Intraoperative radiotherapy in gynaecological and genito-urinary malignancies: focus on endometrial, cervical, renal, bladder and prostate cancers

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Abstract
Intraoperative radiotherapy (IORT) refers to the delivery of a single radiation dose to a limited volume of tissue during a surgical procedure. A literature review was performed to analyze the role of IORT in gynaecological and genito-urinary cancer including endometrial, cervical, renal, bladder and prostate cancers. Literature search was performed by Pubmed and Scopus, using the words “intraoperative radiotherapy/IORT”, “gynaecological cancer”, “uterine/endometrial cancer”, “cervical/cervix cancer”, “renal/kidney cancer”, “bladder cancer” and “prostate cancer”. Forty-seven articles were selected from the search databases, analyzed and briefly described. Literature data show that IORT has been used to optimize local control rate in genito-urinary tumours mainly in retrospective studies. The results suggest that IORT could be advantageous in the setting of locally advanced and recurrent disease although further prospective trials are needed to confirm this findings.

Keywords: Intraoperative radiotherapy, Endometrial cancer, Cervical cancer, Renal cancer, Bladder cancer, Prostate cancer

Background
Intraoperative radiotherapy (IORT) refers to the delivery of a single large dose of radiation to a limited volume of tissue during a surgical procedure.

Radiotherapy (RT) has a major role in the management of most gynaecological and genito-urinary cancer as adjuvant or neoadjuvant treatment or as radical treatment in combination with chemotherapy or hormone therapy. IORT has the capability to increase the radiation dose with very limited or no increase of toxicity thanks to the target exposition during the surgical procedure. For this reason, IORT can be used in various settings of gynaecological and genito-urinary tumours aiming at dose intensification and consequently at increasing tumour control rate.

IORT can be delivered using dedicated linear accelerator producing electron beams, X-rays sources delivering low-energy radiation or high dose-rate brachytherapy units through catheters positioned in the tumour bed and loaded with iridium-192. In particular, electrons generated by linacs and brachytherapy sources can be conveniently used for IORT procedures in gynaecological and genito-urinary tumours. Interestingly, the first IORT experience was indeed reported in 1905 for the treatment of a 33 year old woman affected by uterine carcinoma [1]. Over the following decades, IORT was increasingly used for several tumours including gynaecological and genitor-urinary malignancies.

In 1998, the International Society of Intraoperative Radiation Therapy (ISIORT) was founded in order to promote a scientific and professional approach to IORT activity. Among their other activities, ISIORT-Europe collected and...
recorded information regarding IORT treatments, including those of gynaecological and genito-urinary cancers, from the affiliated centres in a database registry [2, 3].

This review focuses on the use of IORT in genito-urinary malignancies, reporting tumour setting and outcome for endometrial, cervical, renal, bladder and prostate cancers.

Research criteria

Literature search was performed through Pubmed and Scopus databases by using the following key words: “intraoperative radiotherapy/IORT”, “gynaecological cancer”, “uterine/endometrial cancer”, “cervical/cervix cancer”, “renal/kidney cancer”, “bladder cancer” and “prostate cancer”. Eighty-four articles were found from 1981 to 2015. Reviews and case reports were excluded as well as clinical series presented as abstract at conferences proceedings. Forty-seven articles were finally selected for the review.

Endometrial and cervical cancers

Patients with endometrial and cervical cancer are usually treated with surgery and RT with or without chemotherapy depending on risk factors. After primary treatment, the risk of local failure is up to 60% [4] and the options for a new treatment are surgery, RT when a reirradiation is feasible, and chemotherapy. After such treatments, disease control has been reported in 25–50% and 18–47% in patients with recurrent endometrial and cervical cancer, respectively [5]. In these recurrent patients, IORT after surgical resection can be considered to increase the probability of local control, especially when a repeated course of EBRT is not feasible. This treatment approach including IORT is reported in the NCCN guidelines with an evidence of category 3 [6].

The use of IORT in the management of endometrial and cervical cancer was explored in 15 studies, most of them analysing retrospectively patients affected by locally advanced primary and recurrent disease. The majority of articles reported on the clinical experience from the Mayo Clinic and the University Hospital Gregorio Marañón in Madrid [7–21] (Table 1). In these clinical series, IORT was delivered to the tumour bed with electrons in the majority of cases and with low kV x-rays or brachytherapy through catheters implanted during the surgical procedure and uploaded with iridium wires in postoperative setting in selected patient series.

