Post operative radiation therapy in endometrial carcinoma : reducing overtreatment and improving quality of life

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Discussion

The main purpose of the Post Operative Radiotherapy in Endometrial Carcinoma (PORTEC) trials has been to provide evidence with regards to risks (short and long-term treatment related morbidity) and benefits (disease control) of adjuvant radiotherapy and by doing so, further define both the indications and methods of radiotherapy with the ultimate goal to improve the overall outcome and quality of life of endometrial cancer patients. In this thesis results from the first and second PORTEC trials are presented. In the PORTEC-1 trial (1990-1997), stage I EC patients with intermediate risk features were randomized after surgery between no additional therapy and pelvic external beam radiotherapy. In the subsequent PORTEC-2 trial (2002-2006), patients with high-intermediate risk features were randomized between pelvic external beam radiotherapy and vaginal brachytherapy. In this chapter the main findings of this thesis and their implications for current patient management are discussed, focusing on future perspectives for research and treatment of endometrial cancer.

Optimal treatment for endometrial cancer patients with high-intermediate risk features

In order to decide on optimal treatment for patients with high-intermediate (HIR) features, risks (treatment related morbidity) and benefits (disease control) of different treatment strategies should be evaluated. Before reaching a conclusion, the following paragraphs discuss the key issues concerning three possible strategies after surgery: pelvic external beam radiotherapy (EBRT), vaginal brachytherapy (VBT), and no additional therapy (NAT).

Risk of disease recurrence

Evidence for the role of adjuvant radiation therapy for intermediate risk EC patients has come from four large randomised trials and a meta-analysis (Table 1).[1-5] All of these trials reached the same conclusion, that EBRT reduces the risk of locoregional (vagina and/or pelvic) recurrence approximately three-fold, but this does not lead to a decrease in the rate of distant metastasis or a benefit in overall survival. Both PORTEC-1 and GOG#99 trials have identified a subgroup of patients with HIR features that had the highest risk of locoregional recurrence without additional therapy. Based on these outcomes, the indication for adjuvant radiotherapy was only maintained for patients with HIR features. This led to a major decrease in indications for radiotherapy, sparing low-intermediate risk patients the risk of radiotherapy related morbidity.

Table 1. Randomized trials establishing the role of postoperative radiotherapy in intermediate risk endometrial cancer.

Trial (ref) acrual period	No. patients, eligibility	Surgery	Randomization	Locoregional recurrence	Survival	Severe complications
Norwegian[1] 1968–1974	540; Stage I	TAH-BSO	VBT vs VBT + EBRT	7% vs 2% at 5 years P < 0.01	89% vs 91% at 5 years P= NS	NA
PORTEC-1[3] 1990–1997	714; IB grade 2–3 IC grade 1–2	TAH-BSO	NAT vs EBRT 10-years 15-years HIR patients	14% vs 4% at 5 years P < 0.001 14% vs 5% 16% vs 6% 18% vs 5% at 5 years	85% vs 81% at 5 years P= 0.31 74% vs 68% 60% vs 52%	3% GI at 5 years, (actuarial)
GOG-99[4] 1987–1995	392; Stage IB, IC Stage II (occult)	TAH-BSO and lymphadenectomy	NAT vs EBRT HIR patients	CIR: 12% vs 3% at 2 years, P < 0.01 CIR: 26% vs 6% at 2 years	86% vs 92% at 4 years P= 0.56	8% GI at 2 years, (crude)
ASTEC/EN5[2] 1996–2005	905; Stage IAB g3, IC, Stage II, serous/cc	TAH-BSO ± lymphadenectomy	NAT vs EBRT*	7%a vs 4% at 5 years P= 0.038	84% vs 84% at 5 years P= 0.98	3 vs 7% gr 3/4
PORTEC-2 2002–2006	427, age >60 IB grade 3 IC grade 1–2 (HIR)	TAH-BSO	VBT vs EBRT	5% vs 2% at 5 years P= 0.17	85% vs 80% at 5 years P= 0.57	GI: 0.5% vs 1.9% Vagina: 1.9% vs 0.5%
Swedish[7] 1997-2008	527; Stage I medium risk	TAH-BSO	VBT vs VBT + EBRT	5% vs 1.5% at 5 years P=0.01	90% va 89% at 5 years P= 0.55	GI: 0% vs 1.8% Vagina: 0.8% vs 0%

cc: clear cell. TAH-BSO: total abdominal hysterectomy with bilateral salpingo-oophorectomy. VBT: vaginal brachytherapy.
EBRT: pelvic external beam radiotherapy. NAT: no additional therapy.
GI: gastro-intestinal. CIR: cumulative incidence of recurrence.
HIR: high intermediat risk. Medium risk: Stage I and (grade 3 or deep invasion or DNA aneuploidy) and nuclear grade 1-2
**VBT was given in both treatment arms at the discretion of the centers: EBRT 52% and NAT 51% of the patients.*

