Predicting and evaluating side effects of radiotherapy in cervical cancer

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Chapter 3

Predictive factors for toxicity after primary chemoradiation for locally advanced cervical cancer: a systematic review

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ABSTRACT

Purpose

Women with locally advanced cervical cancer (LACC) undergoing primary platinum-based chemoradiotherapy and brachytherapy often experience toxicities. Normal-tissue complication probability (NTCP) models quantify toxicity risk and aid in optimizing radiotherapy to minimize side effects. However, it is unclear which predictors to include in an NTCP model. The aim of this systematic review was to provide an overview of the identified predictors contributing to gastrointestinal (GI), genitourinary (GU), and vaginal toxicities and insufficiency fractures for LACC.

Methods and Materials

A systematic search was performed and articles evaluating the relationship between predictors and toxicities in women with LACC treated with primary chemoradiation were included. The Quality In Prognosis Studies (QUIPS) tool was used to assess risk of bias, with high-risk studies being excluded from further analysis. Relationships between dose-volume parameters, patient and treatment characteristics and toxicity endpoints were analyzed.

Results

73 studies were identified. 26 had a low or moderate risk of bias and were therefore included. Brachytherapy-related dose-volume parameters of the GI tract, including rectum and bowel EQD2 D_{2cm3}, were frequently related to toxicities, unlike GU dose-volume parameters. Furthermore, (recto)vaginal point doses predicted toxicities. Few studies evaluated external beam radiation therapy (EBRT) dose-volume parameters and identified rectum EQD2 V_{30Gy}, V_{40Gy}, and V_{55Gy}, bowel and bladder EQD2 V_{40Gy} as toxicity predictors. Also, total reference air kerma and vaginal reference length were associated with toxicities. Relationships between patient characteristics and GI toxicity were inconsistent. The extent of vaginal involvement at diagnosis, baseline symptoms, and obesity predicted GU or vaginal toxicities. Only one study evaluated insufficiency fractures and demonstrated lower pretreatment bone densities to be associated.

Conclusions

This review detected multiple candidate predictors of toxicity. Larger studies should consider insufficiency fractures, assess dose levels from EBRT, and quantify the relationship between the predictors and treatment-related toxicities in women with LACC to further facilitate NTCP model development for clinical use.

INTRODUCTION

The standard treatment for locally advanced cervical cancer (LACC) is definitive chemoradiation treatment combining external beam radiation therapy (EBRT) with concurrent platinum-based chemotherapy, followed by image-guided adaptive brachytherapy [1]. The prospective observational EMBRACE-I study registered patients with LACC who underwent this treatment between 2008 and 2015. The study reported actuarial estimates for severe (grade 3-4) late gastrointestinal (GI), genitourinary (GU), vaginal, and fistula events at five years of 8.5%, 6.8%, 5.7%, and 3.2%, respectively [2]. Additionally, a mono-institutional, retrospective study conducted during the same timeframe reported cumulative incidences of severe late bowel, rectal, bladder, and vaginal toxicity of respectively 0.8%, 3.3%, 3.6%, and 1.4% over five years of follow-up [3]. Moreover, a cumulative incidence of insufficiency fractures of 2.8% was found [3]. Meta-analyses evaluating pelvic insufficiency fractures after radiotherapy for gynecological cancers demonstrated even a higher pooled incidence estimate, ranging between 9.4 and 15.3% [4-6]. This may be due to heterogeneous strategies of detecting such fractures or it may represent differences in treatment techniques. Despite the excellent five-year local control in the EMBRACE-I and the retrospective study (between 90.4% and 92% [3, 7]), treatment-related side effects were shown to reduce quality of life [8-13]. Furthermore, toxicities may limit the use of more intensified systemic therapy regimens or radiation dose escalation, which are emerging research areas [14, 15].

Advancements in cervical cancer treatment over the last decades, including the introduction of plan-of-the-day strategies, more conformal radiotherapy techniques for EBRT, and magnetic resonance imaging (MRI) guidance during brachytherapy, have demonstrated a reduction in toxicity while improving oncological outcomes [16-19]. Planning studies have demonstrated that proton beam radiotherapy (PT) reduces doses to organs-at-risk (OAR) even further and thus might be able to decrease the risk of therapy-associated toxicities when compared to the current standard of care intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc therapy (VMAT) [20-23]. Normal-tissue complication probability (NTCP) models quantify the toxicity risk of an individual patient and can therefore serve as a valuable tool for shared decision making, treatment optimization or the selection of the most beneficial radiotherapy technique, including PT, to minimize toxicity risks [24, 25].

Multifactorial NTCP models should accurately predict treatment-related normal tissue morbidity by combining dosimetric normal tissue parameters and clinical information

[26, 27]. The majority of the studies performs regression analyses to provide risk factors, reflecting a mere correlation between predictive factors and complications. Clinically applicable NTCP models for toxicities in cervical cancer treatment are therefore not yet available. Furthermore, the most relevant predictors to include in the NTCP models have to be selected. This could be based on existing literature and clinical reasoning [26]. Even though multiple studies have established relationships between dose-volume parameters or clinical characteristics and toxicity after cervical cancer treatment, a comprehensive overview of predictors is lacking.

This systematic review aims to identify predictive factors for GI toxicity, GU toxicity, vaginal toxicities and insufficiency fractures in women with LACC treated with definitive chemoradiation, consisting of EBRT, concurrent platinum-based chemotherapy, and image-guided adaptive brachytherapy. An overview of candidate predictors will facilitate the future development of NTCP models for clinical use.

METHODS

Search strategy

A systematic search was conducted in Web of Science, Embase, Medline, and The Cochrane Library for the period from the 1st of January 1995 to the 1st (The Cochrane Library) or 14th (other databases) of March 2023. The search term consisted of four parts, focusing on predictors/model, toxicity, (chemo)radiotherapy, and gynecological cancer, and can be found in Supplementary Material EA. First, the references the search yielded were evaluated for duplicates. After removal of duplicates, the reviewers screened the title of the records to evaluate them for inclusion in the analysis. Subsequently, two reviewers independently screened the records on the basis of the abstract/full text. Disagreements on the inclusion of articles were resolved by consensus-based discussion. Articles were included when fulfilling the following criteria: (1) women with cervical cancer, (2) minimum of 20 cervical cancer patients included, (3) treatment consisted of primary radiotherapy, including both EBRT and brachytherapy, and platinum-based chemotherapy, (4) the relationship between predictive factors and GI, vaginal or GU toxicity or insufficiency fractures was quantified, (5) the article was published after 2005 and an English full-text was available. Records comprising reviews, editorials, guidelines, opinions, letters, and conference abstracts were excluded. This review was not registered.

Quality assessment

The Cochrane Methods Prognosis group recommends the Quality In Prognosis Studies (QUIPS) tool for assessing the risk of bias in prognostic factor finding studies [28, 29]. The focus of this tool is on the validity and bias in studies investigating prognostic factors and comprises six domains that can inform on the risk of bias. For each domain, the article is assigned a judgment of high, moderate, or low risk of bias. In this systematic review, three out of the six domains, namely outcome measurement, study confounding, and statistical analysis and reporting, were considered to be most relevant for evaluating the quality of the included articles. One reviewer used these three domains to initially assess all included articles in the first assessment round. Articles identified as having a high risk of bias, when at least two out of the three domains had a high risk of bias , were excluded from further judgment and analysis. Articles identified as having a low or moderate risk of bias were evaluated by the same reviewer for the remaining three domains in the second assessment round: study participation, study attrition, and prognostic factor measurement. Judgments were discussed with a second reviewer. The sum of the ratings of the six domains determined the final judgment.

