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Fractionated perioperative high dose rate brachytherapy using a tissue equivalent bendy applicator

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Abstract. Intraoperative radiation techniques allow an additional local dose in areas at high-risk for local failure. With brachytherapy techniques, perioperative radiation can be fractionated. Fractionated treatment might offer an interesting alternative to a single dose, both to increase the therapeutic ratio and to protect late reacting tissues at risk. The dose distribution for brachytherapy applicators can be optimized using spacer materials. In this prospective study a new tissue equivalent bendy applicator (TEBA) that can remain *in situ* for several days is introduced, and the feasibility of fractionated perioperative high dose rate (HDR) brachytherapy is examined. 31 patients with different tumours (soft tissue sarcoma, Ewings sarcoma, rectal cancer, and locally infiltrating diseases) were treated. The TEBA was applied, depending on resection status and intraoperative findings. Planning was based on digitized radiographs and CT scans. Perioperative HDR brachytherapy was performed using an individual treatment schedule. In 29 patients perioperative radiation was given and in 26 cases fractionated brachytherapy application was possible. TEBA application time varied from 1 day to 11 days. During this time between 1 and 8 fractions were given with total doses from 10 Gy to 25 Gy. Fractionated perioperative brachytherapy with this technique is feasible and adequate. Further studies will show whether fractionated perioperative treatment using the TEBA technique fulfils its theoretical advantages over single dose intraoperative radiotherapy by decreased late toxicity and increased local tumour control.

Local tumour control of malignant and benign aggressive lesions remains the most important aim in oncologic surgery and irradiation. Post-operative external beam radiation therapy (EBRT) is an important therapy option in the treatment of a variety of tumours. However, dose is often limited because of the risk of acute and late toxicity to normal tissue. With inadequate surgical margins, external beam radiation doses within normal tissue tolerances are often not sufficient for long-term local control.

Intraoperative radiation therapy (IORT) is a treatment modality that aims to sterilize incompletely resected neoplastic tissues by giving a high dose of radiation to the tumour bed [1–4]. Electron-based IORT and brachytherapy increases dose inside the tumour bed and allows careful restriction of irradiation to a relatively small volume. Therefore IORT is commonly used as a boost in addition to EBRT or as the sole radiation modality in pre-irradiated patients.

The results of intraoperative radiation studies show high local tumour control rates and acceptable side effects for a variety of resected tumours. These include sarcomas [5–10], gynaecological malignancies [11], rectal cancer [12–15] and desmoid tumours [16]. Accurate placement of IORT electron applicators within the area of risk is difficult, especially in anatomically complex regions such as the pelvis or retroperitoneum. Brachytherapy applicators are easier to handle, as the material is flexible and can be shaped to the tumour bed. Furthermore, brachytherapy techniques allow perioperative fractionated brachytherapy. The fractionation of intraoperative radiation increases the therapeutic ratio [17] and the biological efficiency of irradiation after surgical resection of the tumour. Hannoun-Lévi et al [18] introduced a technique for post-operative fractionated high dose rate (HDR) brachytherapy for advanced or recurrent pelvic tumours. In this study brachytherapy catheters were fixed directly onto the tumour bed without using spacer materials. This technique is limited if structures at risk, such as peripheral nerves, vessels or ureters, are in contact with the surface of the brachytherapy catheters owing to high surface doses and dose inhomogeneities. The dose distribution can be optimized using spacer

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materials such as flabs [19] or comparable devices such as the Harrison–Anderson–Mick applicator [9, 12].

In the present study the radiobiological advantages of a fractionated radiation schedule and the dose distribution advantages of techniques using spacer materials for HDR brachytherapy are combined. A tissue equivalent bendy applicator (TEBA) that can remain *in situ* for several days was used. The feasibility of applying fractionated perioperative radiation therapy (PORT) using HDR brachytherapy is examined.

Materials, methods and patients

From July 1997 to December 1999, 48 patients with different malignant tumours and locally aggressive infiltrating diseases were considered suitable for intraoperative radiation in our department. Patients were selected after discussion in the interdisciplinary tumour board conference of radiation oncologists, surgeons and medical oncologists. Intraoperative electron therapy was given to 12 patients with gross residual disease after resection. The decision to give PORT was made at the time of surgical intervention. In five cases, planned IORT or TEBA application was not possible owing to intraoperative findings. 31 patients were included in this feasibility study after tumour resection with close margins. In 24 patients the intention was curative, and in 7 patients it was palliative owing to metastatic disease. The median age was 43 years (range 1–81 years). Diagnoses included soft tissue sarcoma, Ewing sarcoma, rectal cancer and desmoid tumour. Table 1 shows the patients' characteristics. PORT was part of a multimodal treatment plan as shown in Table 2.

