The Use of Intraoperative Radiation Therapy (IORT) in Multimodality Management of Cancer Patients: a Single Institution Experience

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Abstract
Background Intraoperative radiation therapy (IORT) is a highly conformal type of radiation therapy given at time of surgery aiming for better tumor local control. It increases the tumor radiation dose without exceeding normal tissues tolerance doses.
Purpose To assess the feasibility of IORT and short-term toxicities in patients with different cancer sites treated with multidisciplinary protocol including IORT.
Patients and Methods Medical records of cancer patients who received IORT as a part of their multidisciplinary treatment at King Faisal Specialized Hospital and Research center (KFSH&RC), Riyadh, Saudi Arabia, from January 2013 until December 2017 were retrospectively reviewed.
Results A total of 188 patients with 210 IORT applications were analyzed. Twenty-two patients had two applications at the same time. One hundred sixteen patients were males. Median age at time of diagnosis was 49.5 years (19–77). One hundred thirty-four patients had primary, while 54 cases had recurrent disease. Gastroesophageal cancer and soft tissue sarcoma were the most frequent diagnosis in 49 patients followed by colorectal cancer in 35 patients. Major surgeries with curative intent done in 183 patients (97.3%). Hyperthermic intraperitoneal chemotherapy (HIPEC) was performed in 118 (62.8%) patients. The 30-day postoperative mortality rate was 3.2%. Fifty-four (28.7%) patients develop grades III–IV complications according to Clavien-Dindo grading system.
Conclusion The data presented discusses using of IORT treatment for different malignant tumors as a part of multimodality treatment. IORT seems safe and feasible; however, a longer follow-up period is needed for proper evaluation and to define the role of IORT in a tailored multimodality approach.

Keywords IORT · Multimodality · Management · Cancer

Introduction

Intraoperative irradiation (IORT) is a highly conformal modality of radiation therapy allowing delivery of radiation at time of surgery. It aims to increase the tumor radiation dose to improve tumor local control rate with respect of surrounding normal tissues tolerance doses [1].

The use of IORT for different cancer types early started about 100 years ago [2]. The benefit of using IORT in addition to external beam radiation therapy (EBRT) in many cancer sites comes from improving the therapeutic ratio by decreasing the radiation “boost” volume by direct tumor/tumor bed visualization, in contrast to the traditional large EBRT fields which encompass the primary tumor and surrounding normal structures for potential microscopic disease...
allowing for more conformal treatment. In addition, IORT decreases the dose to surrounding risk structures by removal of part or all of it by mobilization, shielding or changing beam energy [3, 4].

In our study, we retrospectively evaluate the feasibility, indications, technical aspects, and short-term complications rate for patients treated with IORT in our Center King Faisal Specialized Hospital and Research center (KFSH&RC) as a part of multimodality management for different tumor sites.

**Patients and Methods**

The medical records of patients received IORT as part of their multidisciplinary treatment in our institution KFSH&RC from January 2013 until December 2017 were retrospectively evaluated with particular focus on the technical aspects of IORT treatments. Figure 1 represents the number of patients included in the study each year.

The data collected includes age, sex, cancer site, histopathology, surgical procedure done and its aim (curative or palliative), hyperthermic intraperitoneal chemotherapy (HIPEC) is used or not. IORT details includes (dose, energy, applicator diameter, beam angle, total treatment depth and bolus is used or not).

IORT is used in our center in addition to surgery in management of patients with different cancer sites with the following inclusion criteria: (1) age below 75 years, (2) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, (3) adequate hematological, liver and renal functions, (4) histopathological evidence of malignancy, (5) no evidence of distant metastasis, and (6) signed written informed consent by patients. HIPEC is added only if there is a radiological or pathological evidence of peritoneal involvement.

Major surgical procedures with curative intent were done for majority of patients; immediately at the end surgical procedure, IORT is used using Mobetron®. The delivered IORT dose varies depending on multi factors such as: the margin status (R), distance from nearby risk structures, and dose of previous radiation therapy if any. A dose of 10–15 Gy was used for those patients with R0 resection, while a dose of 15–20 Gy was used for those with R1 resection.

The IORT dose is usually calculated at the iso dose that covers the tumor properly. Electron energies ranged from 6 to 12 MeV. The choice of electron beam energy depends primarily on the target depth. A bolus is used in many cases to increase the surface dose and decrease dose to underlying structures. Figure 2 shows iso dose curves comparison between lower and higher electron beam energies with the effect of using bolus. The choice of applicator diameter usually depends on the size of treatment area taking in consideration preoperative tumor volume [5–7].

In cases with confirmed involvement of peritoneal surface, HIPEC technique was performed after finishing IORT procedure; the operative and HIPEC technique details were published earlier in our previous study [8]. The choice of HIPEC therapeutic agent is a case dependent based on a multidisciplinary discussion.