In endometrial cancer patients, limited loco-regional recurrences have a relatively high control rate of about 60% at 5 years either with pelvic exenteration or local EBRT in non-previously irradiated patients [22, 23]. In this tumour setting, the use of IORT was reported in retrospective studies [14, 15]. Dowdy et al. [14] found that radical resection of the pelvic sidewall with negative margins and IORT resulted in a relatively high overall survival rate (71%) (Table 1). Awtrey et al. [15] reported that the addition of IORT to cytoreductive surgery in 27 recurrent endometrial cancer patients resulted in a 2-year disease free survival (DFS) rate of 78% versus 67% when IORT was not used, although this difference was not statistically significant. Based on these retrospective data, the addition of IORT to surgery could be proposed in patients with isolated endometrial cancer recurrences, especially when margins might be close or microscopically positive.

Patients with a loco-regional recurrence of cervical cancer and candidates for salvage surgery can undergo also IORT with the intent to sterilize the possible residual disease and improve the outcome. This approach was described in three series from Mahe et al. [20], Barney et al. [10] and Martinez-Monge et al. [16] who reported globally the results in 188 patients with recurrent cervical cancer. Intraoperative radiation dose ranged from 6 Gy to 30 Gy, with higher doses in case of macroscopically positive margins (R2). Mahe et al. [20] reported a slightly higher local control, although statistically not-significant, in patients with radical resection versus those who received partial resection (27% vs. 11%), Barney et al. [10] did not observe any influence of margins status for local control and Martinez-Monge et al. [16] reported a risk of distant metastases of 38% in patients with negative margins (R0) and 100% in those with macroscopic residual disease (R2). From these studies, it emerged that the status of the margins is the most important risk factor for treatment and the association of IORT seems to improve the probability of local control.

As far as locally advanced primary cervical cancer is concerned, two series treated by IORT are reported in the recent literature [12, 16]. In both studies, patients underwent radical hysterectomy and 10–25 Gy IORT after neoadjuvant EBRT, concomitantly to chemotherapy, to a total dose of 50.4 Gy. In the Giorda’s phase II trial, patients tolerated radio-chemotherapy quite well, but developed high incidence of toxicity (79%) after surgery and IORT [12]. In the Martinez-Monge’s retrospective series, 15% of side effects were related to IORT [16]. The available data suggests that this aggressive strategy is not advantageous in particular for the risk of severe side effects and that concomitant radio-chemotherapy alone should be considered the best treatment strategy in this patient setting [6].

In conclusion, literature data supports the use of IORT in recurrent endometrial and cervical cancer to improve local control whereas its use appears more controversial in primary locally advanced disease. The potential benefit of this approach is mainly based on retrospective mono-institutional studies and should be further verified by prospective possibly randomized trials investigating the potential advantage compared to EBRT alone.

