Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-260-z Pembrolizumab

Stand: November 2024

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Pembrolizumab **[Behandlung von Patientinnen mit einem lokal fortgeschrittenen Zervixkarzinom]** **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Operation Radiotherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Pembrolizumab L01FF02 Keytruda	Anwendungsgebiet laut Zulassung: Pembrolizumab ist in Kombination mit Radiochemotherapie (perkutane Strahlentherapie, gefolgt von einer Brachytherapie) zur Behandlung des lokal fortgeschrittenen Zervixkarzinoms (Stadium III bis IVA gemäß FIGO 2014) bei Erwachsenen, die keine vorherige definitive Therapie erhalten haben, angezeigt.
Bleomycin L01DC01 BLEO-cell	Bleomycinsulfat wird bei den nachfolgend aufgeführten Indikationen fast immer in Kombination mit anderen Zytostatika angewendet: - Plattenepithelkarzinomen (SCC) von Kopf und Hals, äußeren Genitalien und Zervix
Cisplatin L01XA01 generisch	Cisplatin wird angewendet in Kombination mit einer Strahlentherapie zur Behandlung des Zervixkarzinoms. Cisplatin kann als Mono- oder Kombinationstherapie angewendet werden.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-260z (Pembrolizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	13. November 2024

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse event
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BRT	Bioresonanztherapie
CASP	Critical Appraisal Skills Program
CCRT	chemoradiotherapy
ChT	Chemotherapy
DFS	Disease free survival
EBRT	External Beam Radiotherapy
ECRI	Emergency Care Research Institute
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GTV	Gross tumour volume
HDR	high dose rate
HR	Hazard Ratio
HRCTV	High risk clinical target volume
IGABT	Image-guided adaptive brachytherapy
IMRT	intensity modulated radiotherapy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IRCTV	Intermediate risk clinical target volume
KI	Konfidenzintervall
LACC	locally advanced cervical cancer
LL	Leitlinie
LoE	Level of Evidence
NACT	neoadjuvant chemotherapy
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
OS	Overall survival
PDR	pulse dose rate
PFS	Progression free survival
PRO	prospective cohort
RCT	randomized controlled trial

RET	retrospective cohort
RR	Relatives Risiko
RT	Radiotherapy
SCT	single-arm clinical trial
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung von Patientinnen im FIGO 2014 Stadium III-IVA mit einem lokal fortgeschrittenen Zervixkarzinom, die noch keine definitive Therapie erhalten haben.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Zervixkarzinom* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (https://www.google.com/) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 03.05.2023 durchgeführt, die folgenden am 15.01.2024 und 17.10.2024. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 2837 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt acht Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen

3 Ergebnisse

3.1 Cochrane Reviews

Kokka, F. et al., 2022 [3].

Hysterectomy with radiotherapy or chemotherapy or both for women with locally advanced cervical cancer.

Fragestellung

To determine whether hysterectomy, in addition to standard treatment with radiotherapy or chemotherapy, or both, in women with LACC (Stage IB2 to III).

Methodik

Population:

- women with LACC International FIGO Stages IB2 to III

Intervention/Komparator

- hysterectomy in combination with neoadjuvant, concurrent or adjuvant therapy versus non-surgical interventions:
  - Hysterectomy (radical) with NACT versus chemoradiotherapy alone.
  - Hysterectomy (simple or radical) with NACT versus radiotherapy alone.
  - Hysterectomy (simple or radical) with radiotherapy versus radiotherapy alone.
  - Hysterectomy (simple or radical) with chemoradiotherapy versus chemoradiotherapy alone.
  - Hysterectomy (radical) with chemoradiotherapy versus internal radiotherapy (brachytherapy) with chemoradiotherapy.
  - Hysterectomy (radical) with chemoradiotherapy versus hysterectomy (radical) with NACT versus chemoradiotherapy alone.

Endpunkte:

- OS, PFS, DFS, Quality of life measures, Severe adverse events

Recherche/Suchzeitraum:

- CENTRAL, MEDLINE via Ovid, Embase via Ovid, LILACS, trial registries and the grey literature up to 3 February 2022

Qualitätsbewertung der Studien:

- Cochrane RoB / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

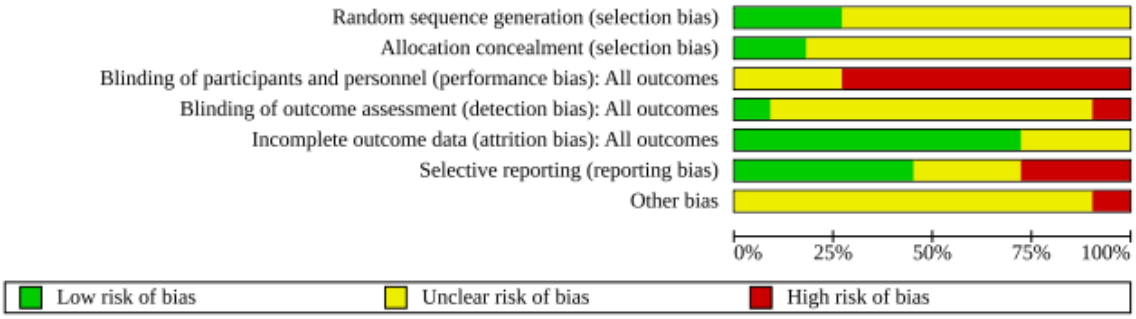
- 11 RCTs (2683 women) of varying methodological quality. This update identified four new RCTs and three ongoing RCTs.

Charakteristika der Population/Studien:

- The included studies compared: hysterectomy (simple or radical) with radiotherapy or chemoradiotherapy or neoadjuvant chemotherapy (NACT) versus radiotherapy alone or chemoradiotherapy (CCRT) alone or CCRT and brachytherapy. There is also one ongoing study comparing three groups: hysterectomy with CCRT versus hysterectomy with NACT versus CCRT.

Qualität der Studien:

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Studienergebnisse:

Note: There were two comparison groups for which it was possible to do a meta-analysis

- Hysterectomy (radical) with NACT versus chemoradiotherapy alone (3 trials included 1364 women)

Patient or population: women with locally advanced cervical cancer

Settings: outpatient

Intervention: NACT + hysterectomy

Comparison: CCRT

Outcomes	Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence(GRADE)	Comments
Overall survival Median follow-up 58.5–98.4 months in the 2 trials	**HR 0.94** (0.76 to 1.16)	1253 (2 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	I^2 = 0%
DFS Median follow-up 58.5–98.4 months in the 2 trials	**HR 1.38** (1.02 to 1.87)	633 (1 RCT)	⊕⊕⊖⊖ **Low**[b]	—
	5-year DFS in the NACT + surgery group was 57% vs 65.6% in the chemoradiotherapy group (P = 0.021)	620 (1 RCT)		
Quality of life	—	—	—	Not reported.
SAEs and toxicity	*SAEs* In first trial, there were no toxic deaths reported. 198 SAEs occurred: 145 in the NACT + surgery arm vs 53 in the CCRT arm. In the second trial there were 114 grade 3 or 4 SAEs: 92 in the NACT + surgery arm vs 22 in the CCRT arm	198 (1 RCT) 114 (1 RCT)	⊕⊖⊖⊖ **Very low**[c]	—
	Toxicity In 1 trial, NACT + surgery group, compared with the chemoradiotherapy group, there was a lower rate of rectal (5.7% with NACT + surgery vs 13.3% with chemoradiotherapy; P = 0.002), bladder (2.8% with NACT + surgery vs 7.3% with chemoradiotherapy; P = 0.017), and vaginal (19.9% with NACT + surgery vs 36.9% with chemoradiotherapy; P = 0.001) toxicity occurring or persisting 90 days after treatment completion. However, 24 months after treatment completion, there was no difference in rectal and bladder toxicities between groups, whereas vaginal toxicity continued to occur at a lower rate in the	114 (1 RCT)		

NACT + surgery group (12.0% with NACT + surgery vs 25.6% with chemoradiotherapy; P = 0.001).	
Treatment-related morbidity No treatment-related deaths in either chemoradiotherapy or NACT + surgery arm. Overall, 89% of participants in the chemoradiotherapy arm and 73% in the NACT + surgery arm had complications, with 18% in NACT + surgery arm experiencing recurrence and requiring adjuvant radiotherapy.	111 (1 RCT)

CI: confidence interval; **CCRT:** concurrent chemoradiotherapy; **DFS:** disease-free survival; **HR:** hazard ratio; **NACT:** neoadjuvant chemotherapy; **SAE:** serious adverse event.

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded one level due to concerns regarding the uncertainty of risk of bias in individual trials and only two trials in meta-analysis (although it is arguable whether the number of included participants represented relatively sparse data).
[b]Downgraded two levels due to risk of bias and sparse data.
[c]Downgraded three levels due to incomplete and poor reporting of important adverse events and toxicities, sparseness of data and risk of bias concerns.

- Hysterectomy (simple or radical) with neoadjuvant chemotherapy versus radiotherapy alone (3 studies)

Patient or population: women with locally advanced cervical cancer

Settings: outpatient

Intervention: neoadjuvant chemotherapy + radical hysterectomy

Comparison: radiotherapy alone

Outcomes	**Relative effect (95% CI)**	**No of participants (studies)**	**Certainty** of the evidence (GRADE)	**Comments**
Overall survival Median follow-up 39–60 months in the 3 trials	**HR 0.71** (0.55 to 0.93)	571 (3 RCTs)	⊖⊖⊖⊖ **Moderate**[a]	—
Disease- or progression-free survival Median follow-up 39–60 months in the 3 trials	**HR 0.75** (0.53 to 1.05)	571 (3 RCTs)	⊖⊖⊖⊖ **Moderate**[a]	There were varying definitions of disease- and progression-free survival. However, we did not consider this merited further

				downgrading to low-certainty evidence.
Quality of life	—	—	—	Not reported.
Severe adverse events and toxicity	*Acute severe toxicity* **RR 1.32** (0.47 to 3.71)	118 (1 RCT)	⊖⊖⊖⊖ **Low**[b]	—
	Long-term severe complications **RR 0.86** (0.49 to 1.50)	409 (1 RCT)		
	Severe late toxicity **RR 0.60** (0.27 to 1.34)	118 (1 RCT)		

CI: confidence interval; **HR:** hazard ratio; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded one level due to concerns regarding the uncertainty of risk of bias in individual trials.
[b]Downgraded two levels due to incomplete and poor reporting of important adverse events and toxicities and sparseness of data.

- Hysterectomy (simple or radical) with radiotherapy versus radiotherapy alone (1 study, 374 women)

Patient or population: women with locally advanced cervical cancer

Settings: outpatient

Intervention: radiotherapy + hysterectomy (simple or radical)

Comparison: radiotherapy alone

Outcomes	Relative effect (95% CI)	No of participants	Certainty of the evidence (GRADE)	Comments
Overall survival Median follow-up 9.6 years	**HR 0.89** (0.61 to 1.29)	256 (1 RCT)	⊖⊖⊖⊖ **Low**[a,b]	12 participants in each regimen (10% with radiotherapy + hysterectomy vs 9% with radiotherapy) were lost to follow-up by 5 years.
Progression-free survival	**HR 0.77** (0.54 to 1.10)	256 (1 RCT)	⊖⊖⊖⊖ **Low**[a,b]	12 participants in each regimen (10% with radio-

Median follow-up 9.6 years				therapy + hysterectomy vs 9% with radiotherapy) were lost to follow-up by 5 years.
Tumour-free actuarial survival at 5 years	5-year, tumour-free actuarial survival for women with Stage IB was 80% in the preoperative radiotherapy + hysterectomy group and 89% in the radiotherapy group. In Stage IIA, these rates were 79% in the preoperative radiotherapy + hysterectomy group and 56% in the radiotherapy group.	118 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b,c]	—
Quality of life	—	—	—	Not reported.
Severe/serious adverse events	1 trial stated that both treatment programmes were well tolerated and there were no differences between groups in adverse effects. There were 18/129 women with a grade 3 or 4 adverse effect in the radiotherapy + hysterectomy group and 19 cases in 18/121 women of severe adverse effects in the radiotherapy group. In another trial, only 1/48 (2%) women with Stage IB disease experienced a severe complication (grade 3) in the radiotherapy + hysterectomy group (ureteral stricture) whereas 5/40 experienced severe complications in the radiotherapy group (including rectovaginal fistula, vesicovaginal fistula, ureteral stricture and pelvic infection) (P > 0.05). Similarly in women with Stage IIA disease, 5/14 (40%) women experienced a severe complication in the radiotherapy + hysterectomy group (including proctitis, rectal stricture, small bowel stricture and ureteral stricture) whereas only 1/16 women experienced a severe complication in the radiotherapy group (rectal stricture) (P > 0.05).	374 (2 RCTs)	⊕⊖⊖⊖ **Low**[a,b]	Relative effect measures were not presented due to the crude combining of adverse events or sparse data, or both.

CI: confidence interval; **HR:** hazard ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded one level due to sparse data leading to imprecision.
[b]Downgraded one level due to small number of trials and a lack of representation.
[c]Downgraded one level due to inadequate reporting of results.