The 30-day postoperative complications rates were evaluated according to the Clavien-Dindo grading system [9].

**Statistical Analysis**

This is a retrospective descriptive study that focuses on the technical details of IORT technique. Descriptive statistics were performed for all available categorical variables expressed in either median with range or numbers. The primary endpoint was 30 days postoperative mortality and morbidity rate.
Results

Medical records of 188 patients with total 210 IORT applications were reviewed; 22 patients had two applications at the same setting. One hundred sixteen patients were male. Median age at diagnosis was 49.5 years (range 19–77). Patients characteristics and detailed cancer-type distribution is listed in Table 1 and Fig. 3.

At the time of surgery and IORT, 134 patients had primary, while 54 cases had recurrent disease (Table 2).

All clinical and technical aspects of IORT treatments (including energy used, doses and applicator diameter) are illustrated in Figs. 4, 5, 6.

Major surgical resections with curative intent were done in 183 patients (97.3%); HIPEC in addition to IORT was performed in 118 patients (62.8%) (Table 2).

Table 1  patients’ characteristics

| Median age at diagnosis | Number of patients |
|-------------------------|--------------------|
| 49.5 (19–77)            | 188                |

Gender

| Cancer type distribution | Number of patients |
|--------------------------|--------------------|
| Males                    | 116                |
| Females                  | 72                 |
| Gastroesophageal cancer  | 49                 |
| Colorectal cancer        | 35                 |
| Soft tissue sarcoma      | 49                 |
| Gynecological malignancy | 16                 |
| Genito urinary cancer    | 6                  |
| Pancreatic cancer        | 9                  |
| Gall bladder/cholangiocarcinoma | 9      |
| Others                   | 15                 |
Table 2  Clinical and therapeutic correlations of surgery performed and technical IORT characteristics according to cancer site

| Tumor site | Gastro-esophageal | colorectal | Soft tissue sarcoma | Gynecological malignancy | Genito-urinary cancer | Pancreatic cancer | Gall bladder cancer/cholangiocarcinoma | Others | All |
|------------|-------------------|------------|--------------------|--------------------------|-----------------------|------------------|--------------------------------------|--------|-----|
| Disease status | Primary | 49 | 22 | 28 | 7 | 4 | 9 | 4 | 11 | 134 |
| | Recurrent | 0 | 13 | 21 | 9 | 2 | 0 | 5 | 4 | 54 |
| Aim of treatment | Curative | 48 | 34 | 48 | 16 | 6 | 9 | 9 | 13 | 183 |
| | Palliative | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 2 | 5 |
| No of HIPEC cases | Single field | 40 | 25 | 23 | 15 | 2 | 3 | 8 | 2 | 118 |
| | Two fields | 1 | 6 | 9 | 2 | 0 | 1 | 2 | 1 | 22 |

Fig. 4  IORT applicator diameters used in different cancer sites

![Fig. 4 IORT applicator diameters used in different cancer sites](image)

Fig. 5  IORT electron beam energy used for each cancer site

![Fig. 5 IORT electron beam energy used for each cancer site](image)
The 30-day postoperative mortality rate was 3.2%, and 54 (28.7%) patients develop grade III–IV complications according to Clavien-Dindo grading system. Tables 3 and 4 showed the incidence of different complications grades for each cancer site and management done for each type of complications.

**Table 3** Postoperative complication grades according to Clavien-Dindo (CD) grading system for different cancer sites

| Treatment site                  | Grade I | Grade II | Grade IIIa | Grade IIIb | Grade IVa | Grade IVb | Grade V |
|---------------------------------|---------|----------|------------|------------|-----------|-----------|---------|
| Gastroesophageal cancer         | 32      | 7        | 3          | 3          | 4         |           |         |
| Colorectal cancer               | 1       | 19       | 10         | 4          | 1         |           |         |
| Sarcoma                         | 1       | 30       | 6          | 7          | 1         | 2         | 2       |
| Gynecological malignancy        | 9       | 3        | 4          |            |           |           |         |
| Pancreatic cancer               | 6       | 1        | 2          |            |           |           |         |
| Others                          | 7       | 8        |            |            |           |           |         |
| Total                           | 9       | 104      | 27         | 20         | 5         | 2         | 6       |