Data extraction and analysis

One reviewer collected data from the articles, which included the source of data, patient enrollment period and number of patients enrolled, chemotherapeutic regimen, scoring system used for endpoint measurements, timepoints of measuring endpoints, modeling method, and characteristics of evaluated predictive factors. Since this systematic review focuses on GI, GU, and vaginal toxicity together with insufficiency fractures, solely predictive factors evaluating these endpoints were collected. Predictive factors were divided into dose-volume parameters and patient or treatment characteristics. Dose-volume parameters were categorized based on the corresponding OAR and dose reporting method. Dose was reported as the equivalent dose in 2 Gy fractions (EQD2). The normalized dose considered of EBRT only (EQD2 EBRT), brachytherapy only (EQD2 BT), EBRT and BT combined by adding the prescribed EBRT dose to the BT spatial dose (EQD2), which makes it a brachytherapy-related dose-volume parameter, or both techniques combined by adding the EBRT spatial dose to the BT spatial dose (EQD2 EBRT + BT). Treatment characteristics were evaluated per treatment modality. Consequently, predictive factors, corresponding endpoints, and statistical analysis method used for relationship quantification were organized in tables. When available,

hazard ratios (HR) or odds ratios (OR) and corresponding 95%-confidence intervals (95% CIs) from multivariable analyses evaluating candidate predictors from dose-volume parameters and patient or treatment characteristics were collected to visualize in figures. If articles reported a dosimetric threshold for toxicity prediction, these cut-off values were included in the figures as well. The majority of the cut-off values represent statistically optimized dosimetric thresholds that are most predictive of the treatment-related morbidity. Lastly, when studies assessed predictive factors for multiple endpoints, the clinically most relevant endpoints were selected for visualization, which is stated in the figure descriptions.

RESULTS

Eligible studies and quality assessment

Figure 1 visualizes the study flow diagram of the article screening process. 73 studies were included in this systematic review and classified for risk of bias using the three domains of the QUIPS tool considered most important in the first assessment round. After this assessment, 47 from the 73 studies were rated as having a high risk of bias and therefore excluded from analysis. Consequently, 26 studies were evaluated in the second assessment round, of which 22 were finally classified as having a moderate risk of bias and 4 as having a low risk of bias. Table 1 provides an overview of the included studies. The QUIPS assessment is provided in Supplementary Material EB. Fifteen articles evaluated prospectively collected data and the median number of patients included for analysis was 227 (range 40 to 1,860). Nineteen articles focused on late toxicity and respectively fourteen, twenty, and one article(s) included GI, GU or vaginal toxicity, and insufficiency fractures as endpoint.

