

■ SPECIAL LECTURE

INTRAOPERATIVE BRACHYTHERAPY —A METHOD TO REDUCE RECTAL CANCER RELAPSES?—

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Abstract: Background / Aims: Intraoperative radiotherapy (IORT) has been introduced as a new concept in the treatment of recurrent and advanced colorectal tumours. In contrast to external irradiation the IORT enables the application of a high local tumour dose while reducing the damage to the adjacent radio-sensitive structures to a minimum. Nevertheless commonly used rigid linear accelerators are often not suited to fit any anatomical site hence the adaptation to the tumour bed is problematic.

In this study we would like to describe a new form of brachytherapy, using a flexible flab which is individually adapted to the tumour bed to apply radiation intraoperatively.

Patients and Methods: Between 10/94 and 6/98 33 patients with advanced primary (n=8) or recurrent (n=25) rectal carcinomas underwent IORT in Afterloading-Flab-Technique at our institution. All patients had been treated by chemo- and external radiotherapy prior to the procedure. 5 rectum resections, 19 rectum amputations and 9 debulking operations were performed. The mean duration of surgery was prolonged by about 30 minutes.

Results: Presently 5 of 9 R0/R1 resections are free from relapse. Out of 24 R2-resected patients 7 showed improvement at the tumour site, in 9 cases the disease has remained stable whereas 8 patients died during the follow-up period. We would like to emphasize the fact that all patients showed remarkable systemic progress.

Conclusions: Showing a low rate of local tumour recurrence and being a technically simple procedure while reducing radiation-caused complications for the patient, the Afterloading-Flab-Technique seems to be a valuable alternative to high risk radical tumour resections in the treatment of rectal cancer. Long-term follow-ups are yet awaited.

Key words: Afterloading-Flab-Method, IORT, Rectal cancer

INTRODUCTION

Primary, advanced and recurrent rectal tumours require multiple therapy concepts. Radiotherapy is a possible approach to accompany surgery. Aim of the intraoperative irradiation is a locally increased tumour dose combined with lowest possible strain to the surrounding tissue. The Afterloading-Flab-Technique, a high-dose brachytherapy, appears to be an alternative treatment to common linear accelerators.

PATIENTS AND METHODS

Between October 1994 and June 1998 we

treated 33 patients with advanced or recurrent rectal cancer with the Afterloading-Flab-Technique. In five of these cases multiple treatment sessions were performed, so that our method was applied 38 times during this period. Indications for this procedure were locally advanced primary tumours (8 cases) and relapses (first recurrent tumour 18, second recurrent tumour 7). Chemo- as well as external radiotherapy had already been carried out on all patients with recurrent carcinomas. The group consisted of 18 male and 15 female patients with an average age of 66 years (range 43-78 years).

Out of the 33 operations (5 anterior resections, 8 abdominoperineal excisions, 11 extended

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abdominoperineal excisions, 9 debulking operations) curative surgery was accomplished only in four patients while in 29 cases only palliation could be achieved (R1-situation 5, R2-situation 24).

The procedure took place in a specially arranged operation theatre in cooperation with our Department of Radiotherapy. During the irradiation the patient was observed and his vital signs were documented by video-surveillance.

The radiation-applicator, a flexible moulage allowing equi-distant implantation of brachytherapy catheters, is responsible for the name of this method. At our institution we use the "Freiburg Flab", a flexible plastic plate consisting of single balls with hollow catheters arranged parallel to each other (Fig. 1). After surgery the target area of the tumour bed is measured and a flab which adequately encompasses the target area is selected. The flab is placed onto the tumour bed and the adjacent tissue is retracted. The applicator itself is fixed by sterile scarfs of cotton (Fig. 2). The plastic catheters are then connected with the afterloading-device (Fig. 3). The radioactive source (micro-Selectron-HDR-IR 192, (rays of 379 keV, half-life-period 72 days) is pushed forward step by step corresponding to the time calculated for the radiation dose. The dose is then emitted at the surface of the flab and consists of the energy emitted at the single source positions. The lingering time should be calculated to give the reference dose at the position which is located at the surface of the flab. A 1 cm security margin

should be added to the target area included by the flab. Flabs of different size and shape allow maximal conformity of target- and treatment volume. Irradiation doses range from 10 to 15 Gy. Because of the abrupt decrease of irradiation dose in deeper layers this method's use is limited to shallow targets. Fig. 4 shows the distribution of dose in a plane perpendicular to the flab-centre. An individual planning with three dimensional imaging of the flab and corresponding isodoses is performed inside the operation theatre (Fig. 5). Consequently the exact placement of the single source positions and herewith optimal adaptation of reference dose to the tumour bed is possible.