**Table 4** management done for patients with CD grades III and IV

| CD grade | Type of complications | No. patients | Management | Outcome   |
|----------|-----------------------|--------------|------------|-----------|
| IIIa     | Abdominal collection  | 17           | US or CT guided drainage | Recovered |
|          | Pleural effusion      | 8            | Thoracocentesis | Recovered |
|          | Obstructive uropathy  | 2            | Nephrostomy tube insertion | Recovered |
| IIIb     | Bowel leakage         | 7            | Exploration | Recovered |
|          | Intra-abdominal bleeding | 3       | Exploration with hematoma Evacuation | Recovered |
|          | Wound infection       | 4            | Debridement and flap | Recovered |
|          | Lymphatic leakage     | 3            | Exploration | Recovered |
|          | DVT                   | 2            | Venous thrombectomy | Recovered |
|          | DVT/PE                | 1            | IVC filter | Recovered |
| IVa      | Respiratory failure   | 2            | ICU admission | Died     |
|          | Disturbed conscious level | 2       | ICU admission | Died     |
|          | Massive PE            | 1            | ICU admission | Died     |
| IVb      | Multi organ failure   | 2            | ICU admission | Died     |

**Discussion**

The use of external beam radiation therapy (EBRT) in a fractionated manner provides a biological advantage over the single large IORT dose; that advantage is well explained by the “4Rs” of classical radiobiology (normal
tissue repair, tumor reoxygenation, tumor redistribution, and normal tissue repopulation). The large doses per fraction in case of IORT may result in increased risk of late effects probably due to small blood vessel injury, so careful planning and administration of IORT should be applied with limiting the radiation dose to non-target tissues by its exclusion from the radiation field whether by direct inspection, mobilization, or shielding [10].

By reviewing our data, it is appeared that the intent of treatment is almost curative in most of cases. One hundred two (54.2%) patients had GIT cancers, 49 (26%) had gastric/esophageal, 35 (18.6%) had colorectal, 9 (4.8%) had gall bladder/cholangiocarcinoma, and 9 (4.8%) had pancreatic cancer. Major surgical resections with curative intent were performed in nearly all patients (except for two patients; 1 gastric/esophageal and 1 colorectal).

The philosophy of using IORT in rectal cancer is to improve tumor local control especially in patients with T4b disease, where pelvic recurrences is high. Multiple studies have addressed the value of using IORT in rectal cancer management [11–15]. A meta-analysis had reviewed studies focusing on benefits of using IORT in rectal cancer. It concludes an improvement in local control (LC), disease-free survival (DFS), and overall survival (OS) [16]; however, the only randomized trial done failed to show an advantage for IORT use; in this trial, 142 patients diagnosed with rectal cancer were included and randomly assigned into 2 groups after receiving preoperative EBRT (40 Gy) (one group underwent surgery alone, while the other one received IORT 18 Gy at the time of surgery). No difference between the 2 groups regarding the 5 years LC as it was 91.8% in the group received IORT in addition to surgery vs 92.8% in surgery alone group ($p = 0.6018$) [17].

Thirty-five colorectal cancer cases were included in this study (22 patients with primary while 13 with recurrent disease). Majority of them (97%) underwent major surgeries with curative treatment intent (6 patients required two IORT fields). Twenty-five (71.4%) patients had HIPEC (15 patients had primary disease, while 10 had recurrences). Four patients performed multiple surgeries with repeated HIPEC. Regarding postoperative complications grades, 19 (54.2%) patients develop grade II, while 10 (28.5%) patients developed grade IIIa requiring intervention under local anesthesia. No patients in the group underwent cytoreductive surgery alone without HIPEC developed grade IIIb complications in comparison to 4 (11.4%) patients developed grade IIIb complications in group of patient underwent surgery in addition to HIPEC (3 patients had bowel leakage required exploration, and one patient developed wound infection required debridement). Most of these complications could be attributed to the complexity of the surgical procedures and/or HIPEC. These complex cytoreductive surgeries with HIPEC were performed in high percentage of the cases (71.4%) (40% of them was presented with recurrent disease with repeated surgeries and redo HIPEC in 4 (19%) patients. No reported grade IV b or V complications. A previous randomized trial conducted by Vic j. verwaal et al., in which they reported that most of the complications from the complex surgical procedures done and HIPEC were related to bowel leakage [18].

EBRT has an established role for years in the postoperative management of gastric cancer patients with significant improvement of LC, DFS, and OS in comparison to surgery alone [19, 20]. Multiple studies support using IORT as a treatment option in gastric cancer resulting in decrease loco-regional recurrence without increase in the complications incidence; however, it does not improve OS [21–25].

Forty-nine (26%) patients had gastroesophageal cancer which were included in our study. Majority of them (97.9%) underwent major surgeries with curative treatment intent. Forty patients underwent HIPEC. Regarding postoperative complications grades, 65% developed grade II complications with reported 4 patients died postoperatively (all these patients were more than 70 years). This again raise a concern about safety of HIPEC in combination with cytoreductive surgery in these old people; actually, this concern was addressed in many studies; Spiliotis et al. [26] reported doubled mortality rate in those patients older than 70 years than in younger ones (3.3% in the elderly group versus 1.43% in the younger group). Arslan et al. [27] concluded higher incidence of postoperative mortality (12.9%) in those elderly people versus (7.2%) in younger patients.