- Hysterectomy (simple or radical) with chemoradiotherapy versus chemoradiotherapy alone (2 studies)

Patient or population: women with locally advanced cervical cancer

Settings: outpatient

Intervention: chemoradiotherapy + hysterectomy (simple or radical)

Comparison: chemoradiotherapy alone

Outcomes	Relative effect	No of participants	Certainty of the evidence (GRADE)	Comments
Overall survival Median follow-up 3.8 years	Overall survival was inadequately reported and it was not possible to calculate a hazard ratio. Overall survival time in the chemoradiotherapy + hysterectomy group was 6–40 months, median survival time was 23 months, and 3-year survival rate was 82.7%. Total survival time in the chemoradiotherapy group was 5–41 months, median survival time was 22.5 months and 3-year survival rate was 81.8%. Trial authors reported differences between arms were not statistically significant (P = 0.56).	102 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b]	—
Progression or event-free survival Median follow-up 3.8 years	Progression-free survival was inadequately reported in both trials and it was not possible to calculate a hazard ratio. In 1 trial, progression-free survival time in the chemoradiotherapy + hysterectomy group was 3–40 months, median survival time was 23 months and 3-year survival rate was 73.1%. The progression-free survival time in the chemoradiotherapy alone group was 5–41 months, median survival time was 22 months and 3-year survival rate was 64.8%. There was no significant difference between arms (P = 0.76). Another trial included 61 women and compared chemoradiotherapy + simple or radical hysterectomy vs chemoradiotherapy alone. There was no difference in 3-year event-free (death) survival rate (86% in the chemoradiotherapy + hysterectomy group vs 97% in the chemoradiotherapy alone group; log rank P = 0.15).	163 (2 RCT)	⊕⊖⊖⊖ **Very low**[a,b]	—
Quality of life	—	—	—	Not adequately reported.
Severe/serious adverse events	—	—	—	Not adequately reported.

RCT: randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded two levels due to sparse data leading to imprecision.
[b]Downgraded one level due to small number of trials and a lack of representation.

- Hysterectomy (simple or radical) with chemoradiotherapy versus internal radiotherapy (brachytherapy) with chemoradiotherapy (1 study, 211 women)

Patient or population: women with locally advanced cervical cancer

Settings: outpatient

Intervention: chemoradiotherapy + hysterectomy (simple or radical)

Comparison: chemoradiotherapy alone

Outcomes	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
Overall survival Median follow-up 3 years	**HR 0.65** (95% CI 0.35 to 1.21)	211 (1 RCT)	⊕⊕⊖⊖ **Low**[a,b]	—
Progression or event-free survival Median follow-up 3 years	**HR 0.70** (95% CI 0.31 to 1.34)	211 (1 RCT)	⊕⊕⊖⊖ **Low**[a,b]	—
Quality of life	—	—	—	Not reported.
Severe late complications	There was no difference in the proportion of women with severe late complications in the brachytherapy and radical hysterectomy groups (P = 0.53). There were 4 cases of grade 3 or 4 proctitis in the brachytherapy group vs 2 cases in the radical hysterectomy group; 3 cases of severe cystitis in the brachytherapy group vs 0 in the radical hysterectomy group; 0 cases of grade 3 or 4 hydronephrosis in either group. Of the 211 participants, chemoradiotherapy with cisplatin and gemcitabine appeared to be reasonably well tolerated, although nearly a third of women experienced severe neutropenia (most grade 3). Of the 86 women who received a radical hysterectomy, the number of intraoperative and early surgical complications appeared to be reasonably low, with bleeding (9/86) being the most common.	211 (1 RCT)	⊕⊕⊖⊖ **Low**[a,b]	—

CI: confidence interval; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

[a]Downgraded one level due to sparse data leading to imprecision.
[b]Downgraded one level due to small number of trials and a lack of representation.

Fazit der Autoren

From the available RCTs, we found insufficient evidence that hysterectomy with radiotherapy, with or without chemotherapy, improves the survival of women with LACC who are treated with radiotherapy or CCRT alone. The overall certainty of the evidence was variable across the different outcomes and was universally downgraded due to concerns about risk of bias. The certainty of the evidence for NACT and radical hysterectomy versus radiotherapy alone for survival outcomes was moderate. The same occurred for the comparison involving NACT and hysterectomy compared with CCRT alone. Evidence from other comparisons was generally sparse and of low or very low-certainty. This was mainly based on poor reporting and sparseness of data where results were based on single trials. (…).

3.2 Systematische Reviews

Ronsini, C. et al., 2024 [8].

Locally Advanced Cervical Cancer: Neoadjuvant Treatment versus Standard Radio-Chemotherapy-An Updated Meta-Analysis.

Fragestellung

to provide a solid overview of the topic, focusing on the oncological outcomes of LACC patients undergoing standard treatments compared to adjuvant surgery after CCRT or NAC.

Methodik

Population:

- patients treated for local advanced cervical cancer FIGO 2009 stage IB2-IVA, with or without nodal involvement, or **FIGO 2018 stage IB3-IVA**

Intervention:

- Siehe Ergebnisteil

Komparator:

- Siehe Ergebnisteil

Endpunkte:

- OS, DFS, AEs

Recherche/Suchzeitraum:

- PubMed database and Embase database was performed in April 2023

Qualitätsbewertung der Studien:

- Newcastle-Ottawa scale (NOS)

Ergebnisse

Anzahl eingeschlossener Studien:

- 24 studies matched the inclusion criteria and were included in the metaanalysis. Of those, 16 were comparative studies between CCRT and CCRT followed by surgery, and nine compared CCRT with NACT followed by surgery. → *Hinweis FBMed: Die markierten Studien sind prospektive/randomisierte Studien.*
- One study being included, the one by Shanmugam S. et al., showed data from both comparison groups. → *Hinweis FBMed: Diese Studie war zum Zeitpunkt der Erstellung des CR noch nicht abgeschlossen.*

Charakteristika der Population/Studien:

Comparative Studies

Name	Country	Study Design	Study Year	FIGO Stage	N of Partecipant (NADJ/CCRT)	Mean FUP * Months
Albert A., 2019 [18]	USA	Retrospective Case-Control Monocentric Study	2010–2014	IB2 IIA	1546 (139/1407)	33.3
Cetina L., 2013 [19]	Mexico	Prospective Case-Control Monocentric Study	2004–2009	IB2 IIA2 IIB	211 (111/100)	36
Cetina L., 2009 [20]	Mexico	Retrospective matched Control Monocentric Study	1999–2003	IB2 IIA IIB	140 (40/100)	29
Chereau E., 2013 [21]	France	Retrospective Case-Control Monocentric Study	2002–2012	IB2 II	80 (46/34)	30.7
Darus C., 2008 [22]	USA	Retrospective Case-Control Monocentric Study	1994–2004	IB2	54 (24/30)	46.8
Fanfani F., 2019 [23]	Italy	Retrospective Case-Control Multicentric Study	1999–2013	IIIA IIIB	150 (73/77)	40
Gupta S., 2018 [7]	India	Randomized Control Monocentric Trial	2003–2015	IB2 IIA IIB	633 (316/317)	58.5
Hass P., 2017 [24]	Germany	Retrospective Case-Control Multicentric Study	2003–2011	IB2-IVA	248 (87/161)	57
Hsieh H., 2019 [25]	Republic of China	Retrospective Case-Control Monocentric Study	2002–2016	IB2	66 ^ (39/27)	66.2
Lèguevaque P., 2011 [26]	France	Retrospective Case Control Multicentric Study	1989–2006	IB1-IVA	111 (67/44)	-
Mazeron R., 2016 [27]	Russia	Retrospective Case-Control Monocentric Study	2004–2008	IB1 IB2 IIA IIB	211 (54/157)	57,4
Morice P., 2012 [28]	France	Randomized Control Multicentric Trial	2003–2006	IB2 II	61 (31/30)	44
Ryu H., 2007 [29]	Korea	Retrospective Observational Multicentric Study	1995–2005	IB2	132 ^ (81/51)	120
Sala P., 2022 [30]	Italy	Retrospective Case-Control Multicentric Study	2006–2018	IB2-IVA	106 (55/51)	33
Shanmugam S., 2019 [17]	India	Randomized Control Monocentric Trial	2014–2018	IB2 IIA2 IIB	100 (34/33/33)	28
Sun L., 2014 [31]	China	Retrospective Case-Control Monocentric Study	1992–2012	IIB III IVA	378 (192/186)	190
Sun Y., 2022 [32]	China	Retrospective Case-Control Multicentric Study	2013–2019	IB2 IIA2 IIB	147 (63/84)	60
Tian T., 2021 [33]	China	Retrospective Matched Control Monocentric Study	2013–2017	IB2 IIA2 IIB IIIB	56 [a] (28/28)	-
Wang N., 2014 [34]	China	Prospective Case-Control Monocentric Study	2004–2011	IIB	240 (119/121)	33
Yang J., 2020 [35]	China	Retrospective Case-Control Monocentric Study	2004–2018	IB IIA IIB III	175 (78/97)	20.5
Yang S., 2015 [36]	China	Retrospective Case-Control Monocentric Study	2007–2009	IIB	244 (103/141)	67

Yin M., 2011 [37]	China	Retrospective Case-Control Monocentric Study	2000–2005	IB2 IIA IIB	281 (187/94)	82.8
Yoshida K., 2020 [38]	Japan	Retrospective Matched Case-Control Monocentric Study	2005–2015	IB2 IIA IIB	245 (122/123)	64.8
Zheng D., 2018 [39]	China	Retrospective Case-Control Monocentric Study	2008–2013	IB2 IIB	314 (163/151)	60

* Follow-up, ^ Sub-analysis of the entire cohort. [a]: After propensity score matching, NADJ: neoadjuvant treatments; CCRT: radiochemotherapy.

Studienergebnisse:

- Recurrence Risk:

Metaanalyse (14 studies comparing CCRT and CCRT plus surgery were enrolled, 2544 patients were analyzed)

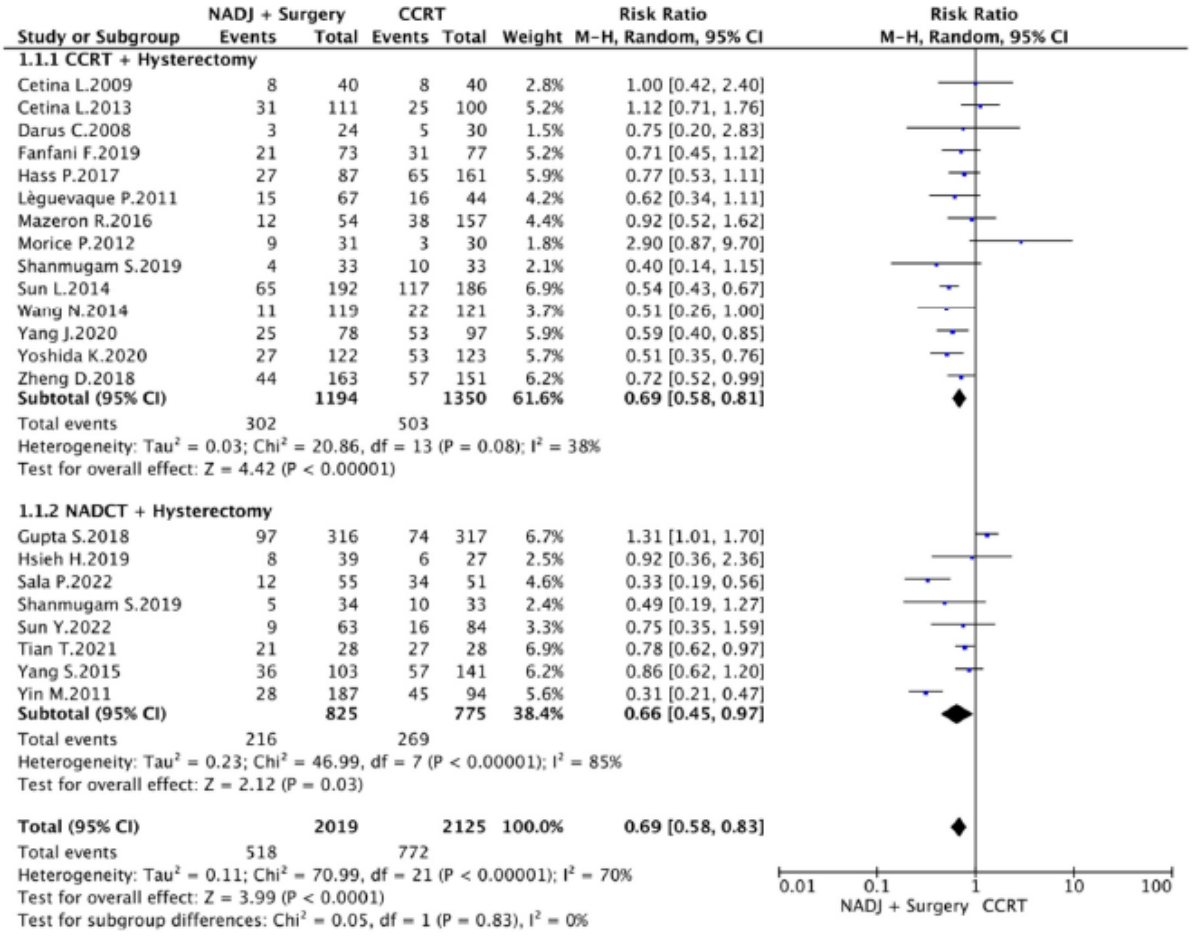


Figure 2. Recurrence Risk [7,17,19,20,22–28,30–39].