Renal cancer

Historically, the standard therapy for renal cell carcinoma is radical nephrectomy. Local control and survival
| Reference | N.pts | Type of cancer | Primary/recurrent | EBRT N. pts Dose (Gy) | IORT dose (Gy) | Technique | Median follow-up months (range) | Local Control | Overall Survival | Toxicity |
|-----------|-------|----------------|------------------|-----------------------|----------------|----------|-------------------------------|---------------|-----------------|----------|
| Sole [7] | 61 Uterus 18 Cervix 32 Other 11 | Pelvic recurrent 35 (57%) Paraortic recurrent 26 (43%) | Mean 31 Gy (29–45) | R0: 10–12.5 Gy R1: 15 Gy | IOERT | 42 (2–166) | 5-years 65% | 5-years 42% | RTOG acute ≥ G3: 23 RTOG late ≥ G3: GI 8 GU 3 Neuropathy 1 |
| Foley [8] | 32 Cervix 21 Uterus 6 Other 5 | Pelvic recurrent 26 (81%) Primary 6 (19%) | Mean 13.5 Gy (10–22.5) | IOERT | Median 26 (3–196) | 5-years R1 73% 5-years R2 71% | 5-years 70% R1 77% R2 55% | ≥G3 47% 5 IORT-related GU 2 Bone 1 Lymphedema 2 |
| Backes [9] | 32 21 IORT | Cervix 21 Other 11 | Recurrent 32 (100%) | Median 17.5 Gy (10–20 Gy) | IOERT HDR IORT | NA | Median PE + IORT 10 months LEER + IORT 9 months PE 33 months | Median PE + IORT 10 months LEER + IORT 17 months PE 41 months | NA |
| Barney [10] | 86 Cervix | Pelvic recurrent 73 (85%) Primary 13 (15%) | 61 pts (71%) No prior RT: median 45 Gy Prior RT: median 39.6 Gy | median 15 Gy (6–25 Gy) | IOERT | 32 (1–306) | 3-years 62% 70% primary 61% recurrent | 3-years 25% | ≥G3 GI 4 GU 1 Neuropathy 1 Other 4 |
| Calvo [11] | 35 Uterus 7 Cervix 20 Other 8 | Pelvic recurrent 35 (100%) | 16 pts: 45 Gy no previous RT 30.6 Gy previous RT | R0: 10–12.5 Gy R1: 15 Gy | IOERT | 46 (3–166) | 5-years 58% | 5-years 42% acute ≥G3: 14 late ≥G3: GI 5 GU 2 Neuropathy 1 |
| Giorda [12] | 35 Cervix | Primary 35 (100%) neoadj 50.4 Gy | Mean 11 Gy (10–15) | IOERT | NA | 2-years 89% | 5-years 49% | Peri/post-surgery GU 10 |
| Tran [13] | 36 Cervix 17 Uterus 11 Other 8 | Recurrent 32 (88%) | 18 pts (50%) mean 44 Gy | Median 11.5 Gy (6–17.5) | Orthovoltage-IORT | Mean 50 (2–198) | 5-years 44% Cervix 45% Uterus 58% | 5-years 42% | ≥G3 10 pts 28% |
| Dowdy [14] | 25 Uterus | Recurrent 25 (100%) | 21 pts 45 Gy | Median 15 Gy (10–25 Gy) | IOERT | Median 34 | 84% | 5-years 71% R0 47% R1 0% R2 | Neuropathy 8 GU 5 Fistulas 5 Bone fractures 2 |
| Autrey [15] | 27 Uterus | Pelvic Recurrent 27 (100%) | 12 pts NA | IOERT 9 pts | Median 24 (5–84) | NA | 2-years 78% | NA |
| Martinez-Monge [16] | 67 Cervix | Pelvic Recurrent 36 (54%) Primary 31 (46%) | 36 pts : 45 Gy Primary: 12 Gy median (10–23) Recurrent: 15 Gy (10–20) | IOERT | Primary: 58 (8–144) Recurrent 19 (10–138) | 10-year 69% 93% primary 47% recurrent | 10-year 35%; 58% primary 14% recurrent | 15% IORT related |
| Gemignani [17] | 17 Cervix 9 Uterus 7 Other 1 | Recurrent 17 (100%) | 2 pts dose NA | Mean 14Gy (12-15Gy) | HDR-IORT | 20 (3–65) | 67 | 54 | NA |
| DelCarmen [18] | 15 Cervix 5 Uterus 3 Other 7 | Pelvic Recurrent 14 (93%) Primary 1 (7%) | - | IOERT | (3–36) | 54% | 74% | Neuropathy 4 GU 3 Lymphedema 2 |

Table 1: IORT studies for endometrial and cervical cancer
| Study     | N  | Site     | Recurrence Type | Total Pts | Median Age (Range) | IOERT Dose (Range) | 5-year Local Control | 5-year OS | 3+ Grade GI AEs | 3+ Grade GU AEs | Neuropathy | Notes               |
|-----------|----|----------|-----------------|-----------|-------------------|---------------------|----------------------|----------|-----------------|-----------------|------------|---------------------|
| Garton    | 39 | Cervix   | Pelvic Recurrent | 28       | Median 45 Gy (1–67) | Median 17.3 Gy (10–25 Gy) | 5-years 67% | 5-years 32% | ≥G3 14 (36%) | IORT related 6 |
| Mahé      | 70 | Cervix   | Pelvic Recurrent | 30 pts (20–45) | R0 mean 18 Gy (10–25) | R1 biopsy mean 19 Gy (10–30) | Mean 15 Gy (2–69) | 21% R0 27% R1-2 11% | 3-years 8% | 10-IORT related GI 1 GU 4 Neuropathy 5 |
| Stelzer   | 22 | Cervix   | Pelvic Recurrent | 6 pts: 26–50 Gy, 7 pts: 45–62.4 Gy | 22 Gy median (14–27.8 Gy) | Minimum 15 months | 5-years 48% | 5-years 43% | Neuropathy 7 |  |