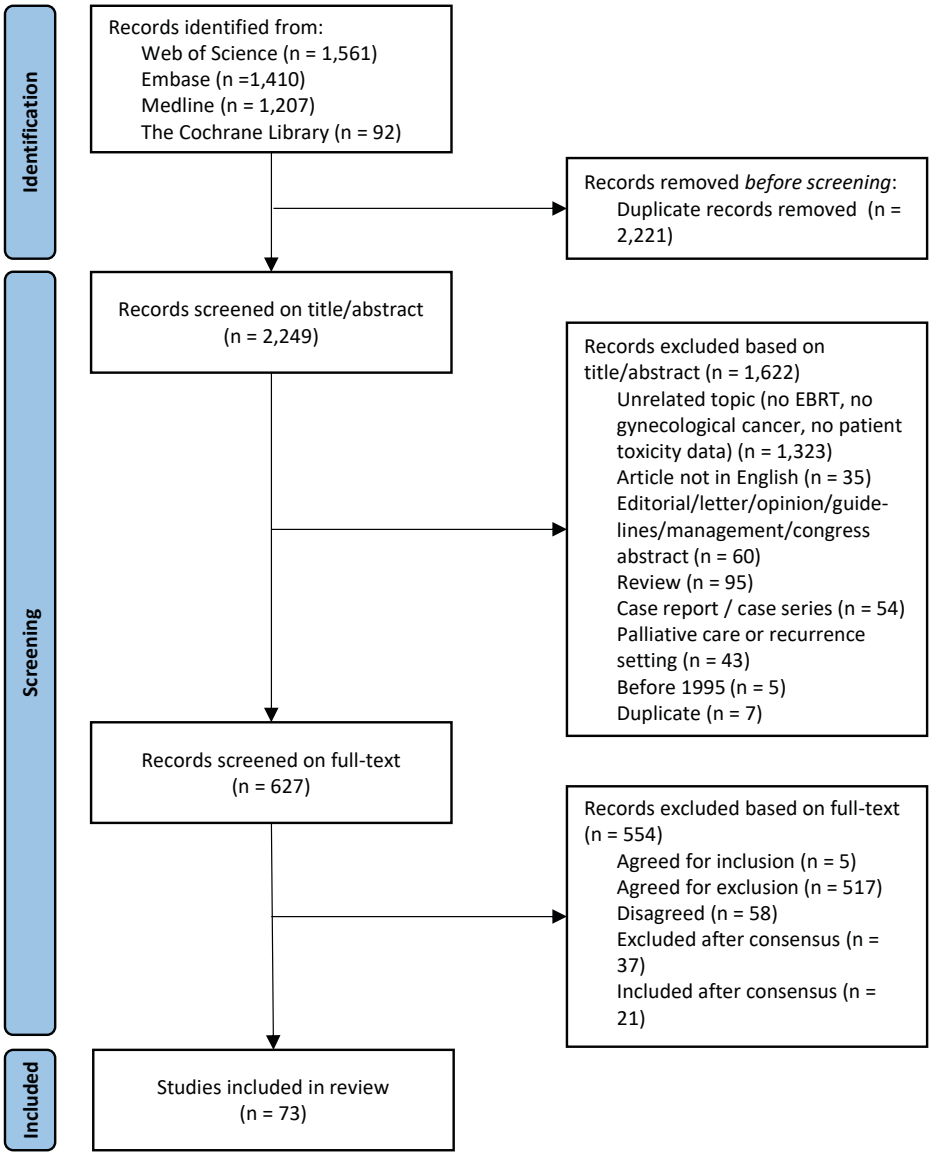

Figure 1: *PRISMA flow diagram summarizing the article screening process [56].*

Table 1: *Overview of the included articles.*

Reference	Source of data	Period of enrollment	No of patients	Chemotherapy (no patients, %)	Measured endpoint	Timing	Statistical analysis method	Predictive factors with respect to dose	Other predictive factors
Abbas et al (2018)	Prospective	UK	227	Cisplatin (227, 100%)	RTOG GI, GU, skin	Acute	Logistic regression MVA	NA	GST polymorphisms
Beller et al (2021)	Retrospective	1998 - 2012	126	Cisplatin 40 mg/m^2 (102, 90.3%)	Urologic complications (Clavien-Dindo grade 3+)	After radiotherapy treatment	Logistic regression MVA	NA	Patient/treatment characteristics
Bockel et al (2019)	Retrospective	2004 - 2016	227	Cisplatin (210, 81.4%) Carboplatin (31, 12%)	CTCAEv4 GI	Late	Log rank or Cox regression MVA	EQD2 small volume parameters	Patient/treatment characteristics
Chen et al (2009)	Retrospective	1993 - 2006	392	Cisplatin (143, 37%)	RTOG rectum, bladder	Late	Logistic regression MVA	EQD2 EBRT parametrial dose, EQD2 bladder and rectal dose	Patient/treatment characteristics
Chen et al (2010)	Retrospective	2001 - 2007	212	Cisplatin (184, 86.8%)	RTOG rectum, bladder and NRRIIII	Late	Logistic regression MVA	EQD2 EBRT parametrial dose, EQD2 bladder and rectal dose (MVA)	Patient/treatment characteristics (group comparison)
Dankulchai et al (2022)	Retrospective	UK	97	Cisplatin 40 mg/m^2 (62%, 60) or weekly carboplatin (33%, 32)	CTCAEv4 vaginal stricture	Late	Probit regression MVA*	EQD2 small volume parameters and point doses	Patient/treatment characteristics
Fokdal et al (2019)	Retrospective and prospective	1998 – 2015	1860	Cisplatin 40 mg/m^2 (1654, 88.9%)	CTCAEv3 ureteral strictures	Late	Cox regression MVA	EQD2 small volume parameter (MVA)	Patient/treatment characteristics (MVA)
Georg et al (2011)	Retrospective	1998 - 2003	141	Cisplatin 40 mg/m^2 (82, 58%)	LENT-SOMA rectum, sigmoid, bladder	Late	Group comparison and MVA	EQD2 small volume parameters and point dose (group comparison)	Patient/treatment characteristics (MVA)
Ishikawa et al (2021)	Retrospective	2011 - 2013	42	Cisplatin or cisplatin with paclitaxel (29, 69%)	Fractures in L4/L5 or pelvic bones	Post treatment	Cox regression MVA	EQD2 EBRT + BT V_{xGy}, D_{2cc} and D_{mean}	Patient characteristics
Jensen et al (2021)	Prospective	2008 - 2015	900	Cisplatin (92%)	CTCAEv3 diarrhea or EORTC QLQ-C30 (both with LAPERS)	Late	Cox regression or binary logistic regression MVA	EQD2 small-dose volume parameter, point dose, and V_{60Gy}	Patient/treatment characteristics

Reference	Source of data	Period of enrollment	No of patients	Chemotherapy (no patients, %)	Measured endpoint	Timing	Statistical analysis method	Predictive factors with respect to dose	Other predictive factors
Kim et al (2013)	Prospective	2004 - 2006	77	Cisplatin (66, 85.7%) Cisplatin + 5-FU (1, 1.3%)	RTOG rectum and sigmoid and RMC/ LRC scores	Late	Stepwise logistic MVA	EQD2 small-dose parameters and point doses	Patient/treatment characteristics
Kirchheiner et al (2016)	Prospective	2008 - 2015	630	Cisplatin (UK)	CTCAEv3 vaginal stenosis	Late	Cox proportional hazard MVA	EQD2 point dose	Patient/treatment characteristics
Lee et al (2018)	Retrospective	2004 - 2015	245	Cisplatin (208, 84.9%)	CTCAEv3 GI	Acute and late	Cox proportional hazard MVA	EQD2 EBRT V_{xGy}	Patient/treatment characteristics
Manea et al (2018)	Retrospective	2004 - 2015	297	Cisplatin (278, 93.6%)	CTCAEv4 urinary	Late	MVA	EQD2 small-dose volume parameter, $D_{50\%}$, and point dose	Patient/treatment characteristics
Naik et al (2016)	Prospective	2014 - 2015	40	Cisplatin (40, 100%)	CTCAEv4 GI, GU	Acute	Group comparison with randomized groups	NA	Treatment characteristics
Pathy et al (2015)	Prospective	2009 - 2012	50	Cisplatin 40 mg/m^2 or 20 mg/m^2 (25 v.s. 25, 100% in total)	CTCAEv4 GI, GU	Acute	Group comparison with randomized groups	NA	Treatment characteristics
Rodriquez-Lopez et al (2021)	Retrospective	2007 - 2017	242	Cisplatin (UK)	CTCAEv4 ureteral stenosis	Late	Logistic regression MVA	EQD2 small-dose volume parameter and CTV-D_{90}	Patient/treatment characteristics
Ruanla et al (2022)	Retrospective	2015 - 2020	54	Cisplatin 40 mg/m^2 (48, 88.9%)	Modified Dische score vagina mucosal reaction	Late	Logistic regression MVA	EQD2 small-dose volume parameters and point doses	Patient characteristics
Seppenwoolde et al (2021)	Prospective	2014 - 2018	48	Cisplatin (41, 92%) Capecitabine (3, 6.25%)	CTCAEv4 all toxicity, GI, GU PRO QoL-C30 and EORTC QLQ-CX24	Acute	LASSO followed by logistic regression MVA	EQD2 EBRT V_{xGy}	Patient/treatment characteristics
Sharma et al (2022)	Prospective	2018 - 2019	54	Cisplatin 35 mg/m^2 (UK)	CTCAEv4 GU, GI	Acute	Group comparison with randomized groups	NA	Treatment characteristic

Reference	Source of data	Period of enrollment	No of patients	Chemotherapy (no patients, %)	Measured endpoint	Timing	Statistical analysis method	Predictive factors with respect to dose	Other predictive factors
Spampinato et al (2021)	Prospective	2008 - 2015	1153 for CTCAE, 884 for EORTC analysis	Cisplatin (98%) Other (2%)	CTCAEv3 bladder fistula, bleeding, cystitis, EORTC-CX24 "pain during urinating" and "difficulty emptying bladder"	Late	Cox regression MVA	EQD2 small-dose volume parameter and point dose	Patient/treatment characteristics
Spampinato et al (2021)	Prospective	2008 - 2015	1153 for CTCAE, 884 for EORTC analysis	Cisplatin (98%) Other (2%)	CTCAEv3 urinary frequency, urgency, incontinence, EORTC-CX24 "pass urine frequently" and "leaking" (both including LAPERS)	Late	Cox regression MVA	EQD2 small-dose volume parameter and point dose	Patient/treatment characteristics
Spampinato et al (2022)	Prospective	2008 - 2015	1199 for CTCAE, 1002 for EORTC analysis	Cisplatin (1170 in CTCAE group, 97.6%)	CTCAEv3 GI, flatulence, fecal incontinence, proctitis, and anal/rectal bleeding, EORTC-C30 and CX24 constipation, abdominal cramps, difficulty in bowel control, and blood in stools (both including LAPERS)	Late	Cox regression MVA	EQD2 small-dose volume parameters and point dose	Patient/treatment characteristics
Ujaimi et al (2017)	Prospective/ retrospective	2008 - 2013	106	Cisplatin 40 mg/m^2 (82, 76%; others ≤ 4 cycles)	CTCAEv4 bladder, rectum (no diarrhea)	Late	Logistic regression MVA and group comparison	EQD2 V_{xGy} and small-dose volume parameter	Patient/treatment characteristics
Wang et al (2022)	Prospective	2016 – 2018	351	Cisplatin 25 mg/m^2 or cisplatin 25 mg/m^2 combined with paclitaxel 135 mg/m^2 (UK)	CTCAEv3 vaginal stenosis	Late	Group comparison and cox regression MVA	EQD2 point doses	Patient/treatment characteristics
Westerveld et al (2022)	Prospective	2008 - 2015	301	Cisplatin 40 mg/m^2 (97%)	CTCAEv3 vaginal stenosis	Late	Cox regression MVA	EQD2 EBRT, EQD2 BT and EQD2 EBRT+BT dose points	Patient/treatment characteristics