The very long-term analysis of the PORTEC-1 trial confirmed the importance of the prognostic factors age, grade and depth of myometrial invasion for selection of HIR patients. In patients with HIR features the risk of developing a locoregional recurrence was reduced from approximately 20% after NAT to 5% after EBRT. The majority (75%) of locoregional recurrences in the NAT-arm were isolated vaginal recurrences. Salvage treatment, usually consisting of EBRT combined with VBT, was most effective in patients with isolated vaginal recurrences; in 80-90% a complete remission was achieved, with 70% 5-year survival after recurrence.[6] This explains in part why upfront EBRT does not improve overall survival. In contrast, patients with isolated pelvic or combined pelvic and vaginal recurrences are at high risk of developing distant metastasis and their survival rate is similar to that of patients who initially present with distant metastasis. EBRT does not seem to prevent the development of distant metastasis, which occurred in approximately 8% of the patients in both treatment arms. Overall survival rates at 5, 10 and 15 years after treatment were approximately 80%, 65% and 50%, irrespective of receiving adjuvant radiotherapy or not. The vaginal recurrence risk of 2% at 5 years after VBT in the PORTEC-2 trial was strikingly similar to that obtained after EBRT both in PORTEC-2 and in PORTEC-1, demonstrating the efficacy of VBT in preventing vaginal recurrences. At 5 years the rate of total pelvic recurrences was 0.5% after EBRT vs. 3.8% after VBT. However, first failure analysis showed that most patients (5 of 8) with a pelvic recurrence had simultaneous distant metastases and the pelvic recurrence rate as first failure was 0.5% after EBRT vs. 1.5% after VBT, with similar rates of distant metastasis and overall survival in both arms. These findings were confirmed in a recently published Swedish trial in which 527 patients with intermediate risk EC were randomized between VBT and combined EBRT and VBT. The rate of vaginal recurrences was low in both arms of the trial (crude rates 2.7% vs. 1.9%), while in the VBT alone arm a higher rate of locoregional recurrences was found (5.0% vs 1.5% at 5 years, p=0.01) without differences in 5-year relapse-free (86 vs 87%) and overall survival (89 vs 90%), results very similar to those of PORTEC-2.[7] For approximately 3% of patients EBRT might be beneficial compared to VBT in preventing both vaginal and pelvic lymph node recurrences, but as distant

metastasis will ultimately dictate their prognosis and overall survival is not improved, this benefit is debatable.Due to the low total number of vaginal and pelvic events in PORTEC-2, a multivariate analysis of prognostic factors for pelvic recurrence was not included in the publication of the outcome analysis. The GOG99 trial investigators identified lymph vascular space invasion (LVSI) as an independent prognostic factor for any relapse and included LVSI in their HIR definition.[4] Other authors have confirmed the strong adverse prognostic impact of LVSI, both in presence and absence of nodal metastases[8,9] In the PORTEC-1 analysis which included the registered group with grade 3 EC with deep invasion, LVSI was also found to be a risk factor, especially for distant relapse.[10] The Swedish trial included DNA-aneuploidy in their definition and did not include LVSI or age.[7] Despite the differences in HIR definitions, testing of the GOG HIR definition in the PORTEC-1 analysis yielded very similar results. In clinical practice, LVSI should be considered an adverse factor and as such, grade 3 EC with superficial invasion but with clear LVSI is considered high-risk, and these patients receive EBRT and are eligible for trials investigating chemotherapy, such as PORTEC-3 and GOG249. Similarly, grade 2 with very deep invasion close to the serosa and clear LVSI represents the upper end of the HIR spectrum and might also be considered high risk.

Overall survival and recurrence rates for patients with HIR features in PORTEC-2 were remarkably similar to those obtained in all of the randomized trials in patients with intermediate risk EC (Table 1). From a clinical point of view, given that low-intermediate risk patients do not receive adjuvant treatment and are in fact regarded low risk, patients with HIR features have become the intermediate group. Thus, it would seem more appropriate to group current low-risk and low-intermediate risk features as low risk EC, and designate those with HIR features as intermediate risk EC, which would be in line with the prognosis and therapeutic consequences.