- OS:

Metaanalyse: Data on the OS were presented in 15 out of the 16 selected studies. A total of 5694 patients were anayzed.

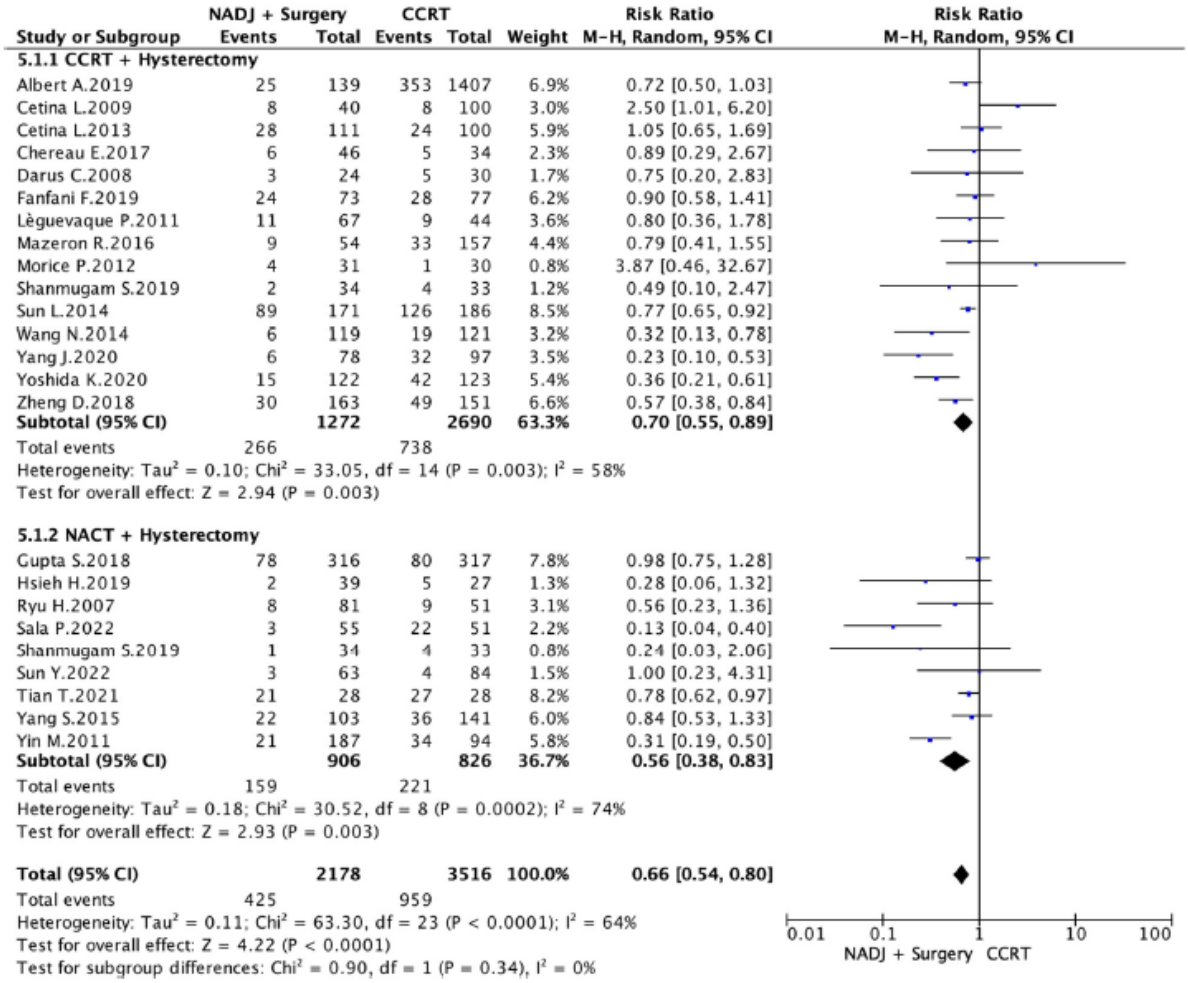


Figure 3. Death Risk [7,17–39].

<u>Nur RCTs:</u> <u>A sub-analysis of the published DFS and OS results of three RCTs, 175 in the CCRT+ surgery group and 163 for the CCRT group</u>

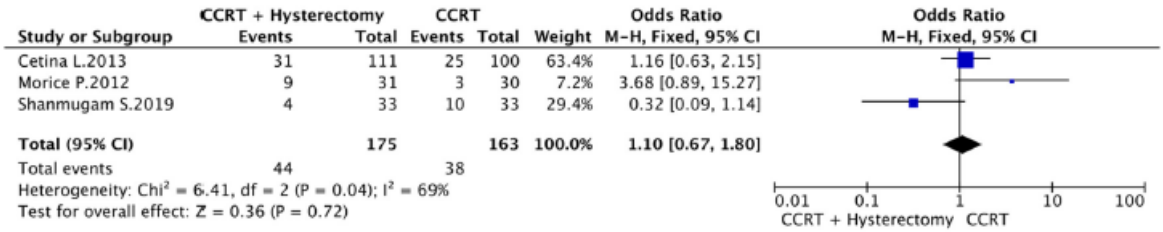


Figure 4. Recurrence Risk RCT [17,20,28].

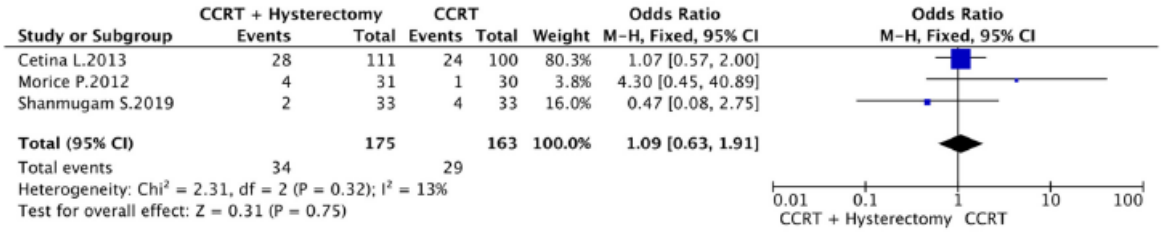


Figure 5. Death Risk RCT [17,20,28].

Fazit der Autoren

Currently, the standard treatment for LACC patients is definitive CCRT, but several controversial treatments still exist in the literature. One of these is represented by the multiplicity of clinical manifestations hidden under the term LACC, which deserves a more personalized treatment. Although the best management strategy remains to be characterized, our work provides updated findings about the efficacy of neoadjuvant treatments, indicating significantly improved DFS and OS in patients undergoing hysterectomy after CCRT or NACT compared with patients undergoing standard treatments. However, given the certain limitations of our results, future controlled clinical trials are required to confirm or disprove the advantages of adjuvant surgery in these patients.

Bacorro, W. et al., 2022 [1].

Outcomes with definitive radiotherapy among patients with locally advanced cervical cancer with relative or absolute contraindications to cisplatin: A systematic review and meta-analysis.

Fragestellung

This systematic review evaluated the evidence on the effectiveness, survival, compliance, and toxicity outcomes with definitive RT with or without ChTamong patientswith bulky or LACC, who have renal failure, obstructive uropathy, cardiac disease or other contraindications to cisplatin.

Methodik

Population:

- patients with bulky or LACC with relative or absolute contraindications to cisplatin

Intervention/Komparator:

- definitive RT with any one or more of the following interventions were eligible: standard ChT (concurrent weekly cisplatin), modified ChT (other than weekly cisplatin, including nonweekly dosing, cisplatin substitution, or multi-agent regimen), withholding of ChT (RT alone), co-intervention (pre-treatment urinary diversion, hyperthermia, renal replacement therapy, nephroprotective agent) Definitive RT may be standard (EBRT five daily fractions weekly, with or without nodal and/or parametrial boost, followed by BRT), or modified (altered fractionation, replacement of BRT with EBRT boost)

Endpunkte:

- tumor response, acute and late toxicity, compliance, survival outcomes, quality of life

Recherche/Suchzeitraum:

- Letzt Suche: 31. März 2022

Qualitätsbewertung der Studien:

- A Risk of Bias Assessment Template was used based on the Critical Appraisal Skills Program (CASP) Randomized Controlled Trial and Cohort Study Standard Checklists to assess quality and risk of bias for each study
- GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- Twenty studies were included for the synthesis: randomized controlled trial (RCT), 1; single-arm clinical trial (SCT), 1; prospective cohort (PRO), 3; retrospective cohort (RET), 15.

Charakteristika der Population/Studien:

- The included studies were conducted in the Asia Pacific, South America, North America, Europe and Oceania, and included cases treated from 1992 to 2016. The contraindications to cisplatin were multiple and various in 7 studies: age, renal failure, poor PS, comorbidity, etc. Twelve studies were elderly cohorts with different age cut-offs: 65 (4), 70 (6), 75 (1), and 80 (1). One studywas a renal failure cohort.
- Seven studies hadmultiple intervention groups that were eligible for inclusion in the synthesis: three groups in a RET, and two groups each in a RCT and 5 RET. The remaining studies each had a single intervention group that was eligible: a SCT, 3 PRO, and 9 RET. Five intervention categories were represented: standard CRT (1 RCT, 3 RET); modified ChT with standard RT (modified CRT) (1 RCT, 2 PRO, 8 RET); standard RT alone (11 RET); modified RT (1 SCT); and standard ChT with modified RT (1 PRO). The modified ChT regimens included: carboplatin (5), cisplatin +5-fluorouracil (3), daily low-dose cisplatin (1), oral vinorelbine (1), and gemcitabine (1). The modified RT regimens were accelerated EBRT (given six daily fractions weekly) without concurrent ChT, and followed by BRT (1), and definitive EBRT with concurrent cisplatin, without BRT.

Qualität der Studien:

- The only RCT was associated with high risk of bias due to lack of blinding, given that it is a comparison of intravenous cisplatin and oral vinorelbine. The only non-controlled clinical trial was evaluated to be of low risk. One of the three prospective observational cohorts was associated with high risk of bias due to use of a nonconventional EBRT regimen (split-course) and use of only pelvic EBRT despite inclusion of cases with para-aortic nodes (measurement bias). The retrospective cohort studies were associated with high risk of bias mainly due to confounding factors, and some due to selection or measurement bias. In general, however, the studies employed interventions that are current and provide outcomes data for the population and interventions of interest.

Studienergebnisse:

- *Hinweis FBMed:* Die markierte Quelle ist die randomisiert/kontrollierte Studie.

Table 2a
Tumor response rates and survival outcomes according to interventions groups.

Study information		Intervention groups and baseline characteristics								Follow-up (Months)		Tumor response rate		Survival outcomes			
Study ID		N	Patient				Disease			Mdn	Range	Complete response		5y DFS		5y OS	
			MdnAge	AA Cutoff, %	%RF	% PS ≥ 2	% SCC	% FIGO III-IVA	% N1			%	95% CI	%	95% CI	%	95% CI
Standard chemoradiotherapy (n = 4)																	
Coronel 2013	RCT	20	65	≥65, 40	–	–	75	15	–	16	4–19	–	–	–		–	
Caires 2015	RET	18	73	≥65, 100	–	11	95	≥IIB, 100	–	26	–	–	–	–		–	
Guler 2017	RET	224	–	≥65, 100	–	–	94	≥IIB, 84	33	39	2–176	–	–	–		–	
Wang 2019	RET	24	74	≥70, 100	13	–	93	27	15	32	5–119	–	–	80	58–93	82	63–95
Modified chemotherapy with standard radiotherapy (n = 11)																	
Coronel 2013	RCT	19	67	≥65, 47	–	–	84	32	–	16	4–19	–	–	–		–	
Cetina 2004	PRO	9	51	–	100	45	100	90	–	11	6–14	89	52–100	–		–	
Nam 2013	PRO	51	65[b]	≥60, –	100	24	92	32	43	36	4–66	50	36–64	74[a]	60–85	88	76–95
Cetina 2008	RET	59	62	≥70, 15	–	–	88	25	–	20	2–48	83	71–92	–		–	
Park 2010	RET	44	69	≥65, 100	–	7	100	36	39	41	0–120	86	71–95	69[d]	52–81	62	46–76
Au-Yeung 2013	RET	59	73	≥65, –	27	–	92	34	44	38	18-64[c]	–	–	54	41–67	44	31–58
Caires 2015	RET	12	73	≥65, 100	100	11	95	≥IIB, 100	–	26	–	–	–	–		–	
Hanawa 2015	RET	53	72	≥70, 100	–	8	81	30	19	32	2–104	92	80–98	–		76	62–88
Nosaka 2016	RET	20	73	≥70, 100	–	0	65	50	–	26	–	–	–	–		60	36–81
Sebastião 2016	RET	25	64[b]	–	–	17	96	52	–	36	–	78	51–88	–		–	
You 2019	RET	138	68	≥65, 100	–	10	60	79	41	49	19–93	–	–	76	67–82	82	75–89
Standard radiotherapy (n = 11)																	
Chen 2003	RET	79	75	≥70, 100	3	–	95	20	–	56	37–108	–	–	88[e]	78–94	60	48–70
Park 2010	RET	61	71	≥65, 100	–	15	93	32	25	41	0–120	85	73–93	67[d]	54–79	54	41–67
Caires 2015	RET	17	73	≥65, 100	12	11	95	≥IIB, 100	–	26	–	–	–	–	–	–	–
Nosaka 2016	RET	29	77.9	≥70, 100	–	24	86	45	–	26	–	–	–	–	–	42	23–61
Guler 2017	RET	45	–	≥65, 100	–	–	94	≥IIB, 84	33	39	2–176	–	–	–	–	–	–
Hata 2017	RET	30	84	≥80, 100	–	20	100	57	10	24	2–109	–	–	–	–	–	–
Wang 2017	RET	99	79	≥75, 100	–	–	99	9	1	58	–	–	–	–	–	49	39–60
Kobayashi 2019	RET	105	77	≥70, 100	–	–	100	38	26	59	6–203	–	–	89[f]	79–94	62	51–70
Wang 2019	RET	49	74	≥70, 100	–	–	93	27	15	32	5–119	–	–	51	42–71	57	42–71
You 2019	RET	108	71	≥65, 100	–	19	68	71	45	48	10–107	–	–	58	48–68	73	64–81
Gurram 2020	RET	33	57	≥70, –	–	–	98	100	–	30	10–83 (IQR)	85	68–95	26	13–46	34	18–52
Modified radiotherapy (n = 1)																	
Yoon 2006	SCT	43	62	≥65, –	–	–	98	21	30	37	9–60	79	64–90	87[e]	72–98	70	54–83
Standard chemotherapy with modified radiotherapy (n = 1)																	
Mazzola 2017	PRO	30	72	≥70, 100	–	0	100	47	27	32	8–50	–	–	–	–	–	–