Gastrointestinal toxicity

Dose-volume parameters

Out of the fourteen studies evaluating GI toxicity, nine studies reported on the correlation between dose-volume parameters and toxicity. Supplementary Material EC provides an overview of the dose-volume parameters having a significant and those having a non-significant relationship with GI toxicity. The HR or OR of dose-volume parameters that were analyzed in multivariable analyses are indicated with † in Supplementary Material EC and shown in Figure 2. Figure 2 includes HR or OR per 10 Gy increase for continuous dose-volume parameters and per category for categorized dose-volume parameters.

Multiple studies demonstrated that brachytherapy-related parameters D_{xcm3}, representing the minimum doses of the most exposed small volumes, were related to late rectal toxicities or diarrhea. These included the rectum and the bowel EQD2 D_{2cm3}, having HR with relatively small 95% CIs, and the rectal wall EQD2 D_{2cm3} (>70 Gy) and rectosigmoid EQD2 D_{5cm3} (>65 Gy), having wide 95% CIs around the OR. In contrast, the EQD2 D_{2cm3} of the sigmoid colon alone was not significantly correlated with late GI toxicity (no HR or OR was reported). Significant correlations were found between EQD2 rectovaginal D_{ICRU} and mean rectal biologically equivalent dose (RBED) (≥110 Gy) and late GI toxicity. The RBED was calculated by adding the biologically equivalent dose (BED) of EBRT and BT using the linear-quadratic formula [30]. Only three studies evaluated intermediate dose-volume parameters of the GI tract [31-33]. Seppenwoolde et al (2021) and Lee et al (2018) retracted V_{xGy} parameters from EBRT plans [31, 33], whereas Ujaimi et al (2017) calculated rectal EQD2 V_{xGy} by obtaining the absolute volume of the rectum that received the difference between x Gy and the EBRT dose [32]. The rectal EQD2 EBRT V_{30Gy} (>96%), bowel EQD2 EBRT V_{40Gy}, and rectal EQD2 EBRT V_{40Gy} were frequently reported as predictors of acute toxicity, whereas the rectal wall EQD2 V_{55Gy} (>11 cm^3) was associated with late rectal toxicity. Lastly, the body absolute EQD2 EBRT V_{43Gy} and absolute EQD2 EBRT V_{57Gy} (when ≥165 cm^3 from a 60 Gy lymph node boost) were often identified as predictors of late GI toxicity. Parametrial dose and PTV volume were not associated with late GI toxicity.

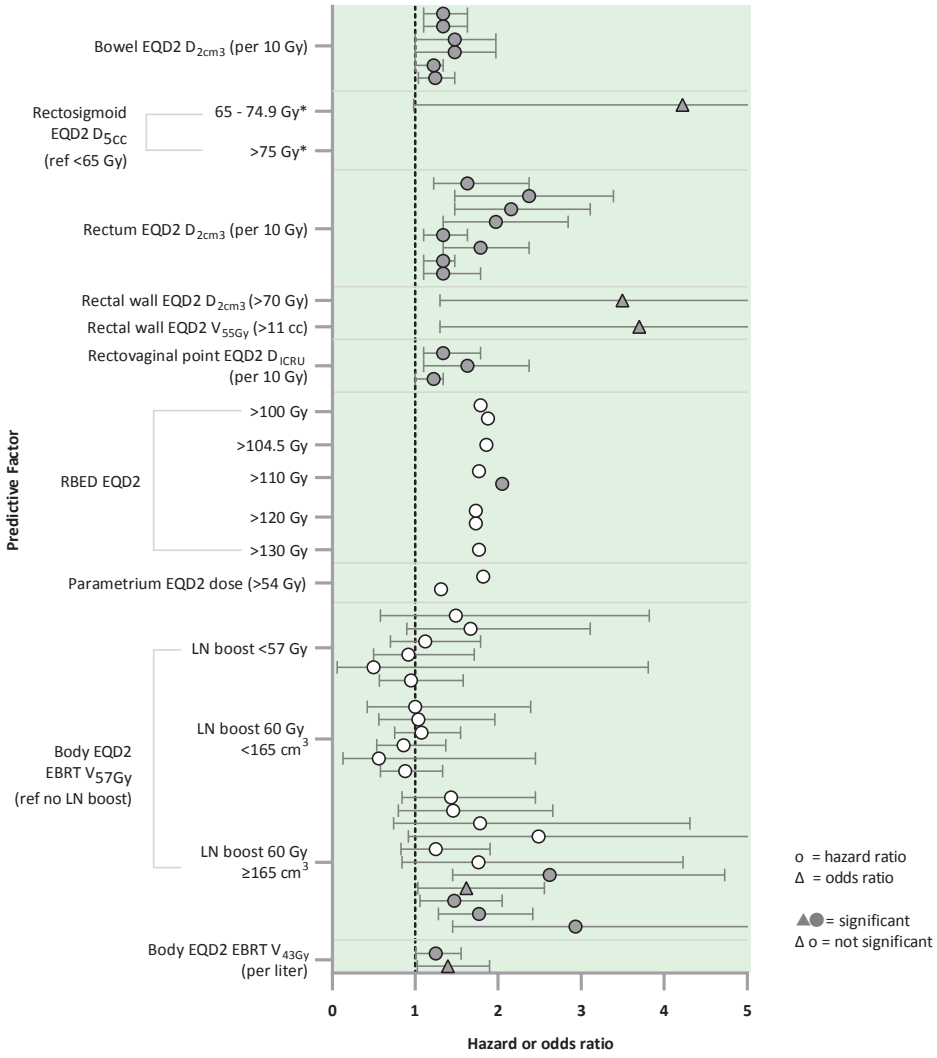

***Figure 2**: Odds and hazard ratios of dose-volume parameters, including 95%-confidence intervals if available, that were evaluated as predictive factors for late gastrointestinal toxicity. All ratios in the figure result from multivariable analyses performed in the analyzed studies. The studies by Jensen et al (2021) and Spampinato et al (2022) assessed multiple endpoints per predictive factor [57, 58]. From these studies, only ratios with respect to CTCAE grade 2+ and EORTC LAPERS (Jensen et al (2021)) or CTCAE grade 2+ and EORTC "quite a bit+" (Spampinato et al (2022)) were included in this figure. EQD2 V55Gy was defined by Ujaimi et al (2017) as the absolute volume of the rectum that received the difference between 55 Gy and the EBRT dose [32]. The rectal biologically equivalent dose (RBED) was calculated by adding the biologically equivalent dose (BED) of EBRT and BT using the linear-quadratic formula [30]. EQD2 = EBRT and BT combined by adding the prescribed EBRT dose to the BT spatial dose reported as equivalent dose in 2 Gy fractions, Dx cm3 = dose [Gy] received by volume x cm3, VxGy = volume of organ [%] receiving ≥ x Gy, DICRU = International Commission for Radiation Units and Measurements point, EQD2 EBRT = only external beam radiotherapy dose reported as equivalent dose in 2 Gy fractions, LN = lymph node, * = ratio falls outside the figure.*

