



GEC-ESTRO/ACROP recommendations

## GEC-ESTRO/ACROP recommendations for performing bladder-sparing treatment with brachytherapy for muscle-invasive bladder carcinoma



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### ABSTRACT

The standard treatment for muscle-invasive bladder cancer (MIBC) is a radical cystectomy with pelvic lymph node dissection with or without neoadjuvant chemotherapy. In selected cases a bladder sparing approach is possible, for example a limited surgical excision combined with external beam radiotherapy and brachytherapy. To perform brachytherapy flexible catheters have to be implanted in the bladder wall. The implantation is done either by the open retropubic approach or the endoscopic surgical approach. The largest experience for brachytherapy is with low-dose rate and pulsed-dose rate, although some short-term experience with high-dose rate is also reported.

The main advantage for this technique is the conservation of bladder function, with comparable local control rates as for cystectomy series in selected cases.

The GEC-ESTRO/ACROP (Groupe Européen de Curiethérapie-European Society for Radiotherapy and Oncology / Advisory Committee on Radiation Oncology Practice) recommendations to perform bladder implantations and brachytherapy as a treatment option for MIBC are described.

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The first papers on brachytherapy for muscle-invasive bladder cancer (MIBC) were published soon after World War II. At that time brachytherapy was performed with radium-226 [1–3]. It was not until the eighties of last century that this treatment was thoroughly analyzed and popularized by van der Werf-Messing [4–7]. Historically cesium-137 and iridium-192 low-dose rate (LDR) sources were used for brachytherapy. In the nineties of the last century LDR brachytherapy was replaced by stepping source pulsed-dose rate (PDR) brachytherapy [8]. The advantage of the stepping source technology, such as PDR brachytherapy, is that it allows more possibilities for dose distribution optimization and a better radiation safety profile for nursing personnel. For the family there is more time to stay with the patient at visiting hours in the hospital. By now there is more extensive literature on the value of brachytherapy for the treatment of bladder cancer. According to the European Association of Urology (EAU) guidelines and to several national guidelines worldwide, the standard treatment for MIBC is a radical cystectomy with pelvic lymph node dissection [9]. However, in selected cases a bladder conserving treatment with brachytherapy can be considered according to the Dutch

and French national guidelines [10,11]. Since the recent publications on this treatment with long-term follow-up there is increased interest for this treatment strategy and several institutes worldwide are starting a program for bladder conserving treatment for MIBC with brachytherapy [12,13]. The major advantage of brachytherapy is that adequate bladder function can be preserved in almost 90% of the patients [14–16]. Aluwini et al. found a cystectomy-free survival rate of 93% and 85% at 5 years and 10 years, respectively [13]. In several studies a 5-year local control rate of 62–100% is reported for T1–T3 tumors with a 5-year overall survival rate of 38–73% [12,13,15–19]. There are no randomized studies comparing cystectomy to a bladder conserving approach with brachytherapy. However, two retrospective comparative studies and one systematic review found similar disease specific and overall survival [19–21]. In the largest cohort of 1040 patients on brachytherapy for bladder cancer local recurrence-free probability, metastasis-free probability, disease-free probability, and overall survival at 5 years of 75%, 74%, 61%, and 62%, respectively were found [12]. In this study 77% of the investigated patients had a clinical T2 disease and for 70% the tumor size was 3 cm or less.

Acute side-effects occurring in 5–10% of cases are urinary tract infection, wound dehiscence, postoperative ileus, hydronephrosis

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due to obstruction at the distal ureter, bladder bleeding, and pulmonary embolism [16,19,22].

In the early days when radium-226 and cesium-137 needles, but also Ir-192 wires, were used severe late effects have been reported such as vesico-cutaneous or vesico-vaginal fistula, stricture of the urethra and ureters, necrosis, and persisting urine leakage [13,19]. Since the introduction of afterloading catheters and computer planning systems the majority of described toxicity is transient local ulceration at the implant site. The reported rate of grade 3 and 4 bladder toxicity is 5.8% and for grade 3 and 4 intestinal toxicity 1% [13].

In this article the UroGEC-ESTRO group (Groupe Européen de Curiethérapie-European Society for Radiotherapy and Oncology) will report recommendations for brachytherapy as a treatment option for MIBC. These recommendations are intended to uniform this treatment across the institutes that are or will start performing it and to help starting institutes with the implementation of their program.

### Pretreatment investigations

The urologist primarily sees MIBC patients, usually with complaints of the urological tract. The examinations to be systematically performed for the diagnosis and work-up for staging of bladder cancer patients should follow the guidelines of the EAU [9] and are listed hereunder.