Radiotherapy related morbidities and their impact on health-related quality of life

In the randomised trials (Table 1) increased early and late (physician-reported) adverse event rates were reported after EBRT, as compared to NAT.[1-4] In PORTEC-1 late toxicity was reported in 6% of patients in the NAT arm and

in 25% after EBRT. Approximately two-thirds of adverse events (AE) in the EBRT arm were mild (grade 1), while 3% were grade 3 complications, with the vast majority of AE related to the gastro-intestinal (GI) tract. In PORTEC-2 the increased gastro-intestinal acute toxicity in the EBRT arm decreased from 6 months onwards, and the difference between the EBRT and VBT arms lost its significance after 24 months. Both HRQL analyses in the PORTEC-1 and PORTEC-2 trials have provided unique insight into the impact these symptoms have on patient-reported health related quality of life (HRQL), and how long this impact persists in the years following treatment.

With HRQL studies the question always remains what size of difference between scores reflects a clinical meaningful or relevant difference. Studies on the magnitude of clinically relevant differences agree on a minimum difference of 5% to 10% of the instrument range as being clinically relevant.[14-16] For the EORTC Core questionnaire, Osoba et al. found that patients valued a change of 5-10% as 'little', 10-20% as 'moderate' and more than 20% as 'very much' difference.[15] These descriptions are used to value the observed differences in HRQL scores.

In the PORTEC-2 trial, EBRT was associated with an early increase of patient reported bowel symptoms (very much diarrhea and little fecal leakage), while scores after VBT remained at baseline level in range of those of an age-matched Dutch norm-population. In the years following treatment the bowel symptoms gradually decreased but remained moderately to a little higher than those of VBT patients and the norm-population. Even in patients treated 12 to 19 years ago with EBRT in PORTEC-1, bowel symptoms were still moderately increased compared to NAT patients. Interestingly, after the longer follow-up period in PORTEC-1, urinary urgency and incontinence were moderately increased after EBRT. While the bladder is known to be a late responding organ, the combination of increased rates of fecal leakage and urinary incontinence are suggestive for a decrease in pelvic floor function.[17-20] In terms of clinical relevance perhaps the most straightforward finding in the long-term PORTEC-1 analysis was the increased use of incontinence materials day and night after EBRT (43% vs 15%), thus very much difference.

Importantly there were clear relationships between increased bowel and bladder symptoms and the moderately increased need to remain close to the toilet, and between increased limitation in daily activities due to these

symptoms and decreased social and (role-) physical functioning. This pattern of combined bowel symptoms and decreased social and (role-) physical functioning was also observed in the Swedish trial that compared VBT alone with the combination of EBRT and VBT.[21] In the PORTEC-1 HRQL questionnaire there was space at the end of the questionnaire for additional comments, several patients commented in there own words on this relationship: 'frequent and unpredictable bowel movements make me uncertain, so I don't leave the house', 'radiotherapy gave me irritated bowels, so I have to keep in mind if there is a toilet in my direct vicinity' and 'when I leave the house for a day trip I always take a loperamide for my stool'. Finally, both from 6 months after treatment onwards in PORTEC-2 and in PORTEC-1 the general functioning scores of both treatment groups did not differ from those of an age-matched Dutch norm population, indicating that for most women the diagnosis and treatment for endometrial cancer has a clear but transient influence on their general functioning.

Both in PORTEC-1 and PORTEC-2 there was no difference in patient reported sexual functioning and symptoms between both treatment arms. In both trials quite a few patients indicated on the questionnaire forms that they were widowed, did not have a partner, or that their partner had a medical condition that withheld them from being sexually active, resulting in a lower response rate to these questions. In PORTEC-2 sexual activity increased from 15% at baseline after surgery to 39% at 6 months, reaching a plateau at a slightly lower level in both treatment arms compared to the age-matched norm population. The increase in sexual activity in the 6 months following treatment was most apparent in patients younger than 65 years, while very few patients older than 75 years were sexually active which did not change over time. In PORTEC-1 there was no difference in sexual activity between both treatment arms, suggesting that the slight decrease in sexual activity in PORTEC-2 patients compared to the age-matched norm population is not radiotherapy related. A statement on one of the returned questionnaires provides meaningful insight: 'for me it was important my spouse had consideration for my situation; sexual changes need adjustment and creativity'.