Pts = patients, IORT = intraoperative radiotherapy, IOERT = intraoperative electron radiotherapy, EBRT = external beam radiotherapy, GU = genitourinary, GI = gastrointestinal, NA = not available, R0 = negative margins, R1 = microscopic residual disease, R2 = macroscopic residual disease.
rates after surgery alone are satisfactory for T1-T2 N0 with rates of 90-100% and 80-90% at 5 years, respectively. The results are less favourable for locally advanced and N+ disease, where the 5-year local control rate and overall survival rates are 70-80% and 0-40%, respectively. In renal cancer, the isolated local recurrence after radical nephrectomy is uncommon (0.7-3.6%) but it is associated with a poor prognosis. An aggressive surgical approach to local advanced or recurrent disease, possibly including the removal of the renal fascia and leading to negative margins, seems to improve outcome and prolong survival [24, 25]. Although renal cell carcinoma has traditionally been considered relatively radiation resistant, recent data using hypofractionation for primary or metastatic lesions suggest that this resistance can be overcome by high dose per fraction, as used in the IORT scenario [26].

The role of IORT in the management of renal cancer was explored in a number of retrospective studies with patients presenting with locally advanced primary or recurrent disease [27–33] (Table 2). IORT doses varied from 10 to 25 Gy depending on the amount of residual tumour after maximal resection and on the dose of the combined EBRT. All cases of these series were characterized by postoperative microscopic or macroscopic residual disease in the renal fossa. A more recent study [27] considered 98 patients with advanced or recurrent renal cell carcinoma treated with IORT at nine institutions. Preoperative or postoperative EBRT to a total dose of 40–50.5 Gy was administered to 27% or 35% of patients, respectively. The median radiation dose administered with IORT was 15 Gy (range: 9.5-20 Gy). Overall survival and disease free survival rates at 5 years were quite similar and only 24% of relapses were local whereas 76% were distant. This fact suggests the potential benefit in local control when IORT is added. Similar results in terms of local control rates were reported in previous studies from other institutions (Table 2). In these series, the acute and late toxicity profile seems acceptable. Many studies, however, are characterized by a limited description of late side effects.

From all published data, although from retrospective series, it emerges that the addition of IORT to surgery and EBRT is associated with high rates of local control with acceptable toxicity. The best candidates could be untreated patients with large tumour volume and high risk of positive margins after radical nephrectomy and patients with locally recurrent tumours. The long-term prognosis is mainly related to the risk of onset of distant relapse that is quite common, especially in patients with recurrent disease. This fact advocates the need for additional systemic effective therapy.

**Bladder cancer**

The goals of treatment for invasive bladder cancer are high long-term overall and disease-free survival rates with acceptable functional outcome, however, radical cystectomy, that is nowadays the standard, needs urinary diversion and results in erectile impotence and infertility. In order to avoid these adverse effects and preserve quality of life, bladder-preserving treatments have been proposed as a viable option in selected patients [34]. Bladder preservation strategies for muscle invasive bladder cancer evolved over time from single modality to multimodality treatment approaches, including transurethral resection and chemo-radiation protocols. The use of an intraoperative radiation boost by brachytherapy or electrons may be advantageous for intensifying the dose and obtaining local control without compromising organ function.

From the literature databases, 15 studies using IORT by brachytherapy implants or electrons were selected for this review [35–49] (Table 3). Brachytherapy was the most used intra-operative modality and was employed either as a single treatment or as a boost dose combined with EBRT. It may represent a curative treatment for selected high-risk superficial and solitary muscle infiltrating tumours. Clinical target volume (CTV) typically includes the macroscopic disease or the tumour bed with safety margin to full thickness of the bladder wall.