Patient and treatment characteristics

Supplementary Material ED demonstrates the evaluated relationships between patient or treatment characteristics and GI toxicity. Available HR or OR from multivariable analyses are indicated with † in Supplementary Material ED and visualized in Figure 3. In contrast to nodal boosts and EBRT technique, prescribed EBRT dose predicted some late GI toxicity endpoints. Studies disagreed on the relationship between para-aortic irradiation and late GI toxicity. Regarding brachytherapy, the total reference air kerma (TRAK) at 1 m distance (>2 cGy) and mean rectal geometric sparing factor (RGSF) (>0.7), which represents the ratio between the ICRU rectovaginal point dose and point A dose, were predictive of late GI toxicity. However, other brachytherapy parameters, including the size of residual vaginal tumor at first brachytherapy, dose rate, and applicator characteristics, did not influence toxicity. Similarly, studies disagreed on the effect of chemotherapy on acute and late GI toxicity. With respect to patient characteristics, the influence of underweight, overweight, age, stage, rectal invasion, and diabetes mellitus on GI toxicity had inconsistent results across studies. Baseline symptoms, grade 2-4 bladder complications after treatment, smoking, and specific genetic polymorphisms of glutathione S-transferase (GST) genotype, which ameliorate toxic reactive oxygen species created by chemoradiotherapy, were significantly correlated with acute or late GI toxicity, but corresponding HR or OR showed wide 95% CIs. Lastly, tumor size, histology, chronic diseases, previous major surgery, pelvic lymph node status, hypertension, and alcohol were not predictive of toxicities.

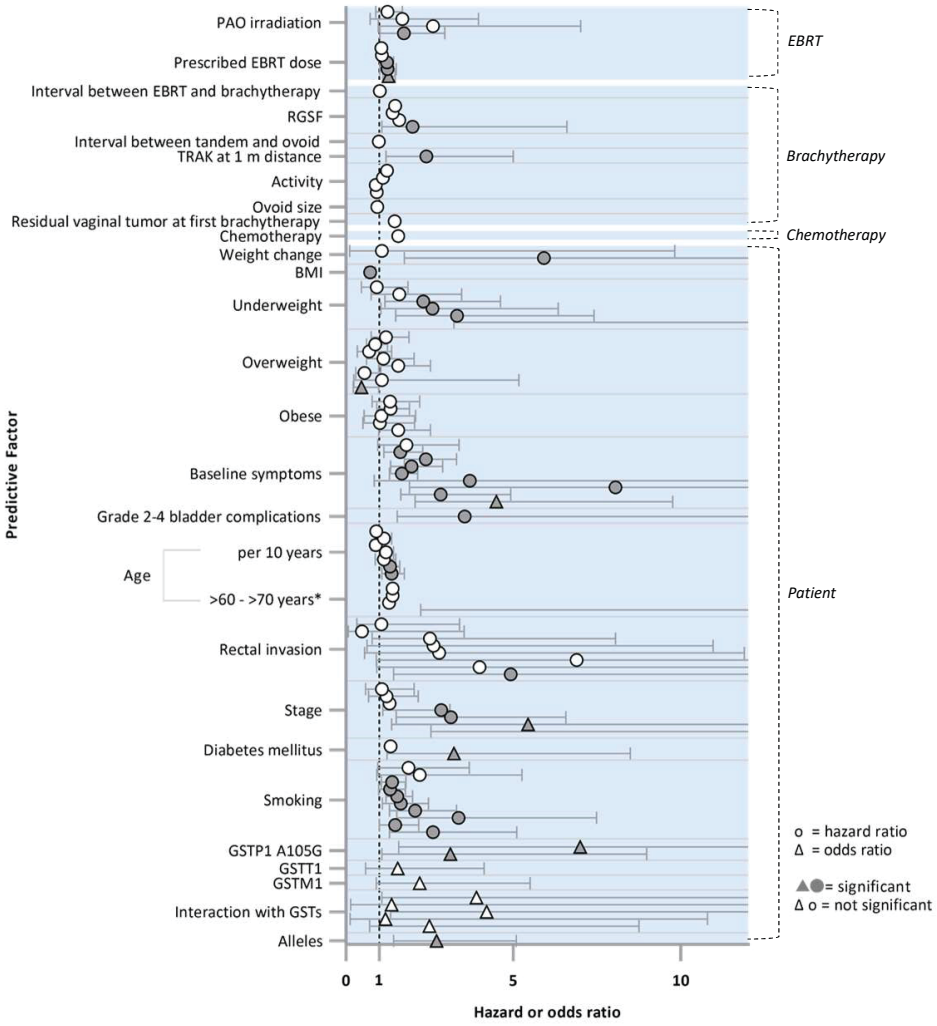

Figure 3: *Odds and hazard ratios, including 95%-confidence intervals if available, of patient and treatment characteristics that were evaluated as predictive factors for gastrointestinal toxicity. On the right Y-axis, subcategories of predictive factors are defined. All ratios in the figure result from multivariable analyses performed in the analyzed studies. The studies by Jensen et al (2021) and Spampinato et al (2022) assessed multiple endpoints per predictive factor [57, 58]. From these studies, only ratios with respect to CTCAE grade 2+ and EORTC LAPERS (Jensen et al (2021)) or CTCAE grade 2+ and EORTC "quite a bit+" (Spampinato et al (2022)) were included in this figure. PAO = para-aortic, EBRT = external beam radiotherapy, RGSF = mean rectal geometric sparing factor, TRAK = total reference air kerma, BMI = body mass index, GST = glutathione S-transferase.*

Genitourinary and vaginal toxicity

Dose-volume parameters

Out of the twenty studies evaluating candidate predictors of GU and vaginal toxicities, fifteen assessed dose-volume parameters, which are outlined in Supplementary Material EE. Available HR or OR are indicated with † and shown in Figure 4. Figure 4 includes HR or OR per 10 Gy increase for continuous dose-volume parameters and per category for categorized dose-volume parameters.