A multichannel HDR afterloading machine (Sauerwein Isotopentechnik; MDS Nordion, Haan, Germany) was used for irradiation. The Iridium 192 source had a 6 mm active length and initial activity was $\leqslant$444 GBq (12 Ci).

A new flexible transparent material (Kabe Labortechnik GmbH; Nümbrecht-Elsenroth, Germany) made of polyvinyl chloride containing the plasticizer di-2-ethylhexylphthalate was used. TEBA material has a tissue equivalent density. It contains a mesh made of polypropylene for better fixation with surgical sutures. TEBA material has been tested in pre-clinical studies for toxicity and metabolism. The procedures used in this study were approved by the local committee on human experimentation (study No. 96060001/GCP) and followed the Helsinki Declaration.

Up to three TEBAs were inserted during surgery. TEBA thickness was 1 cm. Individual TEBA sizes varied from 2.5 cm to 12 cm in length and from 1 cm to 9 cm in width. One to eight parallel hollow tubes were fixed in the TEBA, spaced 1 cm apart and 0.5 cm from the TEBA surface, for afterloading.

Insertion was performed in cooperation with the orthopaedic, surgical and radiotherapy departments. TEBA insertion was performed according to intraoperative findings such as tumour localization, completeness of resection and the proximity of sensitive structures. Standard surgical sutures were used to fix the TEBA to the tumour bed. Because of its flexibility, the TEBA can be shaped to the tumour bed (Figure 1). Where possible an additional TEBA was used as spacer material to keep sensitive structures such as intestine, bladder and peripheral nerves away from the TEBA surface. After TEBA insertion, hollow tubes for afterloading were fixed under sterile conditions. In all cases CT scans were performed to guide appropriate positioning of the TEBA (Figure 2). Additional conventional radiographs

Table 1. Patient characteristics

	No. of patients	%
Gender		
Male	19	61
Female	12	39
Diagnosis		
Soft tissue sarcoma	20	65
Ewings sarcoma	3	10
Rectal cancer	2	6
Desmoid tumour	6	19
Tumour site		
Abdomen/pelvis/retroperitoneum	18	58
Extremities	11	35
Head	2	7
Prior local surgery		
Yes	10	32
No	21	68
Prior local EBRT		
Yes	9	16
No	22	84
Prior chemotherapy		
Yes	3	10
No	28	90

EBRT, external beam radiation therapy.

Table 2. Current treatment

Treatment	No. of patients	%
EBRT	17	55
Before surgery	4	13
After surgery	13	42
PORT		
Yes	29	93
No	2	7
Chemotherapy		
Yes	7	23
No	24	77

EBRT, external beam radiation therapy; PORT, perioperative radiation therapy using high dose rate brachytherapy.

Figure 1. Flexible, transparent, six channel tissue equivalent bendy applicator *in situ* after tumour resection. Note the plastic tubes for high dose rate brachytherapy.

were taken. Where multiple TEBA applications and non-planar TEBAs were used, individualized treatment planning was based on digitized radiographs. This was performed to avoid overdosage and unplanned dose inhomogeneities. Dose distributions were calculated using the Abacus 3.1 Planning System (MDS Nordion, Haan, Germany). Dose distributions were calculated to suit individual circumstances. Total dose and fractionation of PORT were defined individually depending on intraoperative findings, previous treatment and planned treatment after PORT.

An overlay of isodoses as a CT scan is shown in Figure 2. In this case the prescription point for 5 Gy was calculated at 5 mm from the TEBA surface. The 3 Gy and 7 Gy isodoses are also shown. A second TEBA containing no hollow tubes was used as spacer material and the surface dose to the intestine was reduced from approximately 7 Gy to 5 Gy for each fraction. After completing radiation, a second surgical procedure was carried out to remove the TEBA. Patients were monitored during perioperative irradiation for complications such as infection, neurological changes and abnormal laboratory tests.

