

Nordic Society for Gynecological Oncology

Advisory Board of Radiotherapy

Guidelines for irradiation of advanced cervical cancer IIB-IVA



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EBRT = External Beam Radiotherapy

BT = Brachytherapy

Writing committee:

Jacob Lindegaard, Aarhus; Mona Ridderheim, Lund; Kolbein Sundfør, Oslo; Inger-Lena Lamm, Lund; Jens Juul Christensen, Aarhus; Anders Jakobsen, Vejle.

The board of NSGO has approved these guidelines.

The guidelines should be perceived as minimal standards and should not replace independent medical judgment or the use of more advanced technique where this is possible or needed based on the clinical situation.

1. Treatment planning for EBRT

Treatment planning must be based on 3D CT data set, preferably with not more than 0.5 cm slice thickness, and performed on a 3D dose planning system. Before dose planning CT, a marking of the distal tumor extension with silver seeds or metal clips is recommended. Fixation is optional but should at least include knee cushions to ensure reproducible patient positioning. To minimize internal motion emptying of bladder and rectum before dose planning is also recommended unless bladder and rectum volume can be controlled by other methods.

2. Target definition for EBRT

Target definition should be based on integrated information obtained by CT (MRI) and gynecological examination in general or spinal anesthesia.

The volumes of interest (VOI) should be defined according to ICRU and NACP:

GTV: Gross Tumor Volume.

CTV: Clinical Target Volume = GTV + microscopic tumor extension.

ITV: Internal Target Volume = CTV + internal margins to compensate for internal motions.

PTV: Planning target Volume = ITV + set-up margin.

To evaluate competing dose plans it is recommended to define volumes of organs at risk, (primarily bladder, rectum and intestines) and to add internal and set-up margins using the same principles as for PTV to obtain the Planning Organ at Risk Volume.

IMPORTANT: The standard margins used for defining VOI should be modified when more precise knowledge is available.

U-target (uterus and tumor)

- GTV-U: Tumor.
- CTV-U: GTV-U + 1 cm in directions of suspected microscopic spread + uterus with no margin.
- ITV-U: CTV-U + 0.5 cm in all directions.
- PTV-U: ITV-U + 0.5 cm in all directions.

P-target (pelvic nodes and vagina)

Elective irradiation of all pelvic lymph nodes including parametrial, iliaca interna/obturatoria, iliaca externa, sacral and iliaca communis to the level of L5. The inguinal nodes may be included for stage IIIA.

- CTV-P: Cranial border is 1 cm below the L4-L5 interspace, caudal border (vagina) is 2 cm below GTV-U. Ventral and lateral borders are defined by the external iliac vessels with a margin of 0.5-1 cm in the loose connective tissue. The iliac external vessels are included from above the inguinal ligament. Dorsal-caudal border (pelvic nodes) is defined by the muscular rim of the pelvic cavity. CTV-P should always fully include CTV-U and CTV-N (see N-target below).
- ITV-P: CTV-P + 0.0 cm
- PTV-P: ITV-P + 0.5 cm in all directions. A larger set-up margin laterally should be considered for obese patients.

N-target (pathological pelvic nodes)

- GTV-N: lymph node(s)
- CTV-N: GTV-N + 0.0 cm
- ITV-N: CTV-N + 0.0 cm
- PTV-N: ITV-N + 0.5 cm.

3. Dose, fractionation and over all treatment time of EBRT

Irradiation is given with five fractions per week and a dose per fraction of 1.8-2.0 Gy. Dose variation within each PTV should be less than +/- 5%. **Intended maximal treatment time including brachytherapy is 50 days.** Two daily external beam radiotherapy (EBRT) fractions at least 6 hours apart should be used to compensate for unplanned treatment breaks. The dose

accumulation of EBRT should not exceed 12 Gy per week to avoid consequential late damage. For equivalence calculations, it is assumed that the α/β is 10 Gy for tumor effects and 3 Gy for late normal tissue damage.

U-target (uterus and tumor including involved parametria)

- 50 Gy in 25 fractions: Tumors expected to be well covered by brachytherapy (usually stage IIB, centrally located and ≤ 8 cm).
- 60 Gy in 30 fractions: Other tumors (usually lateral stage IIB and stage IIIB).

P-target (pelvic lymph nodes and vagina)

- 45 Gy in 25 fractions

N-target (pathological lymph nodes)

- 64 Gy in 32 fractions.
- Treatment must be individualized if GTV-N is larger than 5 cm or if pathological para-aortic or common iliac nodes are identified.

If intracavitary brachytherapy cannot be performed the patient should be referred for interstitial brachytherapy. Alternatively shrinking field EBRT technique should be used to bring the GTV-U with adequate margins to a minimum of 64 Gy.

4. Technique for EBRT

- Iso-centric technique, normally a combination of box techniques.
- No standard fields. Beam shaping should be individualized according to target definitions, MLC recommended.
- The edge of beams used to cover PTV-U and PTV-N (if present) should be set with no margin for penumbra, as PTV-U and PTV-N both are included in PTV-P.
- Bladder and rectum should be empty before irradiation unless bladder and rectum volume is controlled by other methods.