All the studies about brachytherapy were retrospective analyses of single or multiple co-operative centres. In 2012, a multicentre survey [36], assessed the role of brachytherapy in 1040 patients with early stage bladder carcinoma in a multidisciplinary setting. Patients were treated by pre-operative EBRT and limited surgery with brachytherapy implant. From this analysis, it emerged that this approach can offer adequate results in terms of local control and overall survival in selected patients suitable (Table 3). In this regard, a careful patient selection is particularly important in relation to the non-negligible probability of acute toxicity leading to fistulas or necrosis.

A recent systematic review with meta-regression analysis showed better results after brachytherapy than after cystectomy in terms of overall survival, but not in terms of cause-specific survival in patients with muscle-invasive bladder cancer. The authors commented that this discrepancy can be explained at least in part by the differences in tumour stage between the two groups [50].

The integration of an IORT boost to the whole bladder in a multidisciplinary protocol combining neoadjuvant systemic chemotherapy, preoperative RT, and planned cystectomy has proven to be feasible in the Pamplona’s series [44]. The mean sterilization rate of invasive bladder cancer, confirmed in pathologic studies by the cystectomy specimen, was 65%, and seemed to be increased
| Reference | N. pts | Type of cancer | Primary/recurrent | EBRT | IORT dose (Gy) | Technique | Median follow-up | Local control | Overall survival | Toxicity |
|-----------|--------|----------------|------------------|------|----------------|-----------|-----------------|---------------|----------------|----------|
| Paly [27] | 98     | Advanced or recurrent renal cell carcinoma | Pelvic locally recurrent 100% | 26 pts: 45–40 Gy pre or post surgery | Median dose: 15 Gy (9.5–20 Gy) | IORT | 3.5-years (3–169) | 5-years 39% advanced disease | 5-years 52% recurrent disease | 5-years 37% advanced disease | 5-years 55% recurrent disease |
| Habil [28] | 17     | Locally recurrent disease | Pelvic locally recurrent 100% | - | Median dose: 15 Gy (10–20 Gy) | IORT | 18 months | 2-years 91% | 2-years 73% | No late toxicities |
| Calvo [29] | 25     | Advanced or recurrent renal cell carcinoma | Pelvic locally recurrent 100% | 15 pts: 44 Gy perioperative | Median dose: 14 Gy (9–15 Gy) | IORT | 2.2 years (3.6–26) | 5-years 80% | 5-years 38% 10-year 18% | 6 pts acute/late toxicities ≥ 3 |
| Hallemeir [30] | 22   | Advanced or recurrent renal cell carcinoma | - | 21 pts: 41.5 Gy perioperative | Median dose: 12.5 Gy (10–20 Gy) | IORT | 99 years (3.6–20) | NA | 5-years 40% | 5 pts acute/late toxicities ≥ 3 |
| Master [31] | 14     | Local recurrent renal cell carcinoma | Pelvic locally recurrent 100% | - | Median dose: 15 Gy (12–20 Gy) | IORT | NA | NA | 5 years 30% | NA |
| Eble [32] | 14     | Advanced or recurrent renal cell carcinoma | - | 14 pts: 40 Gy postoperative | 15–20 Gy | IORT | 24.3 months | NA | 11.5 months | 0% |
| Frydenberg [33] | 11 | Local persistence or local recurrent | 11 pts: 45–50.4 Gy preoperative | 10–25 Gy | IORT | NA | NA | NA | NA | NA |

*Pts* patients, IORT intraoperative radiotherapy, IOERT intraoperative electron radiotherapy, EBRT external beam radiotherapy, GU genitourinary, GI gastrointestinal, NA not available
by the addition of neoadjuvant chemotherapy. This finding can be of importance with respect to the development of new protocols aiming at bladder preservation. In the Lyon series [42], an excellent bladder preservation rate of 69% was achieved with the combination of preoperative chemo-RT followed by IORT. This is the only prospective study about IORT in bladder carcinoma. It could be of interest to attempt verifying these results in further studies using an IORT approach.

In conclusion, after a careful patients selection, IORT could be used within a bladder sparing multidisciplinary approach because of the favourable 5-year local control rates aiming at escalating the radiation dose. IORT might have a role also in case of radical surgery for locally advanced disease in order to improve local control rates, as performed in the Pamplona’s series. Multicentric prospective studies could useful to confirm the role of IORT in this tumour setting.

Prostate cancer
The rationale for dose escalation with IORT in prostate cancer is based on the demonstration of a dose–response relationship and a low $\alpha/\beta$ value in the radiobiological linear quadratic model [51]. Likewise, the exploitation of this principle is being increasingly investigated in EBRT with hypofractionation [52].