Advances in pelvic external beam radiotherapy

As with all studies looking at the late effects of treatment, important progress has been made in the delivery of EBRT since 1990 when the first patients were treated in the PORTEC-1 trial. Intensity modulated and image-guided radiotherapy (IMRT, IGRT), have led to a more conformal dose distribution with increased sparing of normal (bowel and bladder) tissues (Figure 1).[22-24]

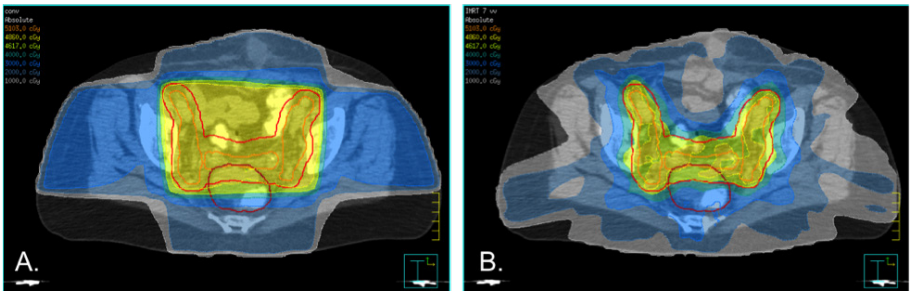

Figure 1. Dose distribution of pelvic external beam radiotherapy; in yellow 95% isodose of 46 Gy. (A) 3-dimensional conformal radiotherapy dose distribution (B) Intensity modulated radiotherapy (IMRT).

Approximately 52% of the patients in PORTEC-1 were treated with a four-field box technique and 18% with a 3-field technique with some form of individualized shielding, while 30% were treated with parallel opposing fields. The use of multiple fields significantly reduced the rate of late complications compared to parallel opposing fields, which increased exposure of bowel structures to high dose levels.[25] Nonetheless, a four-field box technique with individual shielding was required in PORTEC-2 and still led to increased gastro-intestinal toxicity and related sequelae at least up to 5-years after treatment. Studies using IMRT for gynaecological cancer have shown that this leads to more bowel and bladder sparing and less early and late bowel toxicity compared to historic controls. Early results of the RTOG-0418 in which 58 EC patients were included from 25 institutions found a non-significant reduction of short-term bowel adverse event rate of 28% after IMRT compared to 40% in historic controls.[26] Mundt et al. have reported a reduction in early (40 patients, GI grade 2: 60% vs 91% for IMRT vs conventional historic controls) and late (36 patients, median follow-up 19 months, GI all grades: 11% vs 50%) GI toxicity in patients treated for cervical cancer.[27,28] Due to interfraction motion of the target volume due to differences in bladder and rectal filling, even with IMRT

considerable margins are needed to ensure adequate target coverage during the whole period of external beam treatment.[29,30] Further improvement is expected from strategies that incorporate interfraction motion of the target volumes and organs at risk (i.e. IGRT), resulting in reduced margins.[24] Results of studies using IGRT, including daily online soft tissue position verification protocols and a 'treatment plan of the day' concept are being awaited. In the mean time IMRT is an important step forward in reducing treatment related toxicity in patients that need EBRT.

Vaginal brachytherapy: current issues

VBT has been used as adjuvant treatment for EC patients for several decades. A wide variety of dose and fractionation schedules and treated length of the vagina have been reported, resulting in low rates of vaginal recurrences and treatment related toxicity (Table 2).[31-42] However, most studies were retrospective and most included a significant proportion of low to low-intermediate risk patients, which makes it difficult to draw definite conclusions with regard to efficacy.

With increasing dose and increasing irradiated vaginal length, the risk of associated toxicity such as atrophy and shortening of the vagina increases.[36] In a randomized trial reported by Sorbe et al, 290 low-risk EC patients were allocated to receive either 15 Gy in 2.5 Gy fractions, or 30 Gy in 5 Gy fractions of HDR brachytherapy specified at the surface over a period of 8 days.[40] The mean vaginal shortening measured by colpometry was 0.3 cm in the 15 Gy group (ns), and 2.1 cm in the 30 Gy group ($p < 0.001$) at 5 years. In addition, mucosal atrophy and bleeding were significantly more frequent in the 30 Gy group, demonstrating a clear dose-effect relationship.

In PORTEC-2 a dose and fractionation schedule was chosen with the aim to give a similar biological effective dose to the proximal vagina as with EBRT. The dose was specified at 5 mm depth from the surface and top of the cylinder in order to include the full vaginal wall. Due to the steep dose gradient with brachytherapy, the dose from the specification isodose at 5 mm depth towards the surface of the cylinder increases considerably, which can explain the increase rate of grade 2 in mucosal atrophy observed during gynaecological examination after VBT compared to EBRT.[43]

Table 2. Results of postoperative vaginal brachytherapy for endometrial cancer.