Brachytherapy-related dose-volume parameters from the bladder, including EQD2 $D_{0.1cm3}$ and EQD2 D_{2cm3}, were predictive of some late bladder toxicity endpoints. Inconsistent results were reported on the correlation between EQD2 EBRT + BT Posterior-Inferior Border of Symphysis (PIBS) (+ 2 cm and – 2 cm) and EQD2 bladder D_{ICRU} and late urinary or vaginal toxicity, whereas the bladder biologically equivalent dose (BBED) (≥100 Gy) and the EQD2 rectovaginal D_{ICRU} were predictive of late urinary or vaginal toxicity. The BBED was calculated by adding the BED of EBRT and BT using the linear-quadratic formula [30]. Additionally, the mean dose of the left and right lateral vaginal points in 5 mm depth (VLat5mmMeanLR) (continuous or >95 Gy) was associated with late vaginal stenosis grade 2+. Evaluation of volume-based parameters of each separate part of the vagina did not show associations with toxicity [34]. Bladder EQD2 EBRT V_{40Gy} was the only intermediate dose parameter assessed and contributed to acute low-grade bladder toxicities. The impact of the bladder wall, bladder trigone, ureter, CTV-HR, or body dose was only evaluated in univariable analyses. Lastly, parametrial dose did not predict late bladder toxicity.

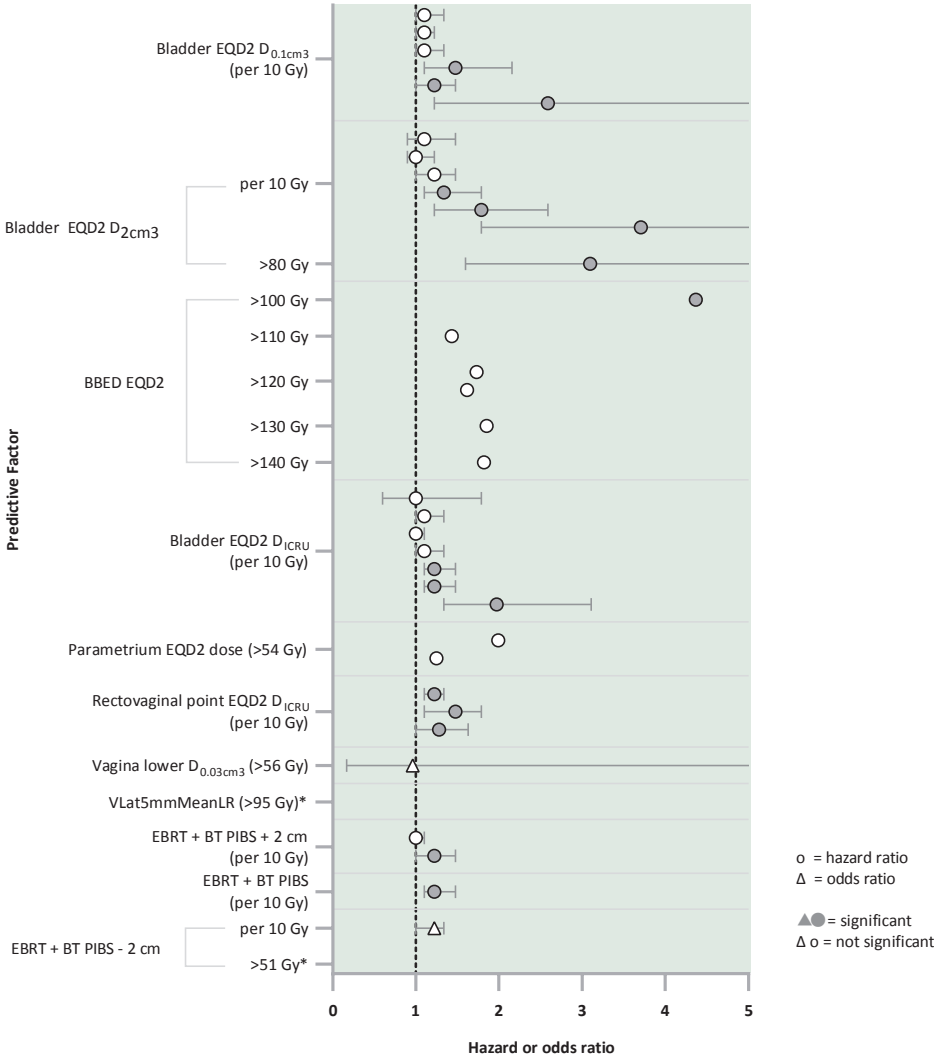

***Figure 4**: Odds and hazard ratios including 95%-confidence intervals of dose-volume parameters, and cut-off values if reported, that were evaluated as predictive factors for late genitourinary and vaginal toxicity. All ratios in the figure result from multivariable analyses performed in the analyzed studies. The studies by Spampinato et al (2021) assessed multiple endpoints per predictive factor [59, 60]. From these studies, only ratios with respect to CTCAE grade 2+ and EORTC "quite a bit+" were included in this figure. The bladder biologically equivalent dose (BBED) was calculated by adding the biologically equivalent dose (BED) of EBRT and BT using the linear-quadratic formula [30]. EQD2 = equivalent dose in 2 Gy fractions, Dx cm3 = dose [Gy] received by volume x cm3, DICRU = International Commission for Radiation Units and Measurements point, VLat5mmMeanLR = mean dose of the left and right lateral vaginal points in 5 mm depth, EBRT = external beam radiotherapy, BT = brachytherapy, PIBS = Posterior-Inferior Borders of Pubic Symphysis, * = ratio falls outside the figure.*

Patient and treatment characteristics

Supplementary Material EF comprises the evaluated relationships between patient or treatment characteristics and GU or vaginal toxicities. Available HR or OR are indicated with † and shown in Figure 5. Dose from EBRT only and EBRT and BT together, EBRT technique, and EBRT boosts were not predictive of GU or vaginal toxicity. Studies found associations between the mean bladder geometric sparing factor (BGSF) (>0.9) and a shorter vaginal reference length and late GU or vaginal toxicity. Studies reported inconsistent results on the impact of brachytherapy technique (intracavitary v.s. a combination of intracavitary and interstitial) and applicator. Other brachytherapy parameters, including dose (rate), ovoid size, and residual vaginal tumor at brachytherapy, were not associated with late GU or vaginal toxicity. One study demonstrated a significant correlation between chemotherapy and late bladder complications with wide 95% CIs for the corresponding HR, but many other studies reported no significant associations between chemotherapy characteristics and GU or vaginal toxicity. Lastly, for patient characteristics, baseline symptoms and extent of vaginal involvement at time of diagnosis were predictors of late GU or vaginal toxicity. Obesity was significantly associated with multiple endpoints, while underweight and overweight were not. Pre-existing hydronephrosis and grade 2+ rectal complications were also significantly associated with GU toxicity, but showed wide 95% CIs. Studies disagreed on the influence of smoking, age, and alcohol. No studies found stage predictive of GU toxicity.