Among 14 IORT literature studies, 9 clinical series and the ISIORT registry were selected and presented in Table 4 [2, 53–61].

Early data on IORT in prostate cancer came from the Kyoto University and the Saitama Cancer Centre in Japan, where the authors treated patients through a perineal IORT approach without prostatectomy [59, 61]. More recent experiences were reported by Italian authors using IORT in combination with radical prostatectomy and regional lymph node dissection before or after the surgical procedure [53–56]. A relevant percentage (81%) of patients was included in prospective institutional study protocols as described in the ISIORT data-registry [2]. From this analysis, it emerged that IORT was used as a boost dose prior to prostate removal in most cases. When a single-shot radiation strategy was adopted, a dose of 18–21 Gy was delivered, similarly to the breast cancer model. The diameter and bevel end angle of the applicators were selected based on target dimensions, considering a margin of at least 5 mm around the prostate and the necessity to reach the target underneath the pubic arch while sparing the bladder. The electron beam energy, between 9 and 12 MeV, depended on...
the depth of the target and the position of the rectum, which should be spared.

Patient selection varied widely in the various studies. The Japanese series included either early or advanced stage disease and in particular the Kyoto University included stages from A2 to C treated with curative intent and even stage D2 treated with palliative intent [59, 61]. The Italian studies accrued only non-metastatic locally advanced disease based on the identification of pre-operative risk factors.

In terms of post-surgical early and late side effects, IORT for prostate cancer resulted an acceptable procedure. In the Japanese series, toxicity resulted in early haematuria, pollakiuria but only very few cases of late chronic cystitis and urethral stricture. Interestingly, Kato et al. reported a reduction in rectal toxicity by using a spacer to reduce the dose to the anterior rectal wall [57].

In the Italian series, surgical complications, such as haematoma and lymphocele, occurred with a similar incidence to that of conventional prostatectomy [53–56]. No major surgical complications were described and patients had no significant difference of estimated blood loss and need of transfusion. In this regard, Rocco et al. reported post-surgical complications in 42% of patients after surgery and IORT and in 30% after prostatectomy alone [54].

Although the relatively short follow-up, the outcome in terms of biochemical disease free survival was quite promising resulting higher than 70% in both the Japanese and Italian series (Table 4). Of note, a recent update of our clinical series of 95 patients showed a 5-years biochemical disease-free survival rate of 78% in high-risk patients (oral presentation at ISIORT-ESTRO Forum, Barcelona, 24–28 April, 2015).

Clinical trials with long follow-up are needed to assess the real efficacy of IORT in locally advanced prostate cancer but preliminary results look quite promising. The best candidates for IORT possibly combined with EBRT, could be the patients staged T3N0 with high risk for positive margins. In the future, multicentre studies should be designed to better clarify the real role of IORT for dose escalation in local advanced prostate cancer patients.

**Conclusions**

The delivery of a high single dose of radiation to a limited volume during the surgical time, achievable with IORT, is

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**Table 4** IORT studies for prostate cancer