- Physical examination, including rectal and vaginal bimanual palpation.
- Urinary cytology.
- Cystoscopy.
- Transurethral resection of bladder (TUR-B).
- Imaging of the pelvic area either by CT-scan or MRI
- CT-urography to examine the upper urinary tract
- Imaging for distant metastases by CT-thorax, CT-abdomen (optional MRI-liver).

With rectal and vaginal palpation a mass can be felt originating from the bladder and invasion into adjacent organs and fixation to the surroundings can be evaluated. This examination should be performed before and after TUR-B.

In case of high-grade urothelial carcinoma or carcinoma in situ, malignant cells can be found in urinary cytology. The appearance of malignant cells is indicative of malignancy anywhere in the urinary tract. A negative cytology does not exclude malignancy.

With cystoscopy direct visualization of the tumor is possible, allowing documentation of the location, size, number of visible tumors, and appearance (solid or papillary). The careful documentation of the topography of the lesion is particularly important for bladder sparing techniques and the use of a bladder diagram to meticulously report on the exact mapping of the lesion is strongly advised. If possible when brachytherapy of the bladder is anticipated, the radiation oncologist should be present when cystoscopy is performed. For definitive diagnosis a TUR-B is mandatory and histopathological examination done. The resection should be deep enough for assessment of invasion in the detrusor muscle layers. All suspicious lesions should be biopsied to rule out multifocal disease.

For local staging both computer tomography (CT) and magnetic resonance imaging (MRI) are used. Particularly important is the detection of perivesical extension or invasion of adjacent organs [23–25]. CT is unable to differentiate the invasion of different bladder wall layers and therefore has a staging accuracy of only 55% [26]. Better local staging can be obtained with MRI when using contrast-enhanced techniques. The accuracy with MRI for local staging is about 85% [27,28].

The detection accuracy of lymph node metastasis is comparable for CT and MRI being 70–98% [29–31]. Patients with a bladder tumor are at higher risk for tumors elsewhere in the urinary tract. Additionally an excretory phase CT-urography is done to exclude urinary tract pathology elsewhere and CT and/or MRI scan to evaluate lung and liver metastases.

### Patient selection for brachytherapy

The option for a bladder preserving therapy for MIBC is only reserved for a selected group of patients. Patients that are good candidates should have:

- A solitary tumor of a maximum diameter of 5 cm.
- No concurrent carcinoma in situ elsewhere in the bladder.
- A tumor classified cT2-T3 following the UICC TNM 7 ed. classification [32].
- Tumor not located in the bladder neck or the prostatic urethra in male patients.
- No distant metastasis.

In the literature cases have been reported of patients with a limited T3 disease, which were treated by brachytherapy after a partial cystectomy [12,13,16,21]. Treatment of a T3 tumor should be reserved for experienced urologists and radiation oncologists with specialization in brachytherapy. Exclusion of carcinoma in situ is because these patients are at high risk to develop a recurrence after radiotherapy. In this case the preferable treatment is a radical cystectomy. Furthermore, due to the deep localization of the bladder neck in the pelvis, this treatment site is difficult to reach complicating proper placement of the catheters. This results in an increased risk of kinking of the catheters preventing the radioactive source to correctly pass. Furthermore at this site there is a risk of prostate invasion.

### External beam radiotherapy

The bladder implantation and brachytherapy are always preceded by an external beam radiotherapy (EBRT) course. The reason for pretreatment with EBRT is to eradicate vital tumor cells prior to the opening of the bladder for implantation of the loops for brachytherapy or accidental puncture of the bladder with the endoscopic surgical approach (see later). An additional reason, next to avoiding entmetastasis, with high-dose EBRT is to treat the lymph node areas with a curative intent.

Two schedules are reported in the literature [17,21,33–35]: a “low” EBRT dose on bladder alone and a “high” EBRT dose on bladder with or without pelvic nodes. Examples of the first schedule (low EBRT dose on the bladder) are: 3 fractions of 3.5 Gy or a single fraction of 8.5 Gy. The high EBRT dose one, on either the bladder alone or on the entire small pelvis, will deliver 20 fractions of 2 Gy or 22 fractions of 2.5 Gy.

Low dose EBRT is followed by high dose brachytherapy and high dose EBRT is followed by low dose brachytherapy. Examples of brachytherapy dose schedules will follow in the section “Planning aim and dose prescription”. The total cumulative dose of EBRT and brachytherapy for all schedules in terms of biological equivalent dose at 2 Gy/fraction (EQD2), is approximately 70 Gy for an  $\alpha/\beta$ -ratio of 10–15 Gy [36].

If EBRT is directed to only the bladder a pelvic lymph node dissection should follow. The standard pelvic area to treat is up to the common iliac bifurcation, and including the external iliac, obturator fossa, internal iliac, and presacral nodes, although there is debate on the extension of pelvic lymph node treatment volume in particular for the selected category of patients with low risk of nodal involvement [9].

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