AA, advanced age; CI, confidence interval; DFS, disease-free survival; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; Mdn, median; SCT, single-arm clinical trial; OS, overall survival; PRO, prospective cohort; PS, performance status; RCT, randomized controlled trial; RET, retrospective cohort; RF, renal failure; SCC, squamous cell carcinoma.

[a] Progression-free survival.
[b] Mean.
[c] Interquartile range.
[d] Cancer-specific survival.
[e] Locoregional failure free survival.
[f] Local control rate.

Table 2b
Compliance rates and toxicity outcomes according to interventions groups.

Study information			Compliance rate					Acute toxicity[a]	Late toxicity[a]	
Study ID		N	ChT		RT		Notes	Grade 3–4 (%)	Grade 3–4 (%)	Others
			%	95% CI	%	95% CI				
Standard chemoradiotherapy										
Coronel 2013	RCT	20	~66	41–85	100	83–100		GI, 0 GU, 0 Neutropenia, 0 Nausea, 5% Vomiting, 10% Renal, 0	0	
Caires 2015	RET	18	63	36–83	–	–	ChT non-completion due to renal toxicity.	GI, 6% Renal, 28%	–	
Guler 2017	RET	224	89	84–93	100	98–100	Study included only those who have completed RT.	–	–	
Wang 2019	RET	24	46	26–67	96	79–100	RT non-completion due to toxicity, 1. ChT non-completion due to toxicity.	GI, 21% GU, 17% Renal, 4%	GI, 0 GU, 4%	
Modified chemotherapy with standard radiotherapy										
Coronel 2013	RCT	19	~66	41–85	95	74–100	RT non-completion due to non-receipt of BRT due to technical reasons	GI, 0 GU, 0 Neutropenia, 32% Vomiting, 5% Renal, 0	Any, 0	
Cetina 2004	PRO	9	100	66–100	100	66–100		GI: colitis, 11%; proctitis, 11% Neutropenia, 66% Nausea/vomiting, 22% Renal, 0	Any, 0	
Nam 2013	PRO	51	90	79–97	–	–	ChT compliance: ≥6 of 9 cycles.	GI, 0 GU, 0 Neutropenia, 10%; Nausea/vomiting, 0 Renal, 2%	–	
Cetina 2008	RET	59	78	65–88	92	81–97	ChT compliance: ≥5 of 6 cycles.	GI, 0 GU, 0 Neutropenia, 14% Nausea/vomiting, 0 Renal, —	Any, 0	
Park 2010	RET	44	75		86		ChT non-completion due to toxicity, 8; comorbidity, 1; and refusal, 2. RT non-completion due to toxicity, 3.	GI, 0 GU, 0	GI, 2% GU, 0	
Au-Yeung 2013	RET	59	–	–				–	–	
Caires 2015	RET	12	67	35–90	–	–	ChT non-completion due to renal toxicity.	GI, 8% Renal, 8%	–	
Hanawa 2015	RET	53	60	46–74	87	75–95	ChT non-completion due to toxicity. Non-receipt of BRT in 13%.	GI: diarrhea, 9% GU, 0 Neutropenia, 36%; Nausea/vomiting, 6% Renal, 0	GI: rectal bleeding, 6%	Insufficiency fractures: pelvic, 4%; femoral, 2%
Nosaka 2016	RET	20	70	46–88	70	46–88	CRT discontinuation due to SIADH, 2; fainting, 1; renal dysfunction, 1; fracture from falling, 1; patient wish, 1.	GI: diarrhea, 10% Neutropenia, 15% Renal: renal dysfunction, 5%	–	
Sebastião 2016	RET	25	84	64–95	–	–	ChT compliance: ≥5 cycles.	Any, 12%	Bladder or rectal fistulae, 17% Renal, 8%	Cystitis, 0 Proctitis/enteritis, 8%
You 2019	RET	138	–	–	–	–		GI: abdominal pain, 6%; diarrhea, 19%; enteritis, 7% Neutropenia, 17% Vomiting, 15%	–	
Standard radiotherapy										
Chen 2003	RET	79	NA	NA	99	93–100		GI, 3%	GI: rectal, 15%; small bowel, 3% GU: bladder, 3%	Avascular necrosis of he femoral head, 1%
Park 2010	RET	61	NA	NA	87	76–94	RT non-completion due to toxicity, 2.	GI, 0 GU, 0	GI, 7% GU, 3%	
Caires 2015	RET	17	NA	NA	82	57–96		Renal, 0	Renal, 0	
Nosaka 2016	RET	29	NA	NA	90	73–98	RT non-completion due to dementia, 1; cerebral infarction, 1; patient wish, 1.	GI: diarrhea, 3%; Intestinal hemorrhage, 3%; enteritis, 10% Neutropenia, 0 Renal, 0	–	
Guler	RET	45	NA	NA	100	94–100	Study included only those who have	–	–	

2017							completed RT.			
Hata 2017	RET	30	NA	NA	80	61–92	RT non-completion due to non-receipt of BRT due to dementia or technical reasons	GI, 0 GU, 0 Nausea, vomiting, 0	Any, 0	
Wang 2017	RET	99	NA	NA	–	–		–	Proctitis, 18% Cystitis, 0	
Kobayashi 2019	RET	105	NA	NA	100	97–100		–	GI: rectum, 2% GU: bladder, 6%	
Wang 2019	RET	49	NA	NA	96	86–100	RT non-completion due to refusal to undergo BRT, 2.	GI, 18% GU, 10%	GI, 4% GU, 2%	
You 2019	RET	108	NA	NA	–	–		GI: abdominal pain, 3%; enteritis, 3%; diarrhea, 6% Neutropenia, 6% Vomiting, 4%	–	
Gurram 2020	RET	33	NA	NA	100	89–100	Study included only those who have completed RT.	–	–	
Modified radiotherapy										
Yoon 2006	SCT	43	NA	NA	93	82–98	Three patients who were excluded from the study cohort due to non-receipt of BRT were accounted for.	GI, 2% GU, 0	GI, 0 GU, 2%	RT-induced osteitis, 5%, insufficiency fracture, 5%
Standard chemotherapy with modified radiotherapy										
Mazzola 2017	PRO	30	83	65–94	100	88–100	CT non-completion due to very advanced age (≥80), 3; renal dysfunction pre-treatment, 1, and in-treatment, 1.	GI, 0 GU, 0 Renal, 3%	Any, 0	

BRT, brachytherapy; ChT, chemotherapy; CI, confidence interval; CrCl, creatinine clearance; GI, gastrointestinal; GU, genitourinary; HEMA, hematologic; NCT, single-arm clinical trial; PRO, prospective cohort; RCT, randomized clinical trial; RET, retrospective cohort; RT, radiotherapy.

[a] No grade 5 toxicity was reported.

Fazit der Autoren

In summary, published literature on treatment outcomeswith definitive RT with or without ChT in LACC patients with contraindications to cisplatin are mostly limited to non-comparative observational studies. For those with relative contraindications, concurrent cisplatin is effective and well-tolerated. For those with absolute contraindications, carboplatin is well-tolerated but with unclear effectiveness. NB is effective and well-tolerated, but is less tolerated when concurrent ChT is given. In elderly patients, the addition and choice of ChT agent is best guided by screening for frailty or a formal geriatric assessment.

3.3 Leitlinien

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften), 2022 [5] & [4].

Diagnostik, Therapie und Nachsorge der Patientin mit Zervixkarzinom; S3-Leitlinie, Langversion 2.2.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Suchzeitraum vom 01.03.2013 bis zum 31.12.2018

LoE/GoR

Tabelle 6: Festlegungen hinsichtlich der Konsensstärke

Konsensstärke	Prozentuale Zustimmung
Starker Konsens	> 95% der Stimmberechtigten
Konsens	>75 – 95% der Stimmberechtigten
Mehrheitliche Zustimmung	50 – 75% der Stimmberechtigten
Dissens	<50% der Stimmberechtigten

Tabelle 7: verwendete Empfehlungsgrade

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

Sonstige methodische Hinweise

- Hinweis zu der in dieser LL verwendeten FIGO Klassifikation:

  Die 2018 publizierte neue FIGO-Klassifikation: Diese integriert lange vorhandene Kritikpunkte, wie zum Beispiel Integration von bildgebenden oder operativen

diagnostischen Verfahren und die Klassifikation der paraortalen Lymphknoten als pN1 und nicht mehr pM1. A**uf Grund der derzeit nicht konkruenten Klassifikation zwischen FIGO (neu) und TNM (alt) ist in der jetztigen überarbeiteten Version aber weiterhin die alte FIGO Version gültig. Auf Grund der erst 2018 publizierten neuen Klassifikation liegen aktuell auch noch keine Daten aus Studien vor, die auf der neuen Klassifikation basieren, so dass die Leitliniengruppe es für gerechtfertigt erarchtet hat, hier die alte Version weiter fortzuführen.**

Empfehlungen

Tabelle 19: Übersicht der TNM-Kategorien/ FIGO-Stadien (modifiziert 2021)

TNM-Kategorien (2017 & 2020)	FIGO-Stadien (2009)	Definition	FIGO-Stadien (2018)	Definition
T3	III	Tumor breitet sich bis zur Beckenwand aus und/oder befällt das untere Drittel der Vagina und/ oder verursacht Hydronephrose oder eine stumme Niere	III	Tumor breitet sich bis zur Beckenwand aus und/oder befällt das untere Drittel der Vagina und/ oder verursacht Hydronephrose oder eine stumme Niere
T3a	IIIA	Tumor infiltriert das untere Drittel der Vagina, keine Ausbreitung zur Beckenwand	IIIA	Tumor infiltriert das untere Drittel der Vagina, keine Ausbreitung zur Beckenwand
T3b	IIIB	Tumor breitet sich bis zur Beckenwand aus und/ oder verursacht Hydronephrose oder eine stumme Niere	IIIB	Tumor breitet sich bis zur Beckenwand aus und/ oder verursacht Hydronephrose oder eine stumme Niere
pN1 bzw. pM1	IVa	Metastasen in pelvinen und/oder paraaortalen Lymphknoten, ungeachtet der Tumorgröße und –ausbreitung	IIIC	Metastasen in pelvinen und/oder paraaortalen Lymphknoten, ungeachtet der Tumorgröße und –ausbreitung[4]
pN1	IVa	Metastasen nur in pelvinen Lymphknoten	IIIC1	Metastasen nur in pelvinen Lymphknoten[4]
pM1	IVa	Metastasen in paraaortalen Lymphknoten (unabhängig, ob pelvine Lymphknoten befallen sind, oder nicht)	IIIC2	Metastasen in paraaortalen Lymphknoten (unabhängig, ob pelvine Lymphknoten befallen sind, oder nicht)[4]
T4	IV	Tumor infiltriert die Schleimhaut von Blase oder Rektum oder überschreitet die Grenze des kleinen Beckens	IV	Tumor infiltriert die Schleimhaut von Blase oder Rektum oder überschreitet die Grenze des kleinen Beckens
T4	IVa	Tumorinfiltriert die Schleimhaut von Blase oder Rektum oder überschreitet die Grenze des kleinen Beckens	IVa	Ausbreitung in Organe des kleinen Beckens