| Reference       | N. pts | Patients’ selection          | Surgical approach         | IORT dose (Gy) | Technique | Adjuvant EBRT | BRFS        | Overall survival | Toxicity     |
|-----------------|--------|-----------------------------|---------------------------|----------------|-----------|---------------|-------------|----------------|-------------|
| Krengli (ISIORT) [2] | 108    | Intermediate-high risk      | NA                        | 8-15 Gy with EBRT 18–21 Gy single shoot | IORT or 50-kV | NA           | NA           | NA             | NA          |
| Krengli [53]    | 38     | Intermediate-high risk      | Retropubic approach       | 10-12 Gy        | IORT      | 46-50 Gy, 2 Gy/fx | 82%         | 2-years 100% | Lymphocele 16% hematoma 6% |
| Rocco [54]      | 33     | Intermediate-high risk      | Retropubic approach       | 12 Gy           | IORT      | 45 Gy, 1.8 Gy/fx | 97%         | 2-years 100% | GU: 17% ≥ G2 Gil: 10% ≥ G2 |
| Saracino [55]   | 34     | Intermediate risk           | Retropubic approach       | 16-22 Gy        | IORT      | No            | 77%         | NA             | No GU/GI toxicities ≥ G1 |
| Orecchia [56]   | 11     | High-risk                   | Retropubic approach       | 12 Gy           | IORT      | 45 Gy, 1.8 Gy/fx | NA           | NA             | No GU/GI toxicities ≥ G1 |
| Kato [57]       | 54     | Stage B2-D1                 | Perineal/retropubic        | 25-30 Gy        | IORT      | 30 Gy, 2 Gy/fx | 74%         | NA             | Early Gl G3: 7% |
| Higashi [58]    | 35     | Stage B-C                   | Perineal/retropubic        | 25-30 Gy        | IORT      | 30 Gy, 2 Gy/fx | NA           | 5-years 87% (stage C) 5-years 92% (stage B) | NA          |
| Abe [59]        | 21     | Stage B2-days               | Perineal                   | 28-35 Gy or 20–25 Gy (if combined with EBRT) | IORT      | 50 Gy         | 5-years 72% | GU: 100% early ematuria 10% early pollakiuria |
| Kojima [60]     | 30     | Stage B-C                   | Perineal/retropubic        | –               | IORT      | NA            | 5-years 43% | NA             | NA          |
| Takahashi [61]  | 14     | Stage B2-days               | Perineal                   | 28-35 Gy or 20–25 Gy (if combined with EBRT) | IORT      | 50 Gy         | NA           | NA             | 0%          |

pts patients, GU genito-urinary, GI gastro-intestinal, BRFS biochemical relapse-free survival, NA not available

*National Comprehensive Cancer Network (NCCN) guidelines NCCN [6]

*Whitemore-Jewett staging system [Whitmore 1956, Jewett 1975]*
useful to avoid normal tissues not at risk of microscopic disease. For gynaecological and genito-urinary cancers, IORT is not a standard treatment but it may be considered a treatment option in selected patients.

In endometrial, cervical and renal cancers, IORT can be used mainly in recurrent disease, whereas in bladder carcinoma it may be part of an organ-sparing treatment approach aiming at patient quality of life preservation. In the case of prostate cancer, IORT can be used in locally advanced high risk disease possibly combined with EBRT to intensify the radiation dose in the attempt to improve long term local control and possibly increase biochemical disease-free and overall survival.

The available literature data are interesting but the present review shows that the majority of published clinical studies are mono-institutional, retrospective and often included a limited number of patients. In order to overcome these limitations, large multicentre collaborations should be established to design prospective clinical trials aiming at better defining the role of IORT in tailored multimodality therapeutic approaches for gynaecological and genito-urinary tumours. For this purpose, the ISIORT could serve as a basis for future collaboration and the ISIORT-Registry could be a platform for sharing data and promote clinical research.

Abbreviations
CTV: Clinical target volume; EBRT: External beam radiotherapy; IOHDR: Intra-Operative high dose rate; IORT: Intraoperative radiotherapy; ISIORT: International society of intraoperative radiation therapy; RT: Radiotherapy

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Authors’ contributions
MK developed the design of the review and contributed to draft and revise the manuscript. CP and LD performed the literature search and analysis, and contributed to draft the manuscript. DS, AV, NS and CT contributed to the study design and to revise critically the manuscript. All the authors read and approved the final version of the manuscript.