Author (ref) acrual period	No. patients, eligibility	Treatment	Vaginal recurrence	Locoregional recurrence	Survival	Severe complications
Institutional series including at least 100 patients						
Sorbe et al.[35] publ 1990	404; Stage I		0,7%	3,0%	92% OS at 5-years	6.9% significant
MacLeod et al.[31] 1985-1993	141; Stage I-IIIA	4 x 8.5 Gy at surface	1,4%	2,0%	91% OS at 5-years	no grade 3/4
Weiss et al.[36] 1987-1993	122; Stage I-II	3 x 7 Gy at surface	1,6%	4,1%	94% NED at 5-years	no grade 3/4
Eltabbakh et al.[28] 1958-1994	332; Stage IA grd 1-2	1 x 30 Gy LDR at surface	0,0%	0,6%	99% DFS at 5-years	2.1% grade 3/4
Petereit et al.[32] 1989-1997	191; Stage IA grd 1-2	2 x 16.2 Gy at surface ovoids	0,0%	0,5%	95% OS at 5-years	0.5% grade 4
Anderson et al.[26] 1990-1996	102; Stage I	3 x 5 Gy at 0.5 cm	1,0%	1,9%	84% OS at 5-years	no grade 3/4
Horowitz et al.[29] 1989-1999	164; Stage I-II	3 x 7Gy at 0.5 cm	1,2%	0,6%	87% OS at 5-years	no grade 3/4
Alektiar et al.[25] 1987-2002	382; Stage I-II	3 x 7Gy at 0.5 cm	0,8%	0,0%	93% OS at 5-years	0.5% grd 3/0.3% grd 4
Solhjem et al.[33] 1998-2004	100; Stage I grd 2-3 and IB grd 1-2 if >2cm	3 x 7Gy at 0.5 cm	0,0%	0,0%	98% OS at 3-years	no grade 3/4
Ataham et al.[27] 1994-2005	128; Stage I	5 x 5.5 Gy at 0.5 cm	0,0%	1,6%	96% OS at 5-years	no grade 3/4

Studies with different brachytherapy dose levels						
Kloetzer et al.[30]	108; Stage I-II	4 x 10 Gy at 0.5 cm	0,0%	2,2%	98% OS at 3-years	2.2% / 0.0% grade 3/4
1981-1990		4 x 10 Gy at 1 cm	3,1%	3,1%	97% OS at 3-years	6.2% / 3.1% grade 3/4
		4 x 10 Gy at 1 cm + vagina	0,0%	0,0%	97% OS at 3-years	6.8% / 12.6% grade 3/4
Osrund et al.[37]	217; Stage I-II	4 x 5.5 Gy at 0.5 cm	1,0%			26% / 8% grade 1/2
1988-1996		4 x 5.5 Gy individualized at 0.3-0.4-0.5 cm	2,5%			17% / 1% grade 1/2 no grade 3/4
Sorbe et al.[34]	290; Stage IA grd 1-2	6 x 2.5 Gy at 0.5 cm vs.	0,7%	1,4%	95% OS at 5-years	vaginal shortening
1989-2003		6 x 5.0 Gy at 0.5 cm				0.3 cm vs. 2.1 cm
Randomized trial VBT versus NAT in low risk endometrial cancer						
Sorbe et al.[47]	645; Stage 1A grade 1-2	3 to 6 x 3 to 8 Gy	1,2%	2,6%	96% OS at 5-years	no grade 3/4
1995-2004		at 0.5 cm vs. NAT	3,1%			
Randomized trials VBT versus EBRT +/- VBT in (high) intermediate risk endometrial cancer						
Norwegian[1]	540; Stage I	1 x 60 Gy LDR at surface		6,9%	91% OS at 5-years	1% grade 4
1968–1974		vs. EBRT + same VBT		1,9%	89% OS at 5-years	1.1% grade 4/5
PORTEC-2	427, age >60 IA grade 3	3 x 7Gy at 0.5 cm vs.	1,8%	5,1%	85% OS at 5-years	GI: VBT 0.5% vs 1.9%
2002–2006	IB grade 1–2 (HIR)	EBRT	1,6%	2,1%	80% OS at 5-years	Vagina: 1.9% vs 0.5%
Swedish[7]	527; Stage I and	6 x 3 Gy at 0.5 cm	2.7%*	5,0%	90% OS at 5-years	grd 3 VBT vs EBRT + VBT
1997-2008	(grade 3 or deep invasion	3 x 5.9 Gy at 0.5 cm				GI: 0% vs 2%
	or DNA aneuploidy) and	1 x 20 Gy LDR at 0.5 cm				Vagina: 0.8% vs 0%
	nuclear grade 1-2	vs. EBRT + same VBT	1.9%*	1,5%	89% OS at 5-years	