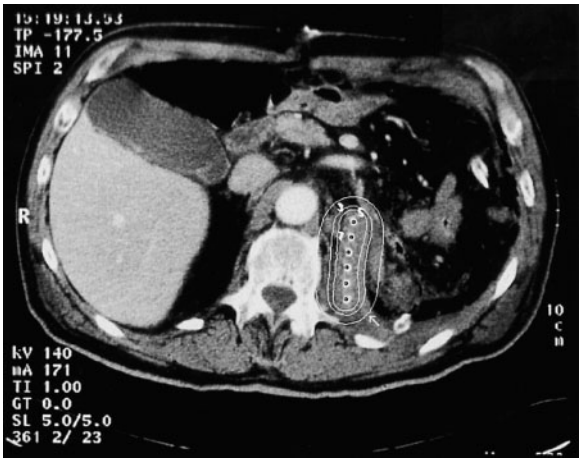


Figure 2. Post-operative CT scan of a patient with a retroperitoneal sarcoma after tumour resection and tissue equivalent bendy applicator (TEBA) application. Tubes used for afterloading are parallel with same distances to the TEBA surface. An additional TEBA (arrow) is used towards the intraabdominal space to keep risk structures such as intestine away. An overlay with isodoses is given. The prescription point for 5 Gy was calculated at 5 mm from the TEBA surface.

Results

Feasibility of the procedure

31 patients were treated with surgery and TEBA application within the observation period, with the intention of giving PORT. In 29 patients, HDR brachytherapy was performed and in 25 patients fractionated brachytherapy was performed. No malfunctioning of the HDR brachytherapy machine was observed during this time. In 13 patients, additional post-operative EBRT was given. In 4 cases pre-operative EBRT had already been given before tumour resection and PORT. Two patients refused EBRT after PORT. In 7 patients post-operative chemotherapy was given. The size and number of TEBAs were individually chosen according to the area to be treated. In 9 patients more than one TEBA was necessary. The median volume of irradiated tissue was 69 cm^3 (range 9–196 cm^3), the individual prescription point being defined as the distance in millimetres from flab surface. In 26 cases, the prescription point was 5 mm, in 1 case 2.5 mm and in 2 cases the TEBA surface itself, owing to the vicinity of critical structures.

The duration of TEBA application varied from 1 day to 11 days. The most common duration time was 5 days (Table 3). Within this period 1 to 8 fractions were given (Table 4) with an interval of at least 6 h. Applied total doses varied from 8 Gy to 25 Gy in fractions of 2–10 Gy. In

Table 3. Number of days the tissue equivalent bendy applicator (TEBA) material remained *in situ*

TEBA duration time (days)	No. of patients
1	3
2	2
3	2
4	6
5	8
6	1
7	2
8	3
9	2
10	1
11	1

Table 4. Number of high dose rate brachytherapy fractions given during tissue equivalent bendy applicator application

No. of fractions	No. of patients
0	2
1	4
2	2
3	4
4	5
5	10
6	1
7	2
8	1

Table 5, a detailed summary of treatments for each of the 31 patients is given, including applied dose, number of fractions and duration of PORT, as well as EBRT doses and the interval between PORT and EBRT.

The dose delivered at a certain depth of irradiated tissue is described by the isodoses using the TEBA technique (Figure 3a). For comparison, a dose distribution is shown for brachytherapy catheters without using spacer material (Figure 3b). A more homogeneous dose distribution, with TEBA surface isodoses of 7 Gy and 3 Gy at approximately 2 cm calculated from TEBA surface, can be obtained compared with dose distributions shown in Figure 3b, which have high surface doses and doses decreasing to 3 Gy within 1 cm.

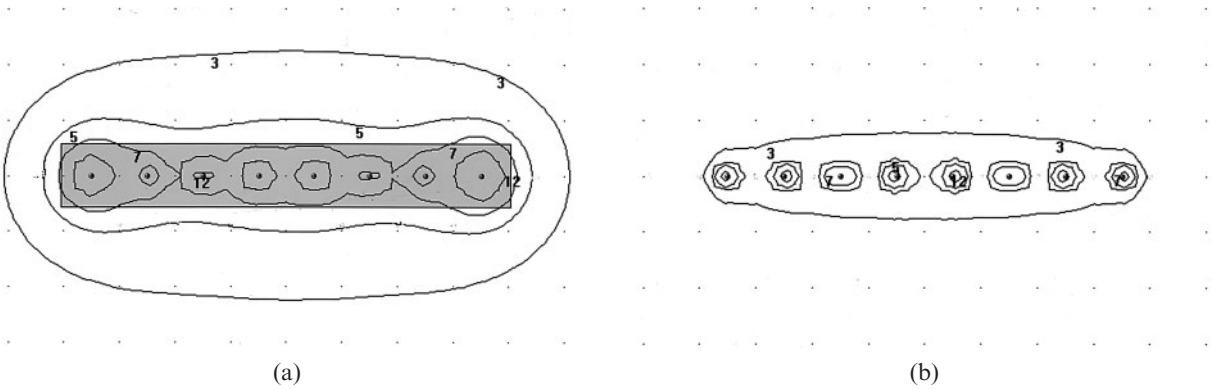
Side effects and complications

In two patients who underwent TEBA application, PORT was not given because post-operative