5. Brachytherapy

Brachytherapy (BT) is given with intracavitary applicators and used as a boost to as large a part of the GTV-U as possible. BT may be delivered by HDR, MDR, LDR or PDR.

The cumulative physical dose at point-A of EBRT and BT (dose rate of 1.0 Gy/h) is 80.0 Gy (NOCECA reference dose). Biologically equivalence calculations for BT at other dose rates and summation of EBRT and BT doses should be performed using the linear quadratic model (Thames, Int.J.Radiat.Biol. 47:319-339.1985). In these calculations the α/β value is assumed to be 10 Gy for tumor effect and 3 Gy for late normal tissue damage:

$$E = \alpha D + \beta D^2 \gamma$$

$$\gamma = 2[\mu t - 1 + \exp(-\mu t)]/(\mu t)^2$$

$$\mu = 0.693/T^{1/2}$$

where t = duration of exposure in h

and $T^{1/2} = 1.5$ h

The equivalent EBRT dose in 2 Gy fractions (EQD₂) of a given BT fraction with a certain dose rate can then be calculated according to Withers (Radiat.Oncol. 1983 1:187-191) as:

$$EQD_2 = D * (\alpha/\beta + \gamma * D) / (\alpha/\beta + 2)$$

D = dose per BT fraction (Gy)

Tabulated calculations for tumor and late normal tissue effects are given in the appendix

- BT dose is prescribed to point-A in relation to the applicator.
- Maximal bladder and rectum doses should be estimated for each BT application at least from orthogonal X-rays
- It is recommended to keep maximal bladder and rectum dose below approximately 70% of the dose to point-A for each BT application.
- It is assumed that the cumulative tolerance dose of EBRT and BT is 78 Gy for bladder and 72 Gy for rectum calculated in EQD₂.
- In terms of biologically effective dose (BED), the tolerance doses for bladder and rectum is assumed to be 130 Gy₃ and 120 Gy₃, respectively.
- Maximal dose per BT application at HDR is 5 Gy per fraction, two fractions per week.
- Maximal dose per BT application at MDR (0.8-2.0 Gy/h) is 10 Gy, 1 fraction per week.

- Maximal dose per BT application at LDR (<0.8 Gy/h) is 15 Gy, 1 fraction per week.
- Frequency for PDR is one pulse per hour with equal sized pulses.
- At least 6 hours should separate BT and EBRT.

6. Hemoglobin

Hemoglobin should be monitored weekly and kept within institutional limits unless otherwise specified in particular protocols.

7. Chemotherapy

Concomitant EBRT and cisplatin is standard unless otherwise specified in particular protocols. Cisplatin is given in accordance with the NSGO-CC-9901 protocol.

- The schedule is weekly cisplatin 40 mg/m² (maximal dose 70 mg) for a total of six cycles.
- Chemotherapy should be initiated on the same day or the day after administration of the first EBRT fraction. Cisplatin should not be given on days with BT.
- Blood tests are repeated once a week. Treatment with cisplatin should be withheld if the total white-cell count falls below 2.5*10⁹ per liter or the platelet count drops below 50*10⁹ per liter. Cisplatin can be resumed once the blood counts exceed these limits.
- Dose of cisplatin should be reduced to 30 mg/m² (maximum 55 mg per week) if two consecutive cycles have been given at dose zero. Cisplatin dose should also be reduced to 30 mg/m² in case of febrile leucopenia.
- Cisplatin should be totally discontinued if blood tests remain unacceptable or febrile leucopenia recurs despite dose reduction.
- Treatment with cisplatin is abandoned if GFR falls below 50 ml/min.

8. Minimal standards for quality assurance

- Verification films of EBRT at start and mid time through treatment.
- In vivo dosimetri for EBRT.
- Orthogonal X-rays should be performed for each BT application.
- In vivo rectal and/or bladder dosimetri is recommended for each BT application.

9. Minimal standards for documentation

EBRT

- Dose plans and simulator and verification films must be stored for inspection.
- ICRU point dose.
- Maximal dose, minimal dose and SD in the targets.
- Maximal dose to bladder and rectum.
- Total dose, dose per fraction and total treatment time.

BT (for each application)


- Date of treatment.
- Dose to point A.
- Dose rate.
- Total Reference Air Kerma (TRAK).
- Maximal dose to bladder and rectum.
- ICRU bladder and rectum dose.
- Dose plans and orthogonal films must be stored for inspection.