The mean duration of surgery was prolonged by about 30 min due to the additional procedure.

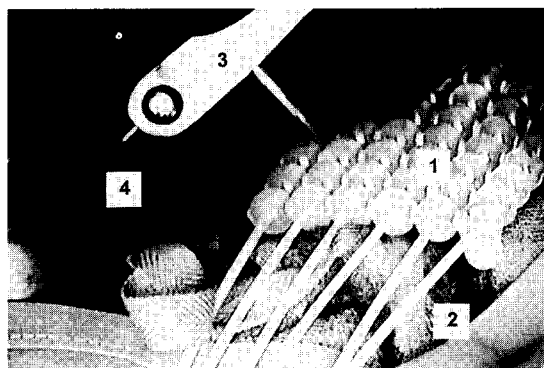


Fig. 2: Intraoperative placement of the flab (1 flab, 2 cotton scarf, 3 retractor, 4 abdominal wall)

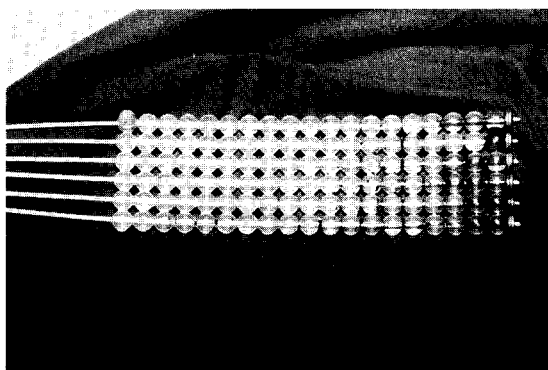


Fig. 1: Radiation applicator for IORT with Afterloading-Flab-Technique



Fig. 3: Afterloading-device for intraoperative brachytherapy

$\gamma = 0.0 \text{ mm}$

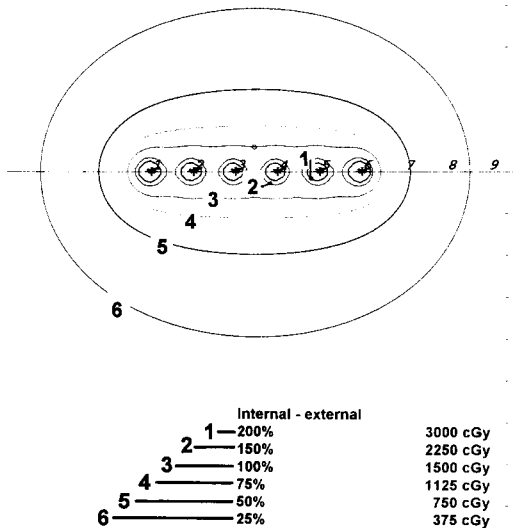


Fig. 4: Distribution of dosage in a plane perpendicular to the flab centre

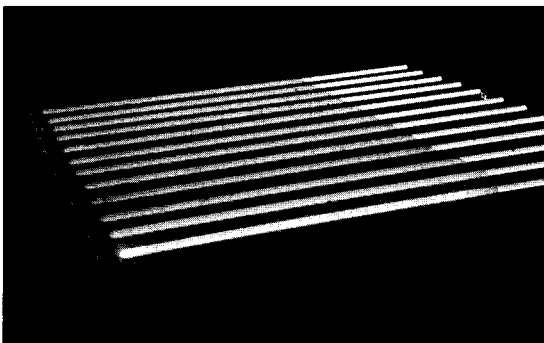


Fig. 5: Intraoperative individual radiation planning

RESULTS

All Patients underwent a close-meshed follow-up (tumour markers, chest x-ray, ultrasonography, CT scan and endoscopy were performed at regular intervals). The average follow up time was 14 months (1-35 months).