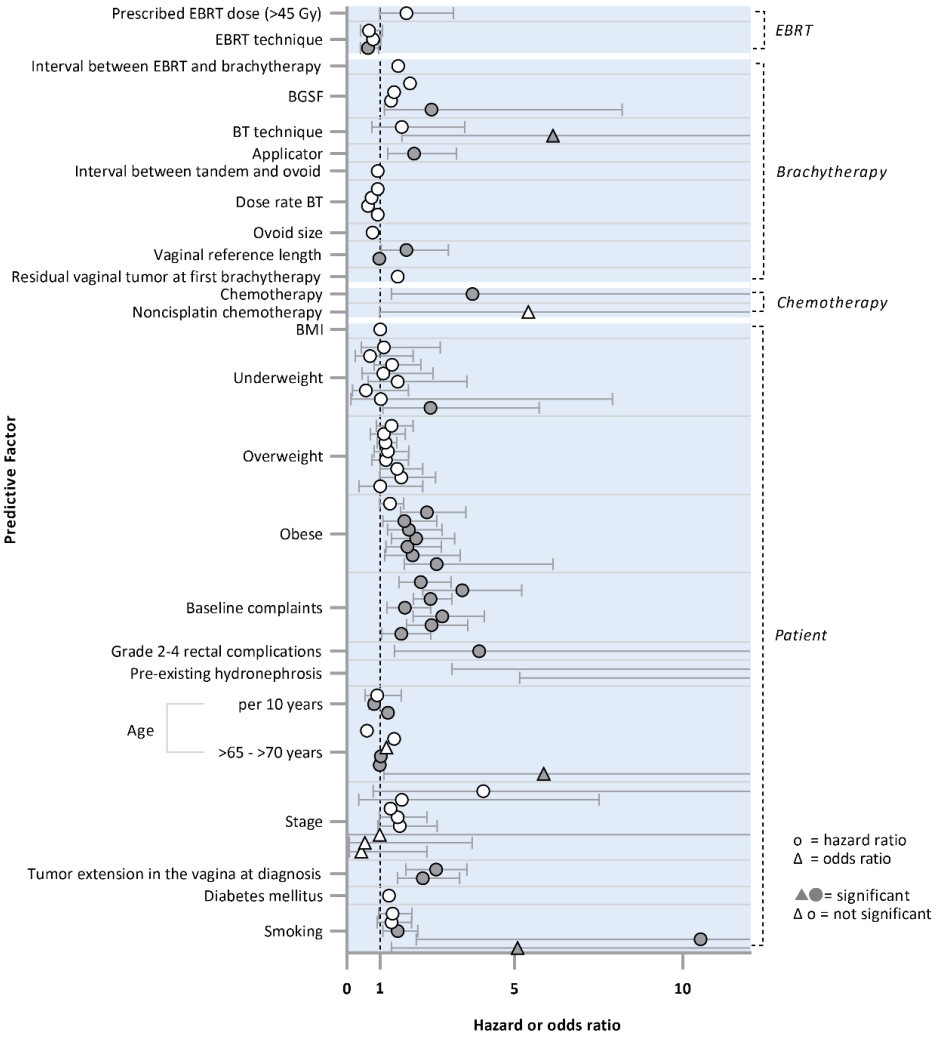

Figure 5: *Odds and hazard ratios including 95%-confidence intervals of patient and treatment characteristics that were evaluated as predictive factors for genitourinary and vaginal toxicity. On the right Y-axis, subcategories of predictive factors are defined. All ratios in the figure result from multivariable analyses performed in the analyzed studies. The studies by Spampinato et al (2021) assessed multiple endpoints per predictor [59, 60]. From these studies, CTCAE grade 2+ and EORTC "quite a bit+" were included in this Figure. For Westerveld et al (2022), the weighted hazard ratio for the factors age and vaginal involvement was calculated and included in the Figure [61]. EBRT = external beam radiotherapy, BGSF = mean bladder geometric sparing factor, BT = brachytherapy, BMI = body mass index.*

Insufficiency fractures

Only one of the included articles in this systematic review evaluated post-treatment insufficiency fractures [35]. Univariable analysis showed that fractures were more frequently identified in patients with advanced age, a low body mass index (BMI), no use of concomitant chemotherapy, and post-menopausal status. Additionally, pretreatment computed tomography (CT) densities were significantly lower among patients with fractures, except at the ilium and the ischium, which may reflect osteoporosis. Lastly, fractures of the pubis were more commonly observed for higher V_{30Gy} (>75%), V_{40Gy} (>55%), and V_{50Gy} (>25%) of the pubic bones. For the multivariable analysis, CT densities and the DVH parameters for pubic fractures were included, as the patient characteristics were correlated with CT densities. Only the CT densities were then found significant for pubic bone fractures.

DISCUSSION

In this systematic review, predictive factors for GI, GU, and vaginal toxicities, and insufficiency fractures after primary chemoradiation with adaptive image-guided brachytherapy for LACC were evaluated. The majority of the analyzed studies focused on brachytherapy-related dose-volume parameters. Brachytherapy-related dose-volume parameters of the GI tract were mainly predictive of late GI toxicities, most notably the EQD2 D_{2cm3} of the rectum and bowel, differing from parameters of the GU tract and GU toxicity. Point doses, including EQD2 rectovaginal D_{ICRU} and VLat5mmMeanLR (continuous or >95 Gy), contributed to late GI and vaginal toxicities. In contrast, a limited number of studies investigated intermediate dose-volume parameters with a large EBRT dose contribution. These studies found that the rectal EQD2 EBRT V_{30Gy} (>96%), bowel EQD2 EBRT V_{40Gy}, rectal EQD2 EBRT V_{40Gy}, and bladder EQD2 EBRT V_{40Gy} were frequently reported as predictors of acute GI or GU toxicity. Rectal EQD2 V_{55Gy} (>11 cm^3) was associated with late rectal toxicity. Lastly, a large volume of the body absolute EQD2 EBRT V_{57Gy} (≥165 cm^3) when boosting lymph nodes and body absolute EQD2 EBRT V_{43Gy} predicted multiple GI toxicities. Furthermore, TRAK at 1 m distance (>2 cGy) and vaginal reference length contributed to respectively late GI toxicity and vaginal stenosis. Studies disagreed on the relationship between chemotherapy and toxicities. Relationships between patient characteristics and GI toxicity had wide 95% CIs or were inconsistent, but baseline symptoms, obesity, and extent of vaginal involvement at diagnosis, were mostly associated with GU toxicity or vaginal stenosis. Only one study evaluated

insufficiency fractures and demonstrated that pretreatment CT densities, which may reflect osteoporosis, were predictive of this type of toxicity.

A restricted number of studies evaluated dose-volume parameters that were to a large extent determined by EBRT spatial dose. However, they detected multiple intermediate dose-volume parameters to be associated with toxicities. Numerous studies examined EBRT-related dose-volume parameters for treatment-related toxicity in other pelvic cancers. For GI toxicity, a systematic review by Holyoake et al (2019) showed a significant relationship between the small bowel V_{5Gy}, V_{10Gy}, V_{30Gy}, V_{45Gy} and acute grade 3+ toxicity in rectal cancer patients treated with chemoradiation [36]. Studies evaluating treatment-related toxicity in anal cancer patients treated with chemoradiotherapy reported intermediate dose-volume parameters of the bowel as predictors of late GI toxicity, including large bowel loops V_{20Gy} [37] or small bowel loops V_{30Gy} [38], or acute GI toxicity, including bowel cavity V_{30Gy} [37, 38] or small bowel loops V_{35Gy} [39]. For GU or vaginal toxicity, studies on anal cancer reported worse urinary function for higher bladder V_{40Gy} [38, 40] and studies on both rectal and anal cancer suggested a vaginal D_{mean}<43 Gy to reduce the risk of severe vaginal stenosis [41]. These studies indicate that the EBRT spatial dose is associated with GI, GU, or vaginal toxicities. Notably, the EMBRACE-group discussed dose planning aims for LACC and advocated for further analysis and reporting and of low and intermediate dose levels (15-60 Gy) to give insights into morbidity development [42]. As summing brachytherapy and EBRT spatial dose is currently challenging, the EMBRACE-group recommends to report EBRT dose-volume parameters to reflect these dose levels. EBRT-related dose-volume parameters should be included in NTCP models and could be improved with advanced radiotherapy techniques such as proton therapy.