Appendix:


Brachytherapy equivalence calculations for tumor effect


Radiobiological parameters											
Time (h)	0,1	0,5	1	5	10	15	20	24	36	48	60
α/β	10	10	10	10	10	10	10	10	10	10	10
$t_{1/2}$ (h)	1,5	1,5	1,5	1,5	1,5	1,5	1,5	1,5	1,5	1,5	1,5
μ	0,46	0,46	0,46	0,46	0,46	0,46	0,46	0,46	0,46	0,46	0,46
γ	0,98	0,93	0,86	0,53	0,34	0,25	0,19	0,16	0,11	0,09	0,07

Dose per BT fraction	Equivalent dose in 2 Gy fractions										
	0,5	0,4	0,4	0,4	0,4	0,4	0,4	0,4	0,4	0,4	0,4
1,0	0,9	0,9	0,9	0,9	0,9	0,9	0,8	0,8	0,8	0,8	0,8
1,5	1,4	1,4	1,4	1,3	1,3	1,3	1,3	1,3	1,3	1,3	1,3
2,0	2,0	2,0	2,0	1,8	1,8	1,7	1,7	1,7	1,7	1,7	1,7
2,5	2,6	2,6	2,5	2,4	2,3	2,2	2,2	2,2	2,1	2,1	2,1
3,0	3,2	3,2	3,1	2,9	2,8	2,7	2,6	2,6	2,6	2,6	2,6
3,5	3,9	3,9	3,8	3,5	3,3	3,2	3,1	3,1	3,0	3,0	3,0
4,0	4,6	4,6	4,5	4,0	3,8	3,7	3,6	3,6	3,5	3,4	3,4
4,5	5,4	5,3	5,2	4,6	4,3	4,2	4,1	4,0	3,9	3,9	3,9
5,0	6,2	6,1	6,0	5,3	4,9	4,7	4,6	4,5	4,4	4,3	4,3
5,5	7,1	6,9	6,8	5,9	5,4	5,2	5,1	5,0	4,9	4,8	4,8
6,0	8,0	7,8	7,6	6,6	6,0	5,7	5,6	5,5	5,3	5,3	5,2
6,5	8,9	8,7	8,5	7,3	6,6	6,3	6,1	6,0	5,8	5,7	5,7
7,0	9,9	9,6	9,4	8,0	7,2	6,8	6,6	6,5	6,3	6,2	6,1
7,5	10,9	10,6	10,3	8,7	7,8	7,4	7,2	7,0	6,8	6,7	6,6
8,0	11,9	11,6	11,3	9,5	8,5	8,0	7,7	7,5	7,3	7,1	7,0
8,5	13,0	12,7	12,3	10,3	9,1	8,6	8,2	8,1	7,8	7,6	7,5
9,0	14,1	13,8	13,3	11,1	9,8	9,2	8,8	8,6	8,3	8,1	8,0
9,5	15,3	14,9	14,4	11,9	10,5	9,8	9,4	9,2	8,8	8,6	8,4
10	16,5	16,1	15,5	12,7	11,2	10,4	9,9	9,7	9,3	9,1	8,9
11	19,1	18,5	17,9	14,5	12,6	11,7	11,1	10,8	10,3	10,0	9,9
12	21,8	21,1	20,3	16,3	14,1	13,0	12,3	12,0	11,4	11,0	10,8
13	24,7	23,9	23,0	18,3	15,6	14,3	13,6	13,1	12,4	12,0	11,8
14	27,8	26,8	25,7	20,3	17,2	15,7	14,8	14,3	13,5	13,1	12,8
15	31,0	29,9	28,7	22,4	18,9	17,1	16,1	15,6	14,6	14,1	13,8
16	34,3	33,1	31,7	24,6	20,6	18,6	17,5	16,8	15,7	15,2	14,8
17	37,9	36,5	34,9	26,9	22,4	20,1	18,8	18,1	16,9	16,2	15,8
18	41,6	40,0	38,3	29,3	24,2	21,7	20,2	19,4	18,1	17,3	16,9
19	45,5	43,7	41,8	31,7	26,1	23,3	21,6	20,8	19,2	18,4	17,9
20	49,5	47,6	45,4	34,3	28,0	24,9	23,1	22,1	20,4	19,5	19,0
25	72,1	69,1	65,7	48,3	38,5	33,7	30,9	29,4	26,7	25,3	24,5
30	98,9	94,5	89,7	64,6	50,5	43,5	39,5	37,3	33,5	31,5	30,2
35	129,7	123,8	117,2	83,1	63,9	54,4	48,9	45,9	40,7	38,0	36,3
40	164,6	157,0	148,3	103,8	78,7	66,3	59,1	55,2	48,4	44,8	42,6
50	246,8	234,8	221,3	151,7	112,5	93,1	81,9	75,8	65,2	59,6	56,2
60	345,4	328,2	308,7	208,4	152,0	124,1	107,9	99,2	83,9	75,8	70,9
70	460,4	437,0	410,4	274,0	197,2	159,2	137,1	125,3	104,5	93,5	86,7
80	591,9	561,2	526,5	348,3	248,0	198,4	169,6	154,2	126,9	112,6	103,8
90	739,7	700,9	657,0	431,5	304,5	241,7	205,3	185,8	151,3	133,1	121,9
100	904,0	856,0	801,9	523,5	366,7	289,1	244,2	220,1	177,5	155,1	141,3

 Dose rate > 2.0 Gy/h

 Dose rate 0.8-2.0 Gy/h

 Dose rate < 0.8 Gy/h

 Noceca reference value, 10 Gy in 10 hours