The IORT through Afterloading-Flab-

Technique was well tolerated by all patients. Severe radiation-caused complications were not noted. Table 1 shows the overall morbidity of our multiple therapy concept. At present 5 of 9 R0 or R1 resections are free from relapse. One patient of this group was not located, three patients died during the follow-up period.

We would like to emphasize the fact that all patients showed remarkable systemic progress. Out of 24 patients with R2 resection 7 showed improvement at the site of tumour, in 9 cases the disease has remained stable and 8 patients died during the follow-up period. The total number of deaths during the observation period was 11 (Table 2).

DISCUSSION

1911 Werner and Caan, both students of the Heidelberg surgeon and radiotherapist V. Cerny, published their first clinical results of the "eventeration therapy"¹⁾. The necrotic part of the stomach was surgically reduced into the abdominal wall and irradiated. In the early 70s Abe reported about the possibility of intraoperative irradiation of carcinoma²⁾. The radiation was applied in one fraction, first through Co-60 (-ray, later with high-energy-electrons³⁾.

The intraoperative radiotherapy (IORT) is a method to increase the local dose to the tumour bed or the exposed tumour⁴⁾. The use of high-energetic-electrons requires rigid tubes and is

Table 1 Morbidity of the multimodal therapy concept in form of Afterloading-Flab-Technique in our department

perianal wound infection	3
sacrovesical fistula	3
anastomosal leakage	1
nerval ureter dysfunction	1

Table 2 Causes of death of in our patient collective

systemic and local progress	2
systemic progress	3
local progress	5
others	1

therefore not suitable for every anatomic site. In contrast, the flexible Afterloading-Flab-Technique allows good adaptation to the tumour bed and renders possible irradiation of target volumes of almost any size and shape.

The application is limited to superficial targets because of the abrupt decrease of irradiation dose in deeper layers. The reason for this phenomenon is not the absorption by the surrounding tissue but rather the mathematical relation between distance from radiation source and the dose. Similarly to the electron irradiation, the choice of an appropriate position allows maximum adjustment of single dose and target volume³⁾.

Regarding the mathematical coherence mentioned above a complete contact of the flab to the tissue surface is extremely important. The correct adjustment of the flab has to be verified by palpation.

The main advantage of the flab method is its simplicity, the short preparation time and therefore the reduction of possible complications during the operation. The lower cost compared to the utilisation of a linear accelerator is another. In addition to this the Afterloading-Flab-Technique requires simpler X-ray protection regulations and the radiation device is more economical (Table 3).

The standardised surgical resection including the radical removal of lymphnodes and proximal occlusion of the supplying vessel is the primary therapy for rectal carcinoma. In the majority of the patients the tumour infiltrates beyond the rectal wall and / or lymph nodes are affected. The relapse rate after isolated surgical treatment for Duke's stage C or higher is reported between 20 and 50%. The prognosis of the patient depends (besides on the manifestation of metastases) on the occurrence of local tumour relapse. Moreover the tumour recurrence is frequently combined with

pain and therefore with severe reduction of the patient's quality of life. A curative resection of relapsed tumours is possible in less than 20% of the cases³⁾. We would like to stress that the alternative therapy is a highly invasive, radical surgical concept with a morbidity rate of 58 to 83%^{6), 7)}.

Not curatively resected tumours and recurrent carcinoma are reported as indications for HDR-Brachytherapy^{3), 8)}. The Afterloading-Flab-Technique enables a locally limited increase of dosage even after external radiation. 50,4 Gy is the recommended total dose for an adjuvant multimodal therapy, which is limited by the radiosensitivity of the small intestine. No efficient analysis of the relation between dose and effect exists. Especially for advanced or relapsed tumours a local dose of 55-60 Gy seems to be promising³⁾.

In respect to the reported data the local tumour control and prognosis seem to have improved compared to a control group of patients treated with external radiation⁹⁾⁻¹¹⁾. At the "Klinikum rechts der Isar" at Munich, Germany, thirty patients with advanced (n=16) or relapsed (n=14) rectal carcinoma were treated with IORT in Afterloading-Flab-Technique between June 1987 and March 1992. 15 Gy were applied intraoperatively to resectable carcinoma which was combined with radio-chemotherapy postoperatively (50,4 Gy; 5 FU). Unresectable carcinomas were treated with fractionated radio-chemotherapy preoperatively (1.1 Gy twice/ day up to 40 Gy). 3-4 weeks later the surgical intervention with IORT was performed. After an average follow-up time of 18 months 1 out of 16 and 3 out of 14 patients showed local tumour relapse. Following Kaplan Meier an estimated 2 - year survival rate of 65% for rectal-carcinoma relapse has to be expected. A further reflection of the lymph node status shows similar survival rates (50%) for either T3 or T4 tumours and recurrent tumours with affected lymph nodes. There was no increase of morbidity noted⁸⁾.