LDR: low dose rate. VBT: vaginal brachytherapy. NAT: no adjuvant therapy. NED: no evidence of disease. OS: overall survival
*crude rate or vaginal recurrence

More recently a study examining vaginal wall specimens found that most lymph vessels are located in the superficial 3 mm of the vaginal wall.[44] While 3-dimensional delineation and treatment planning are mainstay in virtually all tumor sites in radiation oncology, VBT planning has largely remained 2-dimensional. Few studies have used CT for analysis of dose to organs at risk, but CT fails in visualizing the target volume since the vaginal wall cannot be clearly distinguished from the bladder and rectal wall on CT.[45-48] In a pilot study of 10 patients for whom MRI scans were obtained with the vaginal cylinder in treatment position, the maximal distance from the surface of the cylinder to the outer border of the vaginal wall did not exceed 3 mm in dorso-ventral direction, while in the lateral directions the distance was 5 mm on average (Figure 2).[49] However, in the upper (proximal) third of the vagina on the lateral sides, folds of the vaginal wall were observed where the distance from the applicator surface to the outer border of the vaginal wall exceeded 5 mm.

Although excellent vaginal control was seen using a standardized treatment prescription in PORTEC-2, underdosage in these lateral vaginal folds can provide a possible explanation for the very few vaginal recurrences seen after brachytherapy. These results suggest that the brachytherapy prescription dose in the doso-ventral direction could be reduced compared to the lateral sides, and support a more individualized image guided approach. Although such asymmetrical dose distributions can be obtained using multichannel cylinders, care must be taken with regard to an increased mucosal surface dose.[50] Future studies examining the most optimal dose and fractionation schedule as well as target definition and type of applicator ensuring optimal target coverage are warranted.

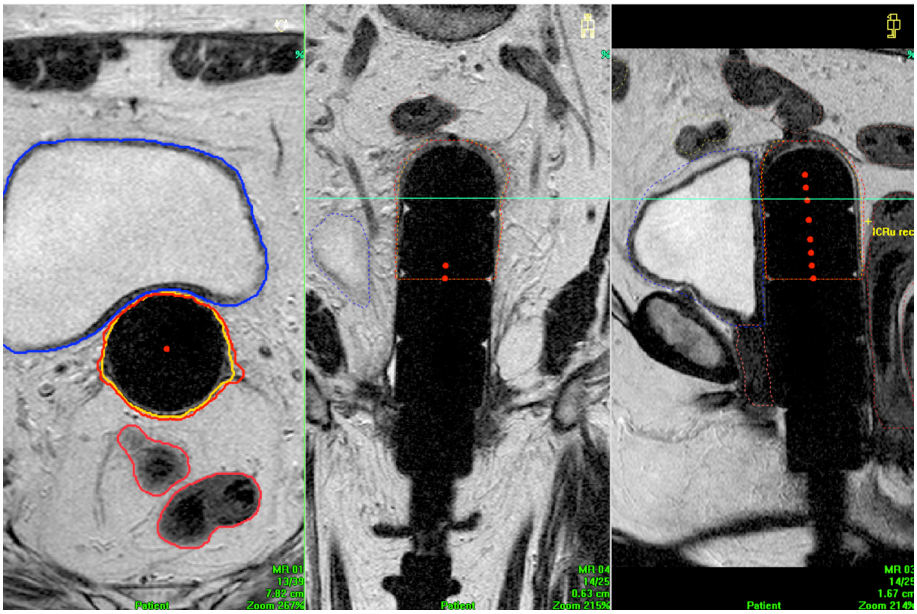

Figure 2. Axial, coronal and sagittal MRI scan of vaginal brachytherapy cylinder in treatment position. A clinical target volume was contoured by two observers (red, orange), organs at risk by one (bladder in blue, rectum in brown).

Optimal treatment for patients with high-intermediate risk features

Taken together, both PORTEC-1 and PORTEC-2 have provided evidence with regard to risks and benefits of three adjuvant treatment strategies for HIR patients: EBRT, VBT or NAT. EBRT leads to an important reduction in the risk of locoregional recurrence, without leading to a reduction in the rate distant metastasis or a benefit in overall survival compared to NAT. Both EBRT and VBT offer similar rates of vaginal control, distant metastasis and overall survival. However, as discussed above, for approximately 3% of patients EBRT might be beneficial in preventing both vaginal and pelvic lymph node recurrences compared to VBT. Since the majority of patients with a pelvic lymph node recurrence have simultaneous distant metastases, overall survival is not improved, and this potential benefit of EBRT is debatable.