8.5.2. Therapie des lokal fortgeschrittenen Zervixkarzinoms (FIGO-Stadium IIB bis IVA und IB2/IIA2 mit mehreren histologischen Risikofaktoren oder pN1 und c/pM0)

Unter einem lokal fortgeschrittenen Zervixkarzinom werden Patientinnen mit einem Stadium IIB bis IVa Zervixkarzinom verstanden. Mittlerweile wird bereits ab einem Stadium IB2 und IIA2 mit mehreren histologisch nachgewiesenen Risikofaktoren (Tumoreigenschaften bzw. befallene pelvine Lymphknoten) ebenfalls von einem lokal fortgeschrittenen Zervixkarzinom gesprochen [273]. Bei einem lokal fortgeschrittenen Zervixkarzinom und damit potentiellem Einsatz von mehreren sukzessiv eingesetzten Therapiemodalitäten, liegt die Indikation zur cisplatinhaltigen Radio(chemo)therapie mit Brachytherapie vor. Gegebenenfalls wird die extended-field-Radiotherapie bei histologisch nachgewiesenen paraaortalen Lymphknoten (pM1) nötig. Hier liegt dann bereits eine metastasierte Situation (UICC-Stadium IVB) vor (siehe Kapitel 8.5.4). Nach der neuen FIGO Klassifikation von 2018 gelten paraaortale Lymphknotenmetastasen als regionäre Lymphknotenmetastasen und nicht wie bisher als Fernmetastasen. Davon unabhängig ist es entscheidend für das Zielvolumen der Radiotherapie zu definieren, ob ein pelviner und/oder paraaortaler Lymphknotenbefall vorliegt. Hierzu wird in Deutschland ein (laparoskopisches) Operatives Staging durchgeführt zur histologische Detektion von Lymphknotenmetastasen (inklusive Mikrometastasen) bzw. zur Diagnostik der pelvinen Ausbreitung (z. B. Peritonealkarzinose, etc.) im Bauchraum haben keine ausreichende diagnostische Sicherheit. Die MRT zur Einschätzung der lokoregionären Ausbreitung des zentralen Tumors bzw. die CT zur Beurteilung der Lymphknoten und der Beckenwände können eingesetzt werden. Die PET hat derzeit keine Bedeutung für die Therapieplanung des primären Zervixkarzinoms und sollte speziellen Fragestellungen in der Rezidiv-Situation vorbehalten sein. Bei V.a. einen Tumor muss die histologische Sicherung vor der Therapieplanung erfolgen.

8.6. Stadienabhängige Therapie

- 8.6.2.4. FIGO-Stadium III: Histologisch gesichertes invasives Zervixkarzinom Stadium III

8.17.	Konsensbasierte Empfehlung	Geprüft 2021
EK	Im *Stadium III* sollte folgendermaßen therapiert werden:	

	Operation:
	• histologische Verifizierung der Ausbreitung
	  ○ Operatives Staging oder interventionelle Abklärung.
	• bei makroskopisch tumorbefallenen pelvinen und/oder paraaortalen Lymphknoten:
	  ○ operative Entfernung vor einer Radio(chemo)therapie.	

	Radio(chemo)therapie: • R(CH)T nach Operativem Staging.	
	Starker Konsens	

Hintergrund:

Unter R(CH)T wird in der vorliegenden Leitlinie die simultane Radiochemotherapie mit Cisplatin als Radiosensitizer verstanden. Diese unterscheidet sich von anderen Regimen einer sequentiellen und konsekutiven Radiochemotherapie, die in verschiedenen Studiendesigns Anwendung finden, aber nicht das Standardverfahren darstellen. Ab Stadium III ist sie der therapeutische Goldstandard (bereits ab Stadium IIB ist der bevorzugte Einsatz indiziert). Kontraindikationen gegen eine kombinierte simultane

cisplatinhaltige Radiochemotherapie sind z.B. eine Niereninsuffizienz. Hier ist eine alleinige Radiotherapie möglich. (…)

- 8.6.2.5. FIGO-Stadium IV: Histologisch gesichertes invasives Zervixkarzinom Stadium IVA und IVB

8.18.	Konsensbasierte Empfehlung	Geprüft 2021
EK	Im *Stadium IVA* sollte folgendermaßen therapiert werden:	
	Operation: • in ausgesuchten Fällen: ○ primäre Exenteration;	
	Radio(chemo)therapie: • R(CH)T ist Therapie der Wahl.	
	Starker Konsens	

Hintergrund:

Die Datenlage zu dieser Empfehlung ist im Kapitel 17 Lokalrezidiv dargestellt. Hier werden auch die speziellen Situationen in denen eine Exenteration möglich ist dargestellt. Insgesamt ist die Datenlage hier aber auch sehr eingeschränkt. So konnte ein aktuelles Cochrane Review von 2014, das die Effektivität und Sicherheit exenterativer Verfahren bei gynäkologischen Malignomen (ohne Ovarialkarzinom) im Vergleich zu anderen Therapieoptionen untersuchte, kein RCT identifizieren, das den Einschlusskriterien entsprach [312].

Unter R(CH)T wird in der vorliegenden Leitlinie die simultane Radiochemotherapie mit Cisplatin als Radiosensitizer verstanden (siehe für Details Abschnitt 8.6.2.4).

10.1.2. Technik der Brachytherapie in der primären kombinierten Radio(chemo)therapie

10.2.	Leitlinienadaptierte Empfehlung	Geprüft 2021
Empfehlungsgrad B	Die Brachytherapie sollte Bestandteil des kurativen Therapiekonzeptes in der Primärtherapie des Zervixkarzinoms, die eine Radio(chemo)therapie beinhaltet, sein.	
Level of Evidence 4	Leitlinienadaptation: [85]	
	Starker Konsens	

10.3.	Konsensbasierte Empfehlung	Modifiziert 2021
EK	In der primären Radiochemotherapie des Zervixkarzinoms sollte die MRT-geplante Brachytherapie eingesetzt werden, um die Rate und den Schweregrad gastrointestinaler und urogenitaler Toxizitäten zu reduzieren	
	Starker Konsens	

Hintergrund:

Die Brachytherapie im Bereich des makroskopischen Tumors ist eine obligate Komponente der Radiochemotherapie des Zervixkarzinoms [358]. Die Brachytherapie sollte bevorzugt als „Image-guided adaptive brachytherapy“(IGABT), durchgeführt werden. Grundlage ist die Durchführung eines MRT der Beckenregion vor Einleitung der Radiochemotherapie und mindestens eines MRT zum Beginn des Afterloadings. Die Empfehlungen zur technischen Durchführung der MRTs sind publiziert, sie sollten einheitlich gehandhabt werden [359]. Repetitiv durchgeführte MRT-Untersuchungen ermöglichen eine adaptive Bestrahlungsplanung. Dabei werden nach MRT-gestützter Planung im HDR- (high dose rate) oder PDR- (pulse dose rate) Verfahren 40 - 50 Gy Äquivalenzdosis (EQD2, Alpha/Beta 10 Gy) in in drei bis fünf Fraktionen appliziert. Die EQD2 im Bereich des Tumors aus perkutaner Bestrahlung und Brachytherapie sollte mindestens 85 Gy erreichen [360]. Die Zielvolumina schließen den Tumorrest nach bzw. unter laufender perkutaner Strahlentherapie als Gross tumour volume (GTV), die gesamte Zervix inklusive des vermuteten mikroskopischen Befall als sog. High risk clinical target volume (HRCTV) ein. Das GTV ist Teil des HRCTV. Als Intermediate risk clinical target volume (IRCTV) wird die initiale Ausdehung vor Beginn der perkutanen Therapie definiert. Die abgestuften Dosisempfehlungen werden in den GEC-ESTRO Empfehlungen und im ICRU Report 89 definiert [361, 362]. Die Dosisverschreibung in der 4D-Brachytherapie entspricht den Zielvolumina und Dosis-Effekt-Kurven. [7,8,9] Die Gesamtbehandlungsdauer aus Tele- und Brachytherapie sollte 45 – 50 Kalendertage nicht überschreiten (6), da jeder zusätzliche Tag das Gesamtüberleben nach fünf Jahren um jeweils ein Prozent reduziert. [2]

10.1.4. Indikation zur primären Radiatio oder Radio(chemo)therapie

10.4.	Evidenzbasierte Empfehlung	Geprüft 2021
Empfehlungsgrad A	Bei der Patientin mit Zervixkarzinom soll bei Indikationsstellung zu einer primären Radiotherapie ab Stadium IB2 diese in Kombination mit einer cisplatinbasierten Chemotherapie erfolgen.	
Level of Evidence 1++	Literatur: [363, 364]	
	Konsens	

10.1.5. Adjuvante Radio(chemo)therapie

10.5.	Konsensbasierte Empfehlung	Geprüft 2021
Empfehlungsgrad B	Die adjuvante cisplatinhaltige Radiochemotherapie sollte bei Patientinnen mit histologisch gesicherten postoperativen Risikofaktoren zum Einsatz kommen.	
Level of Evidence 1-	Literatur: [366, 382]	
	Konsens	

10.1.7. Adjuvante Chemotherapie nach abgeschlossener Radio(chemo)therapie

10.6.	Evidenzbasiertes Statement	Geprüft 2021
Level of Evidence 1-	Der Stellenwert der konsolidierenden Chemotherapie nach abgeschlossener Radio(chemo)therapie ist nicht gesichert.	
	Literatur [367, 399]	
	Starker Konsens	

10.1.8. Neoadjuvante Radio(chemo)therapie

10.7.	Konsensbasierte Empfehlung	Geprüft 2021
EK	Die neoadjuvante Radio(chemo)therapie sollte außerhalb von Studien nicht angewandt werden.	
	Starker Konsens	

10.1.9. Ovarerhalt und Fertilität

10.8.	Konsensbasierte Empfehlung	Geprüft 2021
EK	Zum Erhalt der hormonellen Funktion des Ovars sollte der jungen Patientin die Ovariopexie und hochkonformale Strahlentherapietechniken angeboten werden.	
	Starker Konsens	

NCCN, 2004 [6].

Cervical cancer; Version 4.2024.

Zielsetzung/Fragestellung

Empfehlungen zur Therapie des Zervixkarzinoms.

Grundlage der Leitlinie

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz zu den verschiedenen Therapielinien und der Aktualität, wird die LL jedoch ergänzend dargestellt.

- Repräsentatives Gremium: Trifft teilweise zu
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: Trifft teilweise zu
- Systematische Suche, Auswahl und Bewertung der Evidenz: Trifft teilweise zu
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: Trifft teilweise zu
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;

- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- K.A.

LoE/GoR

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

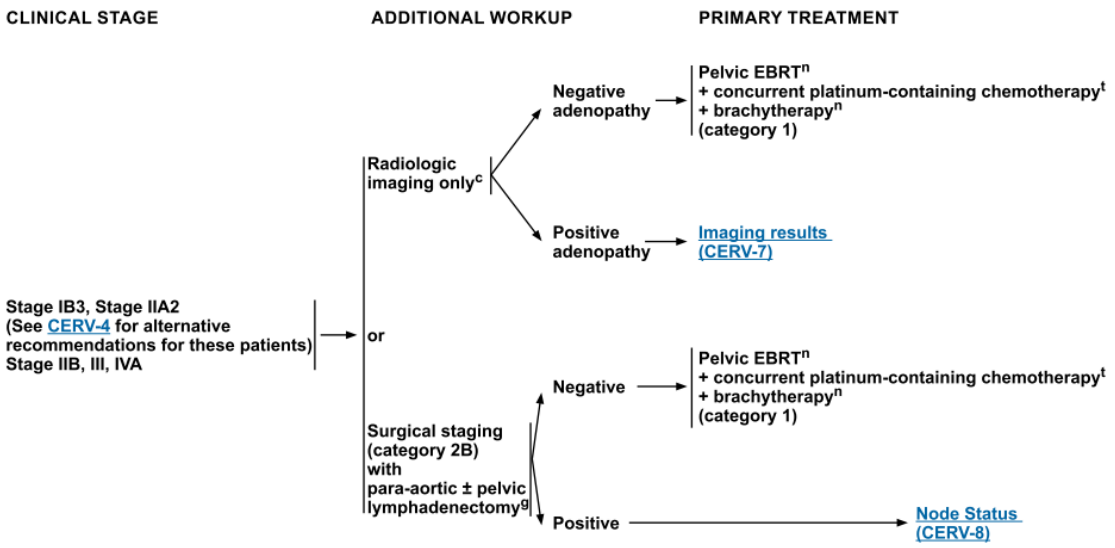
All recommendations are considered appropriate.