Only one of the included studies evaluated predictive factors for insufficiency fractures despite the relatively high incidence reported in literature and the associated morbidity. An explanation could be that the incidence of insufficiency fractures in clinical practice is underestimated, since 40% of the insufficiency fractures is asymptomatic and might therefore remain undetected in the current follow-up routine. However, these cases could become symptomatic and affect the quality of life [6]. Other studies that were identified with the literature search did not fulfill the inclusion criteria or were rated as a high risk of bias. Three recent systematic reviews or meta-analyses evaluating insufficiency fractures in women treated for gynecologic malignancies demonstrated signification associations between older age [4], EBRT technique [6], osteoporosis [5], postmenopausal state [5], or a history of diabetes mellitus [5] and the incidence of insufficiency fractures. These

predictors might be applicable for the patient group evaluated in this systematic review as well. While both the incidence and survival of LACC has increased, insufficiency fractures become a more clinically relevant late toxicity. Additionally, interest in bone sparing radiotherapy has increased since studies reported dose-volume parameters to be associated with insufficiency fractures, including sacrum $D_{50\%}$ [43, 44] and V_{40Gy} [45]. Future clinical trials could further evaluate risk factors for insufficiency fractures and explore the potential and clinical benefit of bone sparing radiotherapy for insufficiency fractures in pelvic cancer patients.

A recent study by Suvaal et al (2023) reported that half of the sexually active women treated with primary chemoradiation for LACC reported vaginal functioning problems and sexual distress, while the majority of the women had no or only mild physician-reported vaginal changes over time [46]. The studies about vaginal morbidity that were analyzed in our review mainly focused on physician-assessed grading using CTCAE or RTOG, but patient-reported endpoints might be more relevant for quality of life.

The studies analyzed in this systematic review did not agree on the associations between patient or treatment characteristics and GI toxicity, but agreed upon the impact of baseline symptoms, tumor extension into the vagina, and obesity on GU or vaginal toxicities. Reviews on other pelvic cancers treated with radiotherapy suggested that older age [37, 47], smoking [37], the addition of EBRT to brachytherapy [47], higher tumor stage [47], and baseline bladder complications [47] were linked to GI toxicity and poor baseline genitourinary function [48], older age [48], presence of diabetes [48], and smoking [48] to GU toxicity.

The lack of clinically applicable NTCP models for toxicities in women with primary LACC treated with platinum-based chemoradiotherapy and brachytherapy was the rationale for this systematic review. The majority of the identified studies pre-selected variables based on univariable analysis to subsequently include these in a multivariable analysis. Full prediction models that allow for predictions of individual patients were not reported. Ideally, studies provide full equations, including regression coefficients and model intercept, and information on model performance to facilitate interpretation and clinical implementation [26, 49, 50].

In order to build a high-quality and reliable NTCP model, relevant candidate predictors and endpoints could be identified based on clinical reasoning and literature [26]. However,

almost half of the studies included in this systematic review were assigned a judgment of high risk of bias and removed for analysis. Potential biases in the domains of outcome measurement, study confounding, and statistical analysis could result in reporting invalid associations between the prognostic factor and the endpoints [28]. Firstly, the variety of outcome measurement methods to classify normal tissue complications make endpoint comparison difficult. As the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) papers pointed out, there is a large variety in endpoint definitions due to different timepoints, grouping of scored toxicities into grades or organ systems, and different grading systems used [51]. Besides, eleven out of the twenty-six included studies had a retrospective design. These studies relied on toxicity data collected from patient records, which is often not reported in a standardized manner, and therefore may lead to a variation in toxicity registration within and between studies. Ideally, centers and cooperative groups would use one standardized scoring system for outcome variables. Additionally, various methods to report EBRT and BT dose were used, which complicates comparison among studies. The majority of the included studies followed the recommendations of the GYN GEC ESTRO working group by presuming a homogeneous EBRT dose and an inhomogeneous BT dose that is spatially identical for each BT fraction [52]. However, other studies considered that toxicities might be dose-spatial dependent and included information on the spatial nature of the dose distribution [53]. Secondly, regarding bias due to study confounding, multicollinearity between predictors was not always reported. As a result, the quantified relationship between selected predictors and endpoints might be less robust [26, 49]. Lastly, the rule of thumb for applying logistic models is that a minimum of ten events per candidate predictor should be used. Even though the validity of this rule has been questioned [54], studies with a relatively low toxicity event rate or a low number of evaluated patients showed large 95%-confidence intervals for HR or OR in this systematic review.

The vast majority of the reported dosimetric cut-off values were determined by optimizing their discriminant ability for toxicities. Dosimetric cut-off values are easy to comprehend and to use during treatment optimization and therefore often reported. However, a statistically optimal cut-off value might underestimate variability within the two groups and overestimate the influence of the variable on the outcome [55]. Preferably, dose-volume parameters are kept continuous and their relationship with toxicities is represented in regression models.

This systematic review was the first review to provide a comprehensive overview of predictors of GI, GU or vaginal toxicity, and insufficiency fractures for primary LACC treated with chemoradiotherapy, including EBRT, platinum-based chemotherapy, and brachytherapy. Brachytherapy-related dose-volume parameters of the GI tract were demonstrated to be predictive of GI toxicities, most notably the EQD2 D_{2cm3} of the rectum and bowel, in contrast to GU parameters and toxicity. Point doses, including EQD2 rectovaginal D_{ICRU} and VLat5mmMeanLR, were related to late toxicities. Only a limited number of studies analyzed intermediate dose-volume parameters with a large EBRT dose contribution, but the rectum EQD2 EBRT V_{30Gy}, V_{40Gy}, and V_{55Gy}, bowel and bladder EQD2 EBRT V_{40Gy} were reported as predictive of GI or GU toxicities. Large body volumes receiving 57 Gy from 60 Gy lymph node boosts and body absolute EQD2 EBRT V_{43Gy} were often identified as predictors of GI toxicities. Mainly brachytherapy-related treatment characteristics were correlated with toxicities, whereas studies disagreed on the influence of chemotherapy. Patient characteristics, including tumor extension in the vagina at time of diagnosis, baseline symptoms, and obesity, were associated with GU or vaginal toxicity. Lastly, only one article evaluated risk factors for insufficiency fractures and found pretreatment bone densities assessed with CT to be predictive. Our systematic review identified and provided an overview of candidate predictors to include in NTCP models. However, more attention should be paid to insufficiency fractures. Further research is required to assess the relationship between dose-volume parameters from EBRT and toxicities. Lastly, larger studies evaluating factors associated with treatment-related toxicities in women with LACC are warranted in order to quantify the associations. Our findings contribute to NTCP model development and validation to facilitate shared decision making, treatment optimization, and the selection of the most beneficial radiotherapy technique, including proton therapy, to minimize toxicity risks in clinical practice.

SUPPLEMENTARY MATERIAL

Supplementary material is available on

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