Table 5. Treatment details for each patient (current treatment)

Patient No.	No. of PORT fractions	Total time for PORT (days)	Total PORT dose (Gy)	EBRT dose (Gy)	Time between PORT and EBRT (weeks)
1	4	3	20	50.4	10
2	4	3	20	refused	—
3	0	0	0	—	—
4	1	1	10	—	—
5	1	1	10	50	3
6	1	1	10	n.d.	n.d.
7	5	3	20	—	—
8	3	2	12	50.4 (pre)	8
9	1	1	10	54 (pre)	6
10	5	3	20	—	—
11	3	2	15	—	—
12	3	2	15	60	3
13	6	4	18	50	4
14	0	0	0	32	—
15	5	3	20	—	—
16	5	3	20	54.4 (pre)	4
17	5	3	20	50.4	7
18	7	9	15.5	50	8
19	2	2	10	—	—
20	7	9	21	49.2	8
21	3	2	15	—	—
22	5	5	25	39.6	10
23	4	3	20	54	17
24	4	3	20	—	—
25	8	7	24	—	—
26	4	3	12	59.4	4
27	5	3	20	n.d.	n.d.
28	5	3	20	refused	—
29	2	2	8	50.4	4
30	5	3	20	50	n.d.
31	5	3	15	44.8 (pre)	4

PORT, perioperative radiation therapy using high dose rate brachytherapy; EBRT, external beam radiation therapy; pre, EBRT before surgery; n.d., no data.



(a) (b)

Figure 3. Isodoses (in Gy) using the tissue equivalent bendy applicator (TEBA) method (a) in comparison to brachytherapy catheters without a spacer material (b). Dimensions are given in centimetres. Prescription point for 5 Gy is 5 mm (calculated in (a) from the surface of TEBA and in (b) from the surface of catheters).

CT scans showed an unsatisfactory TEBA position. One case involved a 63-year-old patient with a retroperitoneal sarcoma and the other a 2-year-old child with a rhabdomyosarcoma of the left petrous bone. In this latter patient, a second application was carried out for recurrent disease in the same area 20 months later and 8 Gy in two fractions was given.

In four patients, post-operative CT scan detected a significant haematoma or seroma, which prohibited adequate dose distribution to the tumour bed. A 55-year-old patient with recurrent neuroendocrine carcinoma in the left gluteal region required an operation to drain the haematoma. The TEBAs were revised and a single intraoperative HDR brachytherapy dose of 10 Gy was given. In another patient the haematoma was evacuated and PORT was given with a total dose of 25 Gy in five fractions. In the case of a 65-year-old patient with a paravertebral desmoid tumour, the haematoma caused displacement of two TEBAs during PORT, therefore new individualized treatment planning was necessary based on digitized radiographs. In another case, a 38-year-old patient with a myxoid sarcoma of the right pelvic region, a haematoma was found after PORT during the second operation.

In three patients, reversible peripheral neuropathy was observed after TEBA application, and in one patient paresis developed prior to surgery and did not recover. In these cases it was not possible to confirm the radiation procedure as the cause of the reported complications. Where possible, the TEBA surface dose was reduced near identifiable peripheral nerves by careful treatment planning. In a patient with myxoid liposarcoma of the right femur, the intended fourth fraction of 5 Gy was not given because of neurological complications, and PORT was stopped at 15 Gy. In one patient, thrombosis was diagnosed after surgery, and a second patient displayed persistent lymphoedema of the leg.

Necrosis of the colon with subsequent peritonitis was observed in a 63-year-old patient with retroperitoneal malignant histiocytoma. This complication was caused by the surgery and unsatisfactory TEBA application. A partial resection of the colon was necessary and radiation was not given. Table 6 records details of treatment toxicity and overall perioperative time in hospital for each patient.