Sonstige methodische Hinweise:

- Diese LL nutzt die FIGO 2018 Klassifikation

Recommendations

Stage IB3, Stage IIA2, and Stages IIB, III, and IVA

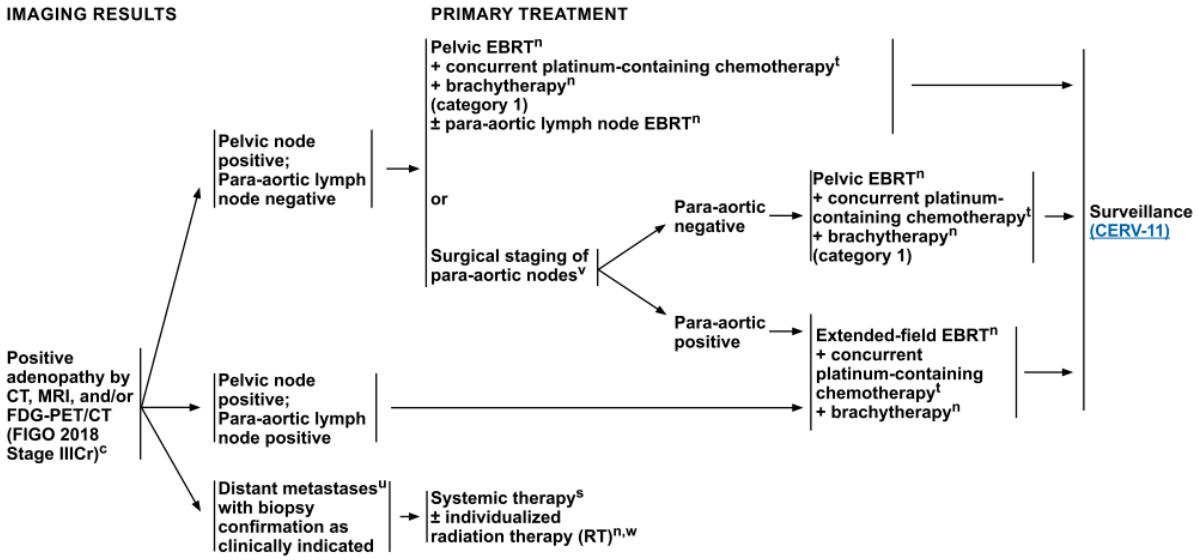


[c] Principles of Imaging (CERV-B).
[g] Principles of Evaluation and Surgical Staging (CERV-C).
[n] Principles of Radiation Therapy (CERV-D).
[t] Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant). Pembrolizumab may be added with chemoradiation (CRT) **ONLY** for patients with FIGO 2014 Stage III-IVA cervical cancer. (See Systemic Therapy for Cervical Cancer [CERV-F]).

Surveillance (CERV-11)

Note: All recommendations are category 2A unless otherwise indicated.

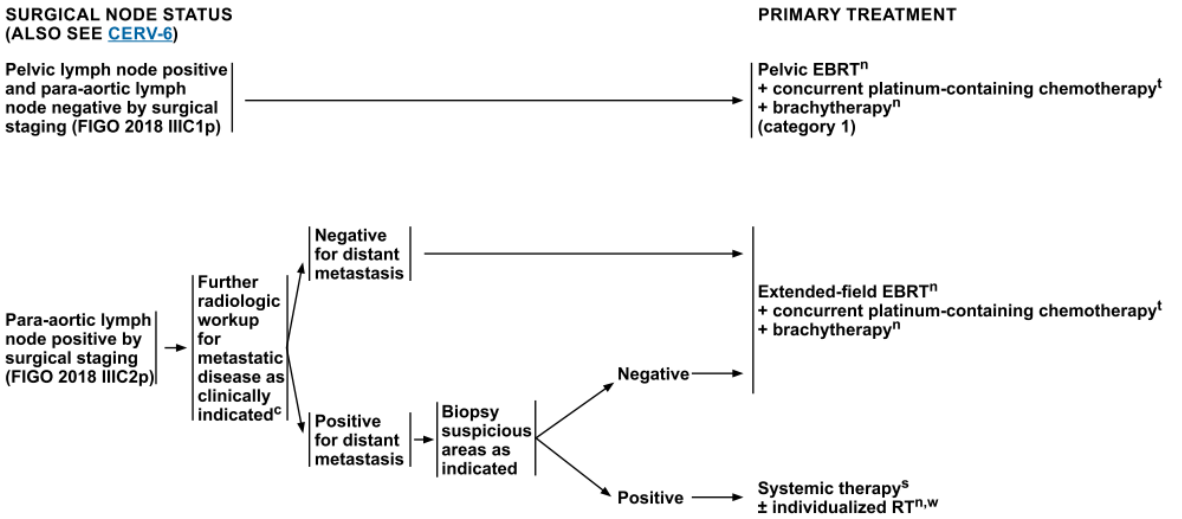
CERV-6



c Principles of Imaging (CERV-B).
n Principles of Radiation Therapy (CERV-D).
s Systemic Therapy for Cervical Cancer (CERV-F).
t Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant). Pembrolizumab may be added with CRT **ONLY** for patients with FIGO 2014 Stage III-IVA cervical cancer. (See Systemic Therapy for Cervical Cancer [CERV-F]).
u Patients with distant metastatic disease confined to the supraclavicular nodes may be treated definitively. (Kim JY, et al. Int J Radiat Oncol Biol Phys 2012;84:741-747.)
v Consider postoperative imaging (abdomen/pelvis CT with contrast or MRI with and without contrast) to confirm the adequacy of node removal.
w Consider ablative therapy for 1–5 metastatic lesions (category 2B) if the primary has been controlled. (Palma DA, et al. Lancet 2019;393:2051-2058.)

Note: All recommendations are category 2A unless otherwise indicated.

CERV-7



c Principles of Imaging (CERV-B).
n Principles of Radiation Therapy (CERV-D).
s Systemic Therapy for Cervical Cancer (CERV-F).
t Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant). Pembrolizumab may be added with CRT **ONLY** for patients with FIGO 2014 Stage III-IVA cervical cancer. (See Systemic Therapy for Cervical Cancer [CERV-F]).
w Consider ablative therapy for 1–5 metastatic lesions (category 2B) if the primary has been controlled. (Palma DA, et al. Lancet 2019;393:2051-2058.)

Note: All recommendations are category 2A unless otherwise indicated.

Surveillance (CERV-11)

CERV-8

PRINCIPLES OF EVALUATION AND SURGICAL STAGING

TABLE 2: Resection of Locally Recurrent Cervical Cancer with No Distant Metastasis[j]

	Comparison of Infralevator Exenteration Types			Comparison of Supralevator Exenteration Types	
	Anterior	Posterior	Total	Posterior	Total
Indication	Central pelvic recurrence Primary therapy for select FIGO stage IVA when primary radiation not feasible				
Intent	Curative				
Uterus, tubes, ovaries	Removed if still present	Removed if still present	Removed if still present	Removed if still present	Removed if still present
Vagina	Removed	Removed	Removed	Removed	Removed
Bladder and urethra	Removed	Preserved	Removed	Preserved	Removed
Rectum	Preserved	Removed	Removed	Removed	Removed
Anal sphincter	Preserved	Removed	Removed	Preserved, colonic anastomosis possible	Preserved, colonic anastomosis possible
Reconstruction options Urinary system	Ileal conduit or Continent diversion	N/A	Double barrel wet colostomy,[n] ileal conduit, or continent diversion	N/A	Double barrel wet colostomy,[n] ileal conduit, or continent diversion
Reconstruction options GI system	N/A	End colostomy	Double barrel wet colostomy[n] or end colostomy	End colostomy or anastomosis with temporary ileostomy	Double barrel wet colostomy,[n] end colostomy, or anastomosis with temporary ileostomy
Neovaginal reconstruction options	Myocutaneous flap (rectus, gracilis, etc.), or split-thickness skin graft with omental J-flap				

[j] Cibula D, Abu-Rustum NR, Benedetti-Panici P, et al. New classification system of radical hysterectomy: emphasis on a three-dimensional anatomic template for parametrial resection. Gynecol Oncol 2011;122:264-268.
[n] Backes FJ, Tierney BJ, Eisenhauer EL, et al. Complications after double-barreled wet colostomy compared to separate urinary and fecal diversion during pelvic exenteration: time to change back? Gynecol Oncol 2013;128:60-64.

References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY[1]

General Principles

- **The use of CT-based treatment planning and conformal blocking is considered the standard of care for EBRT. MRI is the best imaging modality for determining soft tissue and parametrial involvement in patients with advanced tumors. In patients who are not surgically staged, FDG-PET imaging is useful to help define the nodal volume of coverage, and may be useful postoperatively to confirm removal of abnormal nodes.**
- **RT is directed at sites of known or suspected tumor involvement. EBRT is directed to the pelvis with or without the para-aortic region.**
- **IMRT technique is preferred to minimize toxicities in definitive treatment of the pelvis with or without para-aortic treatment. Regular use of image-guided radiation therapy (IGRT) with orthogonal imaging and/or routine volumetric imaging (such as cone beam CT) at the time of treatment delivery, is essential to ensure appropriate coverage of targets and sparing of normal tissues.**
- **Brachytherapy is a critical component of definitive RT for all patients with primary cervical cancer. This is performed using an intracavitary and/or an interstitial approach.**
- **For the majority of patients who receive EBRT for cervical cancer, concurrent platinum-containing chemotherapy is given during the time of EBRT.**
- **Optimal results are achieved when treatment is completed within 8 weeks.**

PRINCIPLES OF RADIATION THERAPY[1]

General Treatment Information—Continued

Definitive RT for an Intact Cervix[a]

- **In patients with an intact cervix (ie, those who do not have surgery), the primary tumor and regional lymphatics at risk are typically treated with definitive EBRT to a dose of approximately 45 Gy (40–50 Gy). The volume of the EBRT would depend on the nodal status as determined surgically or radiographically (as previously described). The primary cervical tumor is then boosted, using brachytherapy, with an additional 30 to 40 Gy using either image guidance (preferred) or to point A (in low dose-rate [LDR] equivalent dose), for a total point A dose (as recommended in the guidelines) of 80 Gy for small-volume cervical tumors or ≥85 Gy for larger-volume cervical tumors. For very small tumors (medically inoperable IA1 or IA2) EQD2 D90 doses of 75–80 Gy may be considered. Grossly involved unresected nodes may be evaluated for boosting with an additional 10 to 15 Gy of highly conformal (and reduced-volume) EBRT. When using image guidance for EBRT, care must be taken to exclude or severely limit the volume of normal tissue included in the high-dose region(s) (see Discussion).**

Posthysterectomy Adjuvant Radiation Therapy[a]

- **Following primary hysterectomy, the presence of one or more pathologic risk factors may warrant the use of adjuvant radiotherapy. At a minimum, the following should be covered: upper 3 to 4 cm of the vaginal cuff, the parametria, and immediately adjacent nodal basins (such as the external and internal iliac, obturator, and presacral nodes). For documented nodal metastasis, the superior border of the radiation field should be appropriately increased (as previously described). A dose of 45 to 50 Gy in standard fractionation with IMRT is generally recommended.[5] Grossly involved unresected nodes may be evaluated for boosting with an additional 10 to 20 Gy of highly conformal (and reduced-volume) EBRT. With higher doses, especially of EBRT, care must be taken to exclude or severely limit the volume of normal tissue included in the high-dose region(s) (see Discussion).**
- **Consider Vaginal cuff brachytherapy for positive or close vaginal margins.**

Intraoperative Radiation Therapy

- **IORT is a specialized technique that delivers a single, highly focused dose of radiation to an at-risk tumor bed or isolated unresectable residua disease during an open surgical procedure.[6] It is particularly useful in patients with recurrent disease within a previously radiated volume. During IORT, overlying normal tissue (such as bowel or other viscera) can be manually displaced from the region at risk. IORT is typically delivered with electrons, brachytherapy, or miniaturized x-ray sources using preformed applicators of variable sizes matched to the surgically defined region at risk, which further constrains the area and depth of radiation exposure to avoid surrounding normal structures.**

Re-irradiation

- **Techniques for re-irradiation may include IORT, intracavitary or interstitial brachytherapy, SBRT, IMRT, or proton therapy. Such cases are highly customized and depend on the target, proximity to critical organs, previous RT dose, extent of overlap, and time intervals since prior RT. The appropriate dose for each case needs to be individualized.**

[a] Normal Tissue Dose Constraints (CERV-D 6 of 9).

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY[1]

General Treatment Information—Continued

Treatment Information - Brachytherapy[a]

- Brachytherapy is a critical component of definitive RT for patients with primary cervical cancer. This is usually performed using an intracavitary approach, with an intrauterine tandem and vaginal colpostats. Depending on the patient and tumor anatomy, the vaginal component of brachytherapy in patients with an intact cervix may be delivered using ovoids, ring, or cylinder brachytherapy (combined with the intrauterine tandem). For more advanced disease, or without sufficient regression, interstitial needles may allow increased dose to the target, while minimizing dose to the normal tissues. MRI immediately preceding or during brachytherapy may be helpful in delineating residual tumor geometry. When combined with EBRT, brachytherapy is often initiated towards the latter part of treatment, when sufficient primary tumor regression has been noted to permit satisfactory brachytherapy apparatus geometry. In highly selected, very early disease (ie, stage IA2), brachytherapy alone (without EBRT) may be an option.
- In rare cases, patients whose anatomy or tumor geometry renders intracavitary brachytherapy infeasible may be best treated using an interstitial approach; however, such interstitial brachytherapy should only be performed by individuals and at institutions with appropriate experience and expertise, and early referral for timely use of their expertise is critical.
- In selected patients who receive post-hysterectomy (especially those with positive or close vaginal mucosal surgical margins), vaginal cylinder brachytherapy may be used as a boost to EBRT. The prescription is typically to the vaginal surface or at 5 mm below the surface. Typical fractionation schemes include 5.5 Gy X 2 fractions dosed at 5 mm or 6 Gy X 3 fractions dosed at the vaginal surface.
- SBRT is not considered an appropriate routine alternative to brachytherapy.
- Consider the use of intraprocedural imaging when placing brachytherapy applicators for intact cervical cancer.