Despite the fact that EC patients in general are elderly with frequent co-morbid conditions such as obesity, diabetes and hypertension, patients with HIR features have a good prognosis and given the increasing population of long-term survivors, both short and long-term treatment related symptoms and their impact on quality of life should be taken into account when deciding

on optimal treatment for these patients. EBRT is associated with long-lasting bowel and bladder symptoms that impact on patient functioning up to 15 years after treatment. VBT is clearly more favourable, with equal vaginal control and HRQL results similar to an age-matched norm population.

When opting for no additional treatment, only the 15-20% patients that develop a recurrence are exposed to salvage treatment. Salvage treatment usually consists of combined EBRT and VBT and offers a high probability of local control but with a risk of increased toxicity compared with EBRT alone.[51-53] However, HRQL and symptom outcome of 14 patients who received salvage treatment for a recurrence in the NAT arm of PORTEC-1 was very similar to that of patients initially treated with EBRT alone. VBT (18-24 Gy in 3-6 fractions) has only been compared to observation in a single, small randomized trial that only included low risk patients.[54] There was no significant difference in the vaginal recurrence rate (VBT 1.2% vs observation 3.1%, p=0.11) and there were few and mild (grade 1-2) side effects. Potential risks of this strategy that remain unquantified are the psychological impact of a watchful waiting policy, and the burden, stress and anxieties of experiencing a recurrence and subsequent more intensive treatment.[55] Finally, there is a lack of data on patient preferences with regard to risks versus benefits of NAT vs VBT.

With the aim to provide both an answer to the question if VBT is more favorable than NAT in terms of reduction of overtreatment, health impact and costs, and ultimate vaginal control, and if a lower dose of VBT is equally effective compared to the standard dose, the PORTEC-4 has been initiated.[56] The recently started PORTEC-4 trial is a multicenter randomized trial in which patients with HIR features are randomly allocated (2:1) to vaginal brachytherapy and observation after surgery, and in the VBT arm 1:1 to the standard dose of 21 Gy in 3 fractions of 7 Gy and the lower dose level (3 fractions of 5 Gy). The primary endpoint is vaginal recurrence and the second primary endpoint is the 5-year probability of vaginal control, including treatment for vaginal relapse. The objective of the brachytherapy dose comparison is to estimate the differences in vaginal relapse, toxicity and quality of life (with emphasis on sexual symptoms and functioning) with sufficient precision. Imaging with CT or MRI with the vaginal cylinder inserted will be performed to provide more detailed data on target volume and doses to rectum and bladder. Importantly,

both patient and health care provider preferences with regard to risks versus benefits of VBT or observation are being investigated in a medical decision making side study to PORTEC-4.

At present, vaginal brachytherapy offers a highly effective therapy to prevent vaginal recurrences and maximize relapse-free survival with a favorable toxicity and HRQL profile and is therefore currently the treatment of choice.

Current issues and future perspectives in adjuvant treatment of endometrial cancer

Improving the outcome of high risk patients

The prognosis of the 15% of EC patients with high risk features, being those with grade 3 and deep invasion, with more advanced stages, or serous or clearcell histology, is predominantly determined by the higher risk of distant metastases.[10,57,58] Improvement of the prognosis of these patients depends on systemic therapy that is effective in preventing the development of distant metastases. Therefore, ongoing trials focus on establishing the role of chemotherapy, either given alone or in combination with radiotherapy. In the ongoing PORTEC-3 trial EBRT alone is compared with combined chemotherapy and EBRT (two cycles of cisplatin during radiotherapy followed by four adjuvant cycles of carboplatin and paclitaxel) in high risk patients.[59] In this trial upfront pathology review is mandatory to ensure only high risk patients are included. Quality of life is assessed which will play an important role in the weighing of risks versus benefits of more intensified treatment in these elderly patients. In the GOG#249 trial stage I-II patients with high-intermediate or high risk features are randomized between EBRT alone and VBT followed by adjuvant chemotherapy (3 cycles of carboplatin and paclitaxel).[60] This trial will potentially answer two questions: if VBT followed by adjuvant chemotherapy can further decrease the relatively low risk of pelvic and distant recurrences in high-intermediate risk patients (and at which cost); and how the toxicity profile of EBRT compares to the combination of VBT and short-course adjuvant chemotherapy. The GOG#258 trial compares the same combined radiotherapy and chemotherapy schedule used in the PORTEC-3 trial with chemotherapy

alone (6 cycles of carboplatin and paclitaxel alone) in patients with stage III and IVA endometrial cancer.[61] This trial will answer the question if there is a role for EBRT at all in patients with advanced stage disease, who are mainly at risk of distant relapse. It is expected that the implementation of technical advances in EBRT such as IMRT and IGRT (discussed in the previous section) will decrease external beam radiotherapy related morbidity. Outcomes of ongoing phase II and III randomized trials comparing IMRT with 3D conformal EBRT including quality of life analysis are awaited.[62,63]