Discussion

Local tumour control is an essential requirement for the successful treatment of malignant tumours. IORT is emerging as an interesting additional treatment in the multimodal management of resectable tumours in an attempt to sterilise the tumour bed, eliminating microscopic disease that may remain after surgical resection. Most studies give a single intraoperative dose with a high biological activity [2, 3, 6, 7, 9, 11–13]. However, for radiobiological reasons and protection of sensitive tissues, fractionated treatment might offer a better alternative by increasing the therapeutic ratio [8, 17, 18, 20]. The main objective of this study was to evaluate the feasibility of fractionated PORT by using a TEBA technique in the treatment of malignant tumours and locally aggressive diseases. The TEBA method, with dose distributions as shown in Figure 2 and Figure 3a, in combination with the fractionation schedule offers predictable dose distributions, taking account of the tolerance dose of sensitive structures, including late reacting tissues.

In 25 of 31 patients, fractionated PORT was given. TEBA was left *in situ* for 1–11 days (median 5 days). Fractionated PORT successfully delivered the intended dose in all patients, even those with TEBA duration time of more than 5 days. This new TEBA material and the fractionation of brachytherapy permit treatment that takes the anatomical, biological and individual

Table 6. Toxicity of current treatment

Patient No.	Complications (major)	Complications (minor)	Overall perioperative hospitalization time (days)
1	—	—	14
2	—	—	12
3	Necrosis of colon	—	134
4	Haematoma/seroma	Thrombosis	46
5	—	—	21
6	—	—	12
7	—	—	28
8	—	—	51
9	—	—	6
10	—	—	25
11	—	Reversible paresis of limb (28d)	50
12	—	Reversible paresis of limb (21d)	7
13	—	—	15
14	—	—	155
15	—	—	25
16	—	—	21
17	—	—	12
18	—	—	35
19	—	—	20
20	—	—	42
21	—	—	190
22	Haematoma/seroma	Lymphoedema (persistent)	61
23	Haematoma/seroma	—	74
24	—	—	28
25	—	—	44
26	—	—	104
27	Haematoma/seroma	Reversible paresis of limb	35
28	—	—	n.d.
29	—	—	72
30	—	—	21
31	—	—	36

d, days; n.d., no data.

patient characteristics into account. Even when complications occurred after TEBA application, a single intraoperative fraction of brachytherapy was still possible in most cases. However, a second operation is required to remove the TEBA material after PORT has been completed. In some patients with sarcomas or desmoid tumours localized in extremities or the pelvic region (treated in cooperation with the department of orthopaedics), a second surgical procedure was beneficial for two stage plastic reconstruction.

Although follow-up has been short, there is no clear evidence of radiation-induced toxicity. In one patient peripheral neuropathy occurred during treatment and after treatment in two patients, but it is not clear whether this was owing to radiation or surgery. The short delay between surgical intervention and neurological problems makes surgery the more likely cause. However, neurovascular damage can be a side effect of IORT [21–24].

Details of operative findings and perioperative CT scans of the tumour bed are necessary to identify structures at risk and avoid complications such as TEBA dislocations and haematoma or seroma. In four cases, a haematoma/seroma located in the tumour bed was detected by CT scans performed routinely during PORT. In one case a displaced TEBA was discovered. These findings underline the importance of appropriate perioperative radiological examination of the area at risk. The rates of observed complications, mainly owing to surgical intervention, might be reduced with increasing experience. This technique enables the modification of radiotherapy planning (an example involving PORT is given in Table 7) as part of a protocol for individual multimodal treatment.

Conclusion

Perioperative brachytherapy together with a new TEBA material permits fractionated HDR

Table 7. Suggested planning and treatment schedule for perioperative radiation therapy (PORT) using high dose rate brachytherapy

	Day 0	Day 1	Day 2	Day 3	Day 4
AM	Su	CT/Ra/Pl	PORT	CT/PORT	PORT
PM		PORT	PORT	PORT	Su

Su, surgery; Ra, conventional radiography; Pl, planning.

brachytherapy in resectable malignant tumours and locally infiltrating disease. This feasibility study shows that the technique is reliable and short-term side effects appear acceptable. This method might be beneficial in complex anatomical situations where normal tissues and structures are at risk, by using fractionated treatment and optimized dose distributions. It has yet to be shown whether fractionated treatment in combination with the TEBA technique is superior to a single intraoperative dose with respect to acute and late toxicity and local tumour control.

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