[a] Normal Tissue Dose Constraints (CERV-D 6 of 9).

Note: All recommendations are category 2A unless otherwise indicated.

Continued

References

CERV-D
4 OF 9

Nout, R. et al., 2023 [7].

European Society of Gynaecological Oncology (ESGO), European Society for Radiotherapy & Oncology (ESTRO) and European Society of Pediatric Oncology (SIOPe)

ESTRO/ESGO/SIOPe guidelines for the management of patients with vaginal cancer.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- January 2000 and January 2022 was carried out using the MEDLINE and EMBASE databases

LoE/GoR

LEVELS OF EVIDENCE	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted, randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts opinions
GRADES OF RECOMMENDATIONS	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Fig. 2. Levels of evidence and grades of recommendations.

Sonstige methodische Hinweise

- LL nutzt u.a. die FIGO 2018er Klassifikation

FIGO 2018 Stage	AJCC 8th Edition Stage	AJCC 8th Edition Grouping	IUCC 8th Edition Stage	Description
0			Tis N0 M0	Carcinoma *in situ*
I	IA	T1a N0 M0	T1 N0 M0	The cancer is only in the vagina and is no larger than 2 cm (4/5 inch) (T1a). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
	IB	T1b N0 M0		The cancer is only in the vagina and is larger than 2.0 cm (4/5 inch) (T1b). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
II	IIA	T2a N0 M0	T2 N0 M0	The cancer has grown through the vaginal wall, but not as far as the pelvic wall and is no larger than 2.0 cm (4/5 inch) (T2a). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
	IIB	T2b N0 M0		The cancer has grown through the vaginal wall, but not as far as the pelvic wall and is larger than 2.0 cm (4/5 inch) (T2b). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
III		T3 N0 M0	T3 N0 M0	The cancer is growing into the pelvic wall and/or has blocked the flow of urine (hydronephrosis) which is causing the kidneys to not work. (T3).
	III	**OR**	**OR**	**OR**
		T1 to T3 N1 M0	T1 to T3 N1 M0	The cancer can be any size and might be growing into the pelvic wall and/or has blocked the flow of urine (hydronephrosis) which is causing the kidneys to not work. (T1 to T3). **AND** It has also spread to nearby lymph nodes in the pelvis or groin (inguinal) area (N1) but not distant sites (M0).
IVA		T4 Any N M0	IVA	The cancer is growing into the bladder or rectum or is growing out of the pelvis (T4). It might or might not have spread to lymph nodes in the pelvis or groin (inguinal area) (Any N). It has not spread todistant sites (M0).
	IVA			
IVB		Any T Any N M1	IVB	The cancer has spread to distant organs such as the lungs, liver, or bones. (M1). It can be any size and might or might not have grown into nearby structures or organs (Any T). It might or might not have spread to nearby lymph nodes (Any N).
	IVB			

Recommendations

Management of adult patients with stages T2-T3-T4, N0M0 or any T-stage, N1M0

- Definitive platinum-based chemoradiotherapy and brachytherapy is the preferred treatment [IV, A].
- In patients with T4a tumours and fistulation, GI and GU diversion should be considered before chemoradiotherapy [IV, A].
- There is no valid evidence to support (neo-)adjuvant systemic therapy in vaginal cancer outside of clinical trials [V, C].

  Hintergrund: Definitive platinum-based chemoradiotherapy consolidated by brachytherapy boost is the preferred treatment of choice for the management of patients with locally advanced or node positive vaginal cancer [23]. Outcomes after (chemo)radiotherapy followed by IGABT for patients with primary vaginal cancer are summarized in Fig. 4. Inprinciple, standard surgicaldebulking of lymph nodes is not indicated, in very exceptional cases very bulky lymph nodes may be removed, mainly for palliation. Although chemoradiation is the mainstay treatment approach in locally advanced disease including T4, in selected cases with large necrotic fistulation/cloacke formation between vagina/bladder/rectum at initial presentation or for patients with contraindication for radiotherapy such as previous pelvic radiotherapy, ulcerative bowel conditions or pelvic kidneys, a pelvic exenteration or GI-/GU- diversion before chemoradiation may be considered. Any exenterative surgery for vaginal cancer should be performed under curative intent with the aim of microscopically clear margins. Exenterative surgery should be combined with reconstructive techniques for urinary- and bowel diversions (continent or not continent) with additional consideration of neovaginal formation. In patients of childbearing age, fertility preserving measures (e.g. ovarian transposition) should be discussed and considered.

Principles of radiotherapy → Keine LoE/GoE Angaben

- **Definitive chemoradiotherapy and brachytherapy**: General aspects Definitive management (without tumour related surgery) consists of concomitant pelvic chemoradiotherapy (platinum based) and brachytherapy. Overall treatment time for the definitive treatment should not exceed 7 to 8 weeks. Delay of treatment and/or treatment interruptions have to be avoided.
- Definitive chemoradiotherapy EBRT can be applied as concomitant chemoradiotherapy with total dose of 45 to 46 Gy (1.8 to 2.0 Gy per fraction) and singleagentradiosensitizing chemotherapy, preferably cisplatin (weekly 40 mg/m2) so that definitive radiotherapy is not compromised. If cisplatin is not applicable, alternative treatment options are fluorouracil or carboplatin. EBRT may also be applied without concomitant chemotherapy according to treatment selection (i.e., patients unfit for any chemotherapy). In such cases, regional hyperthermia may be considered. Tumour and lymph node - related target volume for intensity modulated radiotherapy (IMRT) includes the primary vaginal tumour, the vagina and the adjacent tissues such as the paravaginal space, parametria, uterine cervix if in situ, and the pelvic lymph nodes (obturator, internal, external and common iliac, presacral). In case of pelvic lymph node involvement indicating an increased risk of para-aortic lymph node spread, EBRT may include the para-aortic region up to the renal vessels (45 Gy). In case of para-aortic lymph node involvement, target volume includes at a minimum the region up to the renal vessels. In case of a primary tumour located in the lower third of the vagina, inguino-femoral lymph nodes are part of the EBRT target volume. A reduced target volume for EBRT resulting in a small pelvic field not including the common iliac nodes

may be considered in selected patients with T1-2 tumours with negative lymph nodes on imaging and no LVSI. Boost treatment for involved lymph node(s) may be applied as simultaneous integrated boost within the IMRT treatment or as sequential boost. The total dose including the contribution from brachytherapy should be 55 to 60 Gy (equieffective dose to 2 Gy per fraction [EQD2]).

Image-guided radiotherapy is recommended for IMRT to ensure safe dose application in the tumour-related targets, to account for motion uncertainties, to reduce margins, and to achieve reduced doses to organs at risk. Overall treatment time for EBRT should not exceed 5 to 6 weeks.

- Definitive brachytherapy IGABT is recommended, preferably using MRI at the time of brachytherapy. IGABT is delivered toward the end of or after concomitant chemoradiotherapy. Repeated gynecologic examination is mandatory, and alternative imaging modalities such as CT and ultrasound may be used. The tumour-related targets for brachytherapy include the residual gross tumour volume (GTV-Tres) after chemo-radiotherapy, the adaptive high-risk clinical target volume (CTV-THR) including the GTV-Tres and residual adjacent pathologic tissue, and the intermediate-risk clinical target volume (CTV-TIR). Intravaginal brachytherapy can be performed without anesthesia whereas combined intravaginal/interstitial brachytherapy should be performed under anesthesia. Cylinder-type applicators or individually manufactured applicators (e.g. mold, 3D-printed applicators) with central and peripheral source positions should be used for intravaginal brachytherapy. In tumours located in the upper third, when uterus in situ, an intrauterine tandem may be used to ensure optimal contact and fixation. Combined intravaginal/interstitial applicators should be considered for residual tumours with > 7 mm thickness or for residual tumours with paravaginal diseasein order to achieve a sufficiently high radiation dose in the whole CTV-THR. Depending on the applicator type, interstitial needles can be placed (1) intravaginally through the applicator or (2) perineally with or without the use of a template. In IGABT, the planning aim should be to deliver a brachy- therapy dose of 30 to 40 Gy (EQD2) to reach a total EBRT + brachyther apy dose of equal to or greater than 75 to 85 Gy EQD2 (D90) (assuming 45 Gy through EBRT) to the CTV-THR. Dose volume and point constraints for rectum, bladder, vagina, sigmoid, and bowel are recommended, and they have to be based on the published clinical evidence. The lower third of the vagina is more sensitive and this should be taken into account when deciding on the planning aim. Brachytherapy should be delivered in several fractions as high dose rate (usually 3–4) or in 1 to 2 coursesas pulse dose rate brachytherapy. Care should be taken to optimize patient comfort and to avoid applicator movements during (fractionated) brachytherapy; preferably this includes a multidisciplinary approach.
- Adjuvant radiotherapy or chemoradiotherapy: Adjuvant radiotherapy or chemoradiotherapy follows analog principles for target selection and dose and fractionation as outlined for definitive treatment. The application of IMRT and image-guided radiotherapy is to be considered as treatmentrelated morbidity may be reduced. Adjuvant (additional) brachytherapy should be considered only if a well-defined limited area accessible through a brachytherapy technique is at high risk of local recurrence (e.g., positive margins in vagina, paracolpiaparametria). Such adjuvant brachytherapy should follow the major principles outlined above for imageguided brachytherapy.

Chino, J. et al., 2020 [2].

American Society for Radiation Oncology (ASTRO)

Radiation therapy for cervical cancer: an astro clinical practice guideline full text gudieline.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Ovid MEDLINE from January 1993 through October 2018

LoE/GoR

Table 1. ASTRO recommendation grading classification system

ASTRO's recommendations are based on evaluation of multiple factors including the QoE, individual study quality, and panel consensus, all of which inform the strength of recommendation. QoE is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability of samples, settings, and treatments.

Strength of Recommendation	Definition	Overall QoE Grade	Recommendation Wording
Strong	• Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. • All or almost all informed people would make the recommended choice.	Any (usually high, moderate, or expert opinion)	"Recommend/ Should"
Conditional	• Benefits are finely balanced with risks and burden or appreciable uncertainty exists about the magnitude of benefits and risks. • Most informed people would choose the recommended course of action, but a substantial number would not. • A shared decision-making approach regarding patient values and preferences is particularly important.	Any (usually moderate, low, or expert opinion)	"Conditionally Recommend"

Overall QoE Grade	Type/Quality of Study	Evidence Interpretation
High	• 2 or more well-conducted and highly generalizable RCTs or meta-analyses of such trials.	The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.
Moderate	• 1 well-conducted and highly generalizable RCT or a meta-analysis of such trials **OR** • 2 or more RCTs with some weaknesses of procedure or generalizability **OR** • 2 or more strong observational studies with consistent findings.	The true effect is likely to be close to the estimate of the effect based on the body of evidence, but it is possible that it is substantially different.
Low	• 1 RCT with some weaknesses of procedure or generalizability **OR** • 1 or more RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes **OR** • 2 or more observational studies with inconsistent findings, small sample sizes, or other problems that potentially confound interpretation of data.	The true effect may be substantially different from the estimate of the effect. There is a risk that future research may significantly alter the estimate of the effect size or the interpretation of the results.
Expert Opinion*	• Consensus of the panel based on clinical judgment and experience, due to absence of evidence or limitations in evidence.	Strong consensus (≥90%) of the panel guides the recommendation despite insufficient evidence to discern the true magnitude and direction of the net effect. Further research may better inform the topic.

Abbreviations: ASTRO = American Society for Radiation Oncology; QoE = quality of evidence; RCTs = randomized controlled trials.

*A lower quality of evidence, including expert opinion, does not imply that the recommendation is conditional. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials, but there still may be consensus that the benefits of a treatment or diagnostic test clearly outweigh its risks and burden.

Recommendations

Following primary surgery for cervical cancer, when is it appropriate to deliver postoperative RT with or without systemic therapy?