IORT has been extensively used in patients with soft-tissue sarcoma as a part of multimodality treatment approach especially retroperitoneal site. It takes the advantage of higher radiation dose to the target volume with lower dose to surrounding healthy tissues with encouraging tumor local control rate and survival [28–32].

Forty-nine patients diagnosed with soft tissue sarcomas were included in our study, 22 (42.8%) had recurrent disease, and 30 (61.2%) patients had retroperitoneal site. The aim of the treatment was almost curative with radical resection in majority (98%) of patients. HIPEC performed in 23 patients (47%) with proved peritoneal sarcomatosis. Regarding IORT technical aspects, 23 patients (47%) required 10 cm applicator diameters that could be related to the large tumor extension and large post-resection tumor bed. Moreover, 9 patients required complex irradiations with two IORT fields with high energy electrons up to 12 MeV and doses up to 15 Gy in 20 cases (40.8%).

The role of cytoreductive surgery (with removal of all macroscopic visible disease) in advanced primary epithelial ovarian cancer (EOC) has been established with significant improvement of both DFS and OS [33–35]. However, its role in relapsed epithelial ovarian cancer is still controversial and is not considered the standard of care being not
demonstrated in prospective trials. In retrospective analysis, surgery at first relapse is associated with a better survival only when a complete tumor resection can be obtained [36, 37].

IORT use in gynecological malignancies had been investigated in many series especially in recurrent disease with better loco-regional control rate compared to surgery alone without significant increase in toxicity apart from neuropathy which was more frequent in IORT dose > 20 Gy [38].

The largest series evaluating HIPEC for recurrent EOC include 246 patients (184 with platinum-sensitive recurrent EOC), 92% of whom underwent an optimal cytoreductive surgery. Forty-nine months as an OS was reported in patients underwent HIPEC treatment and 52 months for platinum-sensitive patients. There was a 12% incidence of serious (grade 3/4) complications, including leukopenia (3%), intra-abdominal hemorrhage (2%), and postoperative complications (5%), including one postoperative death due to an anastomotic leak resulting in peritonitis and acute renal failure [39].

Gynecological malignancy was reported in 16 patients in our study (10 patients had ovarian cancer, and 6 patients had uterine sarcoma). Nine (56.2%) patients had recurrent disease. All the patients underwent major surgical procedures aiming for cure. Most of cases (93.7%) had HIPEC with two IORT fields in two cases. Postoperatively, the majority (56%) of cases developed grade II complications, with 4 (25%) patients developed grade IIIb complications rate requiring intervention under general anesthesia.

Pancreatic cancer is considered one of the most aggressive malignancies that had poor outcome; the 5 years OS is less than 5%. Complete surgical resection is feasible only in 20–40% of cases with reported 5-year survival of 30% in those patients with R0 resection. The rationale behind using IORT in pancreatic cancer patients may come from the higher incidence of local recurrence (50% in 5 years) with use of preoperative or postoperative EBRT. IORT could be an interesting therapeutic option for this type of cancer for dose intensification to tumor/tumor bed for better local tumor control especially in locally advanced cases. The benefits of using IORT in selected pancreatic cancer were widely reported in some trials with significant improvement of both local control and survival [40–42].

Nine patients diagnosed with pancreatic cancer were included in our study. All patients had surgery with curative intent. HIPEC performed in 3 (33%) patients with possible carcinomatosis. Two IORT fields applied only in one case. Most of the patients required larger applicator diameter (≥7.5 cm), probably due to the large surgical field with high incidence of lymph node metastasis. Two-thirds of cases developed grade II complications, with only 2 (22.2%) developed grade IIIb complications (bowel leakage) requiring intervention under general anesthesia.

The main limitations of our study are as follows: population heterogeneity with different treatment sites. The retrospective design and all its well known drawbacks.

Conclusion

The data presented discusses using of IORT treatment for different malignant tumors as a part of multimodality treatment. IORT seems safe and feasible; however, a longer follow-up period is needed for proper evaluation and to define the role of IORT in a tailored multimodality approach.

Author Contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Ahmed Elashwah, Ali Alzahrani, and Mohammad Breakeit. Surgical management and postoperative follow-up were done by Tarek Mahmoud Amin and Ayman Zaki Azzam. The radiation therapy indications and all IORT parameters chosen for every patient were done by Abdullah Alsuhaibani, Rana Mahmood, and Ahmed Elashwah. The medical physics work were done by Belal Moffat, Muhammad Hussain, Shada ALramahi, and Zeinab Hassan. The first draft of the manuscript was written by Ahmed Elashwah, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability All data are available with the corresponding author and can be provided upon request.

Declarations

Ethics Approval This research has been approved by the Research Advisory Council (RAC) at the King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia (RAC Project # 2161 246).

Conflict of Interest The authors declare no competing interests.

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