A different afterloading therapy concept is used at the University of Kiel, Germany¹²⁾. Between September 1992 and September 1995 an afterloading device was implanted close to the residual tumour site in 13 patients with non

Table 3 Advantages of the Afterloading-Flab-Technique compared to Linear Accelerators

flexible applicator
high dosage gradient
simple handling
short planning
economy

curatively resected rectal tumours or recurrences. A pulse-dose-rate irradiation was applied after completed healing of the wound (Iridium 192, total dose 20 Gy / 5 days). Percutaneous saturation of 65 Gy in four-field-technique followed the afterloading therapy. Radiation-caused complications requiring treatment did not occur. Two patients died because of metastasis during a follow up time between 10 and 34 months (median: 18 months). At present eleven patients are without local tumour relapse, six are tumour-free.

At the Memorial Sloan-Kettering Cancer Center at New York / USA, Alfred Cohen uses a comparable method (Harrison-Anderson-Mick Applicator). In his study 68 patients, out of these 22 with primarily non resectable, 46 with relapsed rectal carcinoma were treated between 11/92 and 12/96. The applied local dose was set between 10 and 20 Gy. The average follow-up time for the patients at the time of the last follow-up was 17.5 months. The local tumour control of the primarily unresectable rectal carcinoma was reported 81%. In this study high prognostic value was related to the histological analysis of the resected margin (margin free from infiltration in 62% of the cases, infiltrated were 38%). For the relapsed tumours local control was stated at 63% (with 82% free of infiltration and 19% infiltrated). As expected relapse free survival with 69% (margins: 77% and 38%) for primary tumours is higher than for tumour relapses with 47% (margins: 71% and 0%) [personal visit December 1997]. In Japan, starting nation of IORT, only linear accelerators are used at present.

Initially the indication for IORT in Afterloading-Flab-Technique in our collective was limited to recurrent rectal carcinoma and patients that already had received percutane radio- and chemotherapy within a conservative treatment concept. Based on the promising results the indication was extended to advanced primary tumours with potential R1-situations.

In cases of the residual tumour invasion after resection being deeper than one centimetre we took the opportunity of intraoperative sluice implantation and postoperative fractionated irradiation. After CT-scan documentation the planning was performed by Nucletron-Plato-BPS v. 13. The radiation was applied in afterloading

technique using a micro-Selectron-HDR-IR192-device with a total dose of 3-15 Gy. CT-scan follow-up after six to eight weeks showed significant tumour necrosis in the area of 100% isodose of the target volume.

For non resectable rectal carcinoma recurrences the sluices are implanted under CT control transcutaneously in local anaesthesia.

SUMMARY

In respect to our results in this study we have developed the following treatment concept for primary, advanced and recurrent rectal carcinomas:

1. After surgical R1 or R2 tumour resection with tumour residue less than one centimetre (IORT in Afterloading Flab technique)
2. After surgical R2 tumour resection with tumour residue larger than one centimetre (intraoperative sluice implantation and postoperative fractionated irradiation)
3. Technical or biological inoperability (CT - controlled sluice application, postoperative fractionated irradiation)

With the technically simple Afterloading-Flab-Technique more invasive methods are not needed in the therapy of rectal tumour relapse. Even in patients already receiving external irradiation a high dose is applicable locally to the tumour site without damaging adjacent tissue. The flab enables the individual adaptation of the brachytherapy catheters to almost any anatomic site which cannot be accomplished by linear accelerators. Obtaining a low rate of local tumour recurrence the Afterloading-Flab-Technique is a valuable alternative treatment method to extensive high risk resection procedures.

Due to the small number of reported cases the Afterloading-Flab-Technique is still an experimental method and hence not a standardised therapy recommendation as yet. Long time follow-up results are awaited and have to be discussed critically.

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