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For women undergoing surgery for cervical cancer who have high surgicopathologic risk factors, adjuvant EBRT and concurrent platinum-based chemotherapy is recommended.	Strong	High 4-7
Implementation remark: High-risk factors include positive margin(s) or positive lymph node(s) or extension into the parametrial tissue.		
2. For women with cervical cancer and intermediate-risk factors, adjuvant EBRT is recommended to decrease locoregional recurrence. Implementation remark: Intermediate-risk factors include*: • LVSI plus deep one-third cervical stromal invasion with any tumor size • LVSI plus middle one-third stromal invasion and tumor size ≥2 cm • LVSI plus superficial one-third stromal invasion and tumor size ≥5 cm • No LVSI but deep or middle one-third stromal invasion plus tumor size ≥4 cm	Strong	High 8-10

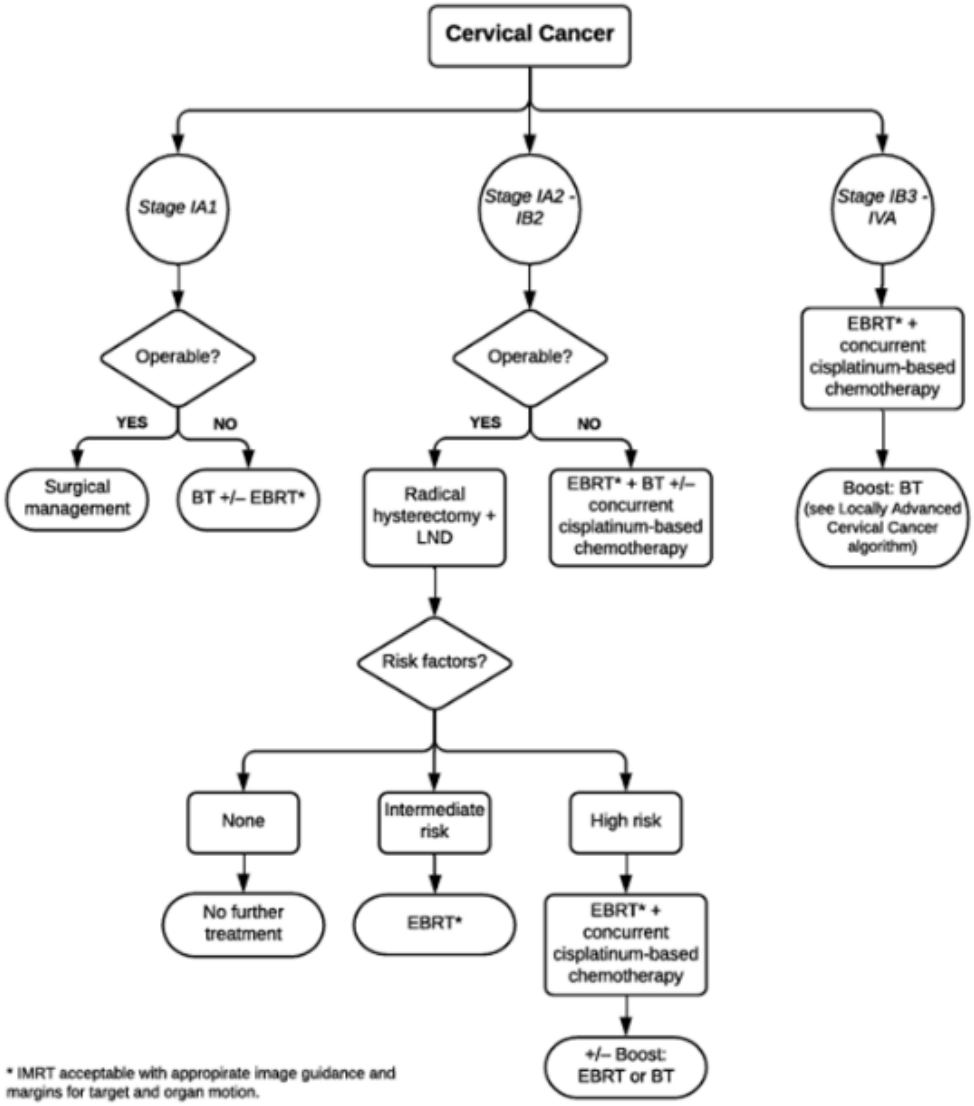
Abbreviations: EBRT = external beam radiation therapy; LVSI = lymphovascular space involvement; RT = radiation therapy.
*The original Gynecologic Oncology Group (GOG) 92 protocol estimated tumor size based on palpation; however, estimation based on pathologic or magnetic resonance imaging findings are an acceptable substitute.

When is it appropriate to deliver definitive RT with and without systemic therapy? When is it appropriate to perform a hysterectomy after RT for cervical cancer?

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For women with FIGO stage IB3-IVA* squamous cell or adenocarcinoma of the cervix, RT with concurrent platinum-based chemotherapy is recommended for definitive treatment. Implementation remark: Recommended dose for cisplatin is 40 mg/m^2 weekly for 5 to 6 cycles.	Strong	High 11,16-23
2. For women with FIGO stage IB3-IVA cervical cancer, a planned adjuvant hysterectomy after RT or chemoradiation is not recommended.†	Strong	High 18,24-26
3. In women with FIGO stage IA1-IB2 that are deemed medically inoperable, RT with or without chemotherapy is conditionally recommended.	Conditional	Expert Opinion

Abbreviations: International Federation of Gynecology and Obstetrics (FIGO); RT = radiation therapy.
*Stage IIA1 cancers may be managed with radical hysterectomy in well-selected (eg, non-bulky, with limited vaginal involvement) cases.

Figure 2. Cervical cancer algorithm



Abbreviations: BT = brachytherapy; EBRT = external beam radiation therapy; IMRT = intensity modulated radiation therapy; LND = lymph node dissection; RT = radiation therapy.

<u>For patients receiving definitive or postoperative RT for cervical cancer, when is it appropriate to deliver IMRT?</u>

KQ3 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. In women with cervical cancer treated with postoperative RT with or without chemotherapy, IMRT is recommended to decrease acute and chronic toxicity.	Strong	Moderate (acute) [50,51] Low (chronic) [50,52]
2. In women with cervical cancer treated with definitive RT with or without chemotherapy, IMRT is conditionally recommended to decrease acute and chronic toxicity.	Conditional	Moderate (acute) [53-58] Moderate (chronic) [53,55,59-62]

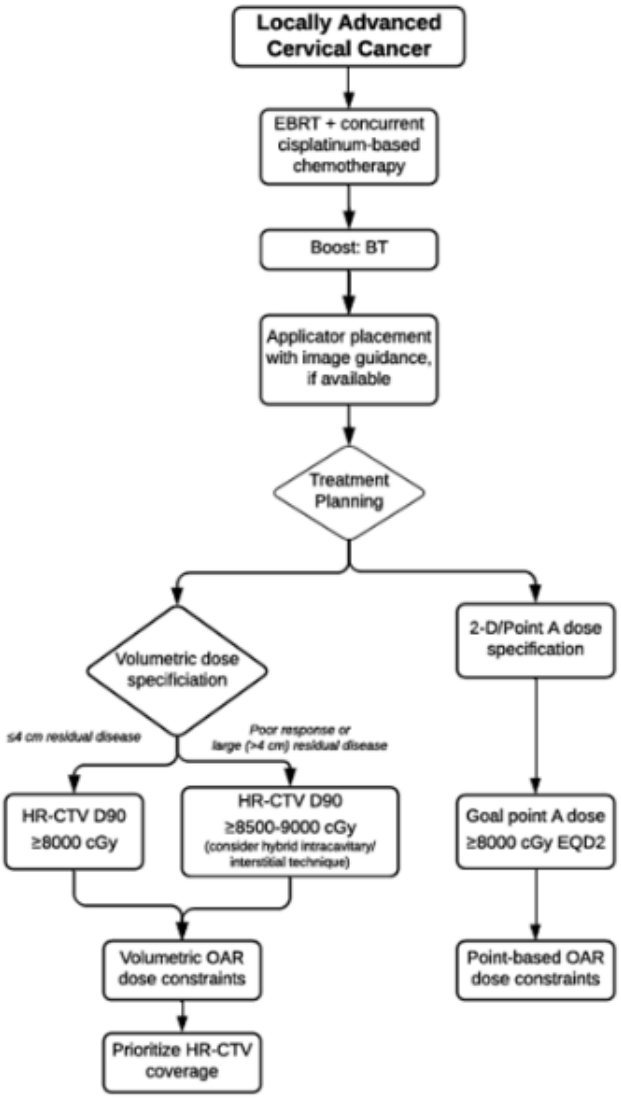
Abbreviations: IMRT = intensity modulated radiation therapy; RT = radiation therapy.

For patients receiving definitive or postoperative RT for cervical cancer, when is brachytherapy indicated?

KQ4 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For women receiving definitive RT for intact cervical cancer, brachytherapy is recommended.	Strong	Moderate [84-88]
2. For women with cervical cancer receiving postoperative whole pelvis radiation, a brachytherapy boost is conditionally recommended in the presence of positive margin(s). Implementation remark: The brachytherapy technique selected is based on the location and volume of the positive margin(s).	Conditional	Low [89]

Abbreviation: RT = radiation therapy.

Figure 4. Locally advanced cervical cancer algorithm



Abbreviations: 2-D = 2-dimensional; BT = brachytherapy; EBRT = external beam radiation therapy; EQD2 = equivalent dose at 2 Gy per fraction; HR-CTV = high-risk clinical target volume; OAR = organ at risk.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 10 of 12, October 2024) am 15.10.2024

#	Suchfrage
1	MeSH descriptor: [Uterine Cervical Neoplasms] explode all trees
2	(cervi* OR endocervi* OR ectocervi*):ti,ab,kw
3	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesion* OR malignan*):ti,ab,kw
4	#1 OR (#2 AND #3)
5	#4 with Cochrane Library publication date from Oct 2019 to present

Systematic Reviews und Leitlinien in PubMed am 15.10.2024

verwendeter Suchfilter für Systematic Reviews ohne Änderung:

Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

verwendeter Suchfilter für Leitlinien ohne Änderung:

Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suche nach Systematic Reviews
1	Uterine Cervical Neoplasms/therapy[mh]
2	cervi*[tiab] OR endocervi*[tiab] OR ectocervi*[tiab]
3	tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR cancer*[tiab] OR lesion*[tiab] OR malignan*[tiab]
4	treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]
5	#2 AND #3 AND #4
6	(#1 OR #5) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR

#	Suche nach Systematic Reviews
	screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
7	(#6) AND ("2019/10/01"[PDAT] : "3000"[PDAT])
8	(#7) NOT "The Cochrane database of systematic reviews"[Journal]
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])
	Suche nach Leitlinien
10	Uterine Cervical Neoplasms[mh]
11	#2 AND #3
12	(#10 OR #11) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
13	(#12) AND ("2019/10/01"[PDAT] : "3000"[PDAT])
14	(#13) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])
15	#9 NOT #14

Iterative Handsuche nach grauer Literatur, abgeschlossen am 17.10.2024

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- National Cancer Institute (NCI)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

1. **Bacorro W, Baldivia K, Yu KK, Mariano J, Gonzalez G, Sy Ortin T.** Outcomes with definitive radiotherapy among patients with locally advanced cervical cancer with relative or absolute contraindications to cisplatin: a systematic review and meta-analysis. Gynecol Oncol 2022;166(3):614-630.
2. **Chino J, Annunziata CM, Beriwal S, Bradfield L, Erickson BA, Fields EC, et al.** Radiation therapy for cervical cancer: an ASTRO clinical practice guideline [online]. Arlington (USA): American Society for Radiation Oncology (ASTRO); 2020. [Zugriff: 17.10.2024]. URL: https://www.practicalradonc.org/cms/10.1016/j.prro.2020.04.002/attachment/b3495c02-3020-4944-9248-122057abef3b/mmc1.pdf.
3. **Kokka F, Bryant A, Olaitan A, Brockbank E, Powell M, Oram D.** Hysterectomy with radiotherapy or chemotherapy or both for women with locally advanced cervical cancer. Cochrane Database of Systematic Reviews [online]. 2022(8):Cd010260. URL: http://dx.doi.org/10.1002/14651858.CD010260.pub3.
4. **Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft (DKG), Deutsche Krebshilfe (DKH), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)).** Diagnostik, Therapie und Nachsorge der Patientin mit Zervixkarzinom; Leitlinienreport, Vers. 2.0 [online]. AWMF-Registernummer 032-033OL. 03.2022. Berlin (GER): Leitlinienprogramm Onkologie; 2021. [Zugriff: 17.10.2024]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Zervixkarzinom/Version_2/LL_Zervixkarzinom_Leitlinienreport_2.0.pdf.
5. **Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft (DKG), Deutsche Krebshilfe (DKH), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)).** Diagnostik, Therapie und Nachsorge der Patientin mit Zervixkarzinom; S3-Leitlinie, Langfassung, Vers. 2.2 [online]. AWMF-Registernummer 032-033OL. Berlin (GER): Leitlinienprogramm Onkologie; 2022. [Zugriff: 17.10.2024]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Zervixkarzinom/Version_2/LL_Zervixkarzinom_Langversion_2.2.pdf.
6. **National Comprehensive Cancer Network (NCCN).** Cervical cancer; vers. 04.2024 [online]. Plymouth Meeting (USA): NCCN; 2024. [Zugriff: 17.10.2024]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf.
7. **Nout R, Calaminus G, Planchamp F, Chargari C, Lax SF, Martelli H, et al.** ESTRO/ESGO/SIOPe guidelines for the management of patients with vaginal cancer. Radiother Oncol 2023;186:109662.
8. **Ronsini C, Solazzo MC, Braca E, Andreoli G, Vastarella MG, Cianci S, et al.** Locally advanced cervical cancer: neoadjuvant treatment versus standard radio-chemotherapy-an updated meta-analysis. Cancers (Basel) 2024;16(14):2542.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

Gemeinsamer Bundesausschuss

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO