2).

63. Mendez LC. Hypofractionated External-Beam RadiOtherapy for Intact Cervical Cancer (HEROICC-Trial): A Feasibility Study 2023 [Available from: https://clinicaltrials.gov/study/NCT04583254.

64. Prasartseree T, Dankulchai P, Sittiwong W, Thephamongkhol K. HYPOCx-iRex (TCTR20210812003) A Phase II RCT: 44 Gy/20F VS 45 Gy/25F CCRT in Cervical Cancer: Six-month Post-RT Update. International Journal of Radiation Oncology, Biology, Physics. 2023;117(2):S41.

65. Kolahdouzan K. Clinical Response and Toxicity of Hypo-fractionated Chemoradiotherapy in Cervix Cancer [Available from: https://clinicaltrials.gov/study/NCT04831437.

66. Horeweg N, Creutzberg CL, Rijkmans EC, Laman MS, Velema LA, Coen VLMA, et al. Efficacy and toxicity of chemoradiation with image-guided adaptive brachytherapy for locally advanced cervical cancer. International Journal of Gynecological Cancer. 2019;29(2):257-65.

67. Pötter R, Tanderup K, Schmid MP, Jürgenliemk-Schulz I, Haie-Meder C, Fokdal LU, et al. MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study. The Lancet Oncology. 2021;22(4):538-47.

68. Horeweg N, Mittal P, Gradowska PL, Boere I, Chopra S, Nout RA. Adjuvant Systemic Therapy after Chemoradiation and Brachytherapy for Locally Advanced Cervical Cancer: A Systematic Review and Meta-Analysis. Cancers. 2021;13(8):1880.

69. Horeweg N, Mittal P, Gradowska PL, Boere I, Nout RA, Chopra S. A systematic review and meta-analysis of adjuvant chemotherapy after chemoradiation for locally advanced cervical cancer. Critical Reviews in Oncology/Hematology. 2022;172:103638.

70. McCormack M, Gallardo Rincón D, Eminowicz G, Diez P, Farrelly L, Kent C, et al. LBA8 A randomised phase III trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer: The GCIG INTERLACE trial. Annals of Oncology. 2023;34:S1276.

71. Eminowicz G, Vaja S, Gallardo D, Kent C, Panades M, Mathew T, et al. Induction chemotherapy followed by chemoradiation in locally advanced cervical cancer: Quality of life outcomes of the GCIG INTERLACE trial. European Journal of Cancer. 2025;220:115375.

72. Lindegaard JC, Petric P, Tan L-T, Hoskin P, Schmid MP, Jürgenliemk-Schulz I, et al. Are we making progress in curing advanced cervical cancer—again? International Journal of Gynecological Cancer. 2024;34(12):1940-5.

73. Enwere EK, Kornaga EN, Dean M, Koulis TA, Phan T, Kalantarian M, et al. Expression of PD-L1 and presence of CD8-positive T cells in pre-treatment specimens of locally advanced cervical cancer. Modern Pathology. 2017;30(4):577-86.

74. Alard E, Butnariu A-B, Grillo M, Kirkham C, Zinovkin DA, Newnham L, et al. Advances in Anti-Cancer Immunotherapy: Car-T Cell, Checkpoint Inhibitors, Dendritic Cell Vaccines, and Oncolytic Viruses, and Emerging Cellular and Molecular Targets. Cancers. 2020;12(7):1826.

75. Lorusso D, Xiang Y, Hasegawa K, Scambia G, Leiva Galves MH, Ramos Elias P, et al. LBA38 Pembrolizumab plus chemoradiotherapy for high-risk locally advanced cervical cancer: A randomized, double-blind, phase III ENGOT-cx11/GOG-3047/KEYNOTE-A18 study. Annals of Oncology. 2023;34:S1279-S80.

76. Mayadev J, Nunes AT, Li M, Marcovitz M, Lanasa MC, Monk BJ. CALLA: Efficacy and safety of concurrent and adjuvant durvalumab with chemoradiotherapy versus chemoradiotherapy alone in women with locally advanced cervical cancer: a phase III, randomized, double-blind, multicenter study. International Journal of Gynecological Cancer. 2020;30(7):1065-70.

77. Chargari C, Pautier P, Chaltiel D, Petit A, Augereau P, Frenel J-S, et al. Academic Randomized Phase II Trial Assessing The Inhibitor Of Programmed Cell Death Ligand 1 (PD-L1) Immune Checkpoint Atezolizumab In Combination With Chemoradiation In Locally Advanced Cervical Cancer (ATEZOLACC Trial). International Journal of Gynecological Cancer. 2025;35(2).

78. Monk BJ, Toita T, Wu X, Vázquez Limón JC, Tarnawski R, Mandai M, et al. Durvalumab versus placebo with chemoradiotherapy for locally advanced cervical cancer (CALLA): a randomised, double-blind, phase 3 trial. The Lancet Oncology. 2023;24(12):1334-48.

79. Lorusso D, Xiang Y, Hasegawa K, Scambia G, Leiva M, Ramos-Elias P, et al. Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): a randomised, double-blind, phase 3 clinical trial. The Lancet. 2024;403(10434):1341-50.

80. Lorusso D, Xiang Y, Hasegawa K, Scambia G, Leiva M, Ramos-Elias P, et al. Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet. 2024;404(10460):1321-32.

81. Randall L, Sukhin V, Colombo N, Korach J, Matsumoto T, Lalondrelle S, et al. Patient-reported outcomes from the phase III, randomized, double-blind, placebo-controlled ENGOT-cx11/GOG-3047/KEYNOTE-A18 Study of pembrolizumab plus concurrent chemoradiotherapy among patients with high-risk, locally advanced cervical cancer. Gynecologic Oncology. 2024;190:S9.

82. Courtney PT, Venkat PS, Shih Y-CT, Chang AJ, Lee A, Steinberg ML, et al. Cost-Effectiveness of Pembrolizumab With Chemoradiotherapy for Locally Advanced Cervical Cancer. JAMA Network Open. 2025;8(3):e250033-e.

83. Zemek RM, Anagnostou V, Pires da Silva I, Long GV, Lesterhuis WJ. Exploiting temporal aspects of cancer immunotherapy. Nature Reviews Cancer. 2024;24(7):480-97.

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