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References
1. Comes C, Pito A. Irradiation movente preventiva intrabdominale, après l’intervention chirurgicale dans un cas de cancer de l’utérus. In: Presented at the Congres International d’Electrologie. Barcelona: Imprenta Francesca Badia; 1906.
2. Krengli M, Calvo FA, Sedlmayer F, Sole CV, Faster G, Alessandro M, et al. Clinical and technical characteristics of intraoperative radiotherapy. Analisis of ISIORT-Europe database. Strahlenther Onkol. 2013;189:739–77.
3. Krengli M, Sedlmayer F, Calvo FA, Sperk E, Piscini C, Sole CV, et al. IORT pooled analysis 2013 update: clinical and technical characteristics of intraoperative radiotherapy. Radiat Cancer Res. 2014;3:48–58.
4. Haddock MG, Martinez-Monge R, Petersen IA, Wilson TO. Locally advanced primary and recurrent gynecological malignancies: EBRT with or without IORT or HDR-IORT. In: Gunderson LL, Willett CG, Calvo FA, Harrison LB, editors. Intraoperative irradiation. Techniques and results. 2nd ed. New York: Humana Press; Springer; 2011.
5. Backes FJ, Martin OD. Intraoperative radiation therapy (IORT) for gynecologic malignancies. Gynecol Oncol. 2015;138:449–56.
6. National Comprehensive Cancer Network (NCCN), Clinical Practice Guidelines in Oncology, Uterine and Cervical Cancer, Version 2.2015.
7. Sole CV, Calvo FA, Lozano MA, Gonzalez-Bayon L, Gonzalez-Sansegundo C, Alvarez A, et al. External-beam radiation therapy after surgical resection and intraoperative electron-beam radiation therapy for oligorecurrent gynecological cancer. Long-term outcome. Strahlenther Onkol. 2014;190:71–80.
8. Foley OW, Ruhl-Hain JA, Clark RM, Goodman A, Growdon WB, Boruta DM, Schorge JO, Del Carmen MG. Intraoperative Radiation Therapy in the Management of Gynecologic Malignancies. Am J Clin Oncol. 2016;39:329–34.
9. Backes FJ, Billingsley CC, Martin DD, Tierney BJ, Eisenhauer EL, Cohn DE, et al. Does intra-operative radiation at the time of pelvic exenteration improve survival for patients with recurrent, previously irradiated cervical, vaginal, or vulvar cancer? Gynecol Oncol. 2014;135:95–9.
10. Barney BM, Petersen IA, Dowdy SC, Bakkum-Gamez JN, Klein KA, Haddock MG. Intraoperative electron beam radiotherapy (IORT) in the management of locally advanced or recurrent cervical cancer. Radiat Oncol. 2013;8:80.
11. Calvo FA, Sole CV, Lozano MA, Gonzalez-Bayon L, Gonzalez-Sansegundo C, Alvarez A, et al. Intraoperative electron beam radiotherapy and extended surgical resection for gynecological pelvic recurrent malignancies with and without external beam radiation therapy: long-term outcomes. Gynecol Oncol. 2013;130:537–44.
12. Giordi G, Boz G, Gadducci A, Lucia E, De Piero G, De Paoli A, et al. Multimodality approach in extra cervical locally advanced cervical cancer: chemoradiation, surgery and intra-operative radiation therapy. A phase II trial, Eur J Surg Oncol. 2011;37:1442–7.
13. Tran PT, Su Z, Hara W, Husain A, Teng N, Kapp DS. Long-Term Survivors Using Intraoperative Radiotherapy For recurrent Gynecologic Malignancies. Int J Radiat Oncol Biol Phys. 2007;69:504–11.
14. Dowdy SC, Mariani A, Ciliby WA, Haddock MG, Petersen IA, Sim FH, et al. Radical pelvic resection and intraoperative radiation therapy for recurrent endometrial cancer: technique and analysis of outcomes. Gynecol Oncol. 2006;101:260–6.
15. Avtrey CS, Cadungog MG, Leitao MM, Alektiar KM, Aghajanian C, Hummer AJ, et al. Surgical resection of recurrent endometrial carcinoma. Gynecol Oncol. 2006;102:480–88.
16. Martinez-Monge R, Jurado M, Aristu JJ, Moreno M, Cambeiro M, Perez-Ochoa A, et al. Intraoperative electron beam radiotherapy during radical surgery for locally advanced and recurrent cervical cancer. Gynecol Oncol. 2001;82:538–43.
17. Gemignani ML, Alektiar KM, Leitao M, Mychalczak B, Chi D, Venkatraman E, et al. Radical surgical resection and high-dose intraoperative radiation therapy (HDR-IORT) in patients with recurrent gynecologic cancers. Int J Radiat Oncol Biol Phys. 2001;50:687–94.
18. del Carmen MG, McIntyre JF, Fuller AF, Nelku N, Goodman A. Intraoperative Radiation Therapy in the Treatment of PelvicGynecologic Malignancies: A Review of Fifteen Cases. Gynecol Oncol. 2000;79:457–62.
19. Garton GR, Gunderson LL, Webb MJ, Wilson TO, Martenson JA, Cha SS, et al. Intraoperative radiation therapy in gynecologic cancer: update of the experience at a single institution. Int J Radiat Oncol Biol Phys. 1997;37:839–43.