While ongoing trials all use the combination of carboplatin and paclitaxcel chemotherapy, knowledge of the biology of endometrial cancer and the underlying pathways that play a role in the development and disease progression is accumulating. Drugs targeting specific pathways known to be of importance in EC have mainly been tested as single agents in phase I and II trials.[64] Since targeted therapies are in clinical use in several types of cancer, more evidence has emerged that a major mechanism of targeted therapy resistance lies in the propensity of tumors to use alternative pathways.[65] Similar to the use of different classical chemotherapeutic agents during a course of chemotherapy, it is expected that multiple targeted agents will need to be used that block several alternative pathways simultaneously.[66] An alternative approach that is being investigated is to target pathways further downstream where alternating routes converge.

Can we further decrease over- and undertreatment in endometrial cancer in the future?

Implementation of the high-intermediate risk criteria to select patients for radiotherapy has led to a substantial reduction of indications for radiotherapy. Nonetheless, there still remains considerable overtreatment and to a lesser extent undertreatment: approximately 5% of the low or low-intermediate risk patients develop recurrent or metastatic disease; approximately 7 patients with HIR features need to be receive VBT to prevent 1 vaginal recurrence and this does not prevent the development of distant metastasis in approximately 8% of the patients; and finally a substantial proportion of high risk patients do not develop metastases and might not have needed adjuvant treatment. An

attractive way to further refine the currently used system for risk assessment is to incorporate new molecular prognostic factors that may better predict the biology, risk of recurrence and metastatic propensity of individual tumours.
Several studies have investigated the prognostic capacity of genetic alterations involved in endometrial carcinogenesis.[64,67-69] For endometrioid type tumors, the majority of studies indicate that activation of the Wnt/ß-catenin signaling pathway is associated with a good prognosis, while mutation of *TP53* and activation of the PI3K-AKT pathway are indicators of tumors with a more aggressive clinical course. Conflicting results have been reported with regard to the prognostic significance of MSI and mutations in PTEN and KRAS as components of the PI3K-AKT pathway. However, most studies are relative small, retrospective and include a heterogenous group of patients including both higher FIGO stages and a combination of endometrioid type and non-endometrioid type tumors and focus on one or two pathways. For these reasons genetic alterations are not yet used as prognostic factors to tailor treatment.
In the pilot study undertaken in 65 selected PORTEC-2 patients, the aim was to investigate these four important pathways simultaneous in a relative homogenous cohort of patients with a similar prognosis based on clincopathologic factors. The combination of multiple activated pathways was the most powerful prognostic factor for decreased disease free survival in a multivariate analysis that included depth of myometrial invasion and age. The most frequent co-occurrence was the combination of *TP53* mutation and PI3K-AKT activation, which has previously been reported to be associated with a poor prognosis.[70] Multiple pathway activation, found in 8% of patients, was strongly associated with aggressive clinical course. In contrast, 40% of patients had no alterations in the investigated pathways and had a very low risk of disease progression. These results indicate that molecular prognostic factors can potentially refine the currently used system for risk classification and lead to a further decrease of over- and undertreatment. Confirmation and further refinement of these findings in a large sample of patients including un-irradiated controls is pivotal. For this purpose a future study is planned using tumor samples of patients from both the PORTEC-1 and PORTEC-2 trials. In future, analysis of tumor samples of patients treated in the PORTEC-3 trial will

provide insight alterations that are predictive for response to chemotherapy, both in endometrioid and non-endometrioid types, and provide rationale for patient selection and future trials incorporating targeted therapies.

Despite their older age at diagnosis and frequent comorbid conditions, the overall prognosis of endometrial cancer patients is good. Improved selection of patients at risk of recurrent and metastastic disease will decrease over- and undertreatment and will be pivotal for future studies applying targeted therapies. In the process of shared decision making on optimal adjuvant therapy, patients need to be informed not only on benefits concerning risk reduction, but also on risks of treatment related morbidity. Quality of life analysis plays a critical role in the interpretation of physician-reported adverse events, and knowledge of the impact treatment related symptoms have on the everyday life of patients. In the near future, the use of postoperative radiotherapy and brachytherapy will be increasingly tailored to the individual patient's needs, sparing many low and intermediate risk patients unnecessary toxicities while identifying the few who need adjuvant treatment, and improving outcomes for patients with high risk disease.

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