Perspectives in intraoperative radiotherapy: improving precision tolerance and intensity in cancer treatment

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Rationale and Indications

Intraoperative radiotherapy (IORT) is a cancer treatment technique that is defined as the delivery of a large single fraction of irradiation (in the range of 10 to 25 Gy), using high energy electron beams, at the time of surgical exploration and/or tumor resection. Radiation therapy is then delivered in a surgically defined area, while mobile and involved tissues are protected by mechanical retraction from the radiation beam. IORT is used in most modern protocol studies as the boost radiation component of multidiciplinary treatment approaches, including best surgical and external beam radiotherapy management (1).

IORT is indicated in the treatment of patients in which the tumor is considered unresectable, resected but with proven residual malignant disease, or as an adjuvant for high risk for local recurrence situations, in which it is known that a frequent component of disease progression after surgery is within loco-regional structures (2).

Loco-regional tumor control promotion is the final goal of IORT. The contribution of this treatment modality in clinical oncology is to achieve high local control rates in combined modality treatment. Local tumor relapse is a catastrophic event in human oncology, associated to slow but progressive symptomatology, requiring major medical support and rarely curable if treated for rescue.

IORT is a safe and excellent quality radiation boost in contemporay multidisciplinary oncology. It is indicated in tumor sites and stages in which alternative techniques to boost the residual tumor or high risk area for recurrence, are more hazardous or less appropriate. IORT is considered a priority developmental program in institutions particularly devoted to cancer treatment, in which among other interests, clinical achievements are an important part of the cancer research efforts (3).

History and evolution

The delivery of radiation during a surgical procedure was described just a few years after the discovery of the x-rays. In 1909, Beck published the first clinical experiences using IORT in patients with gastric and colon cancer, in which he pulled the tumors into the abdominal wounds in order to irradiate them directly (4).

Occasional reports are found in the scientific literature in the following decades, but they are selective work pieces of miscellaneous tumor sites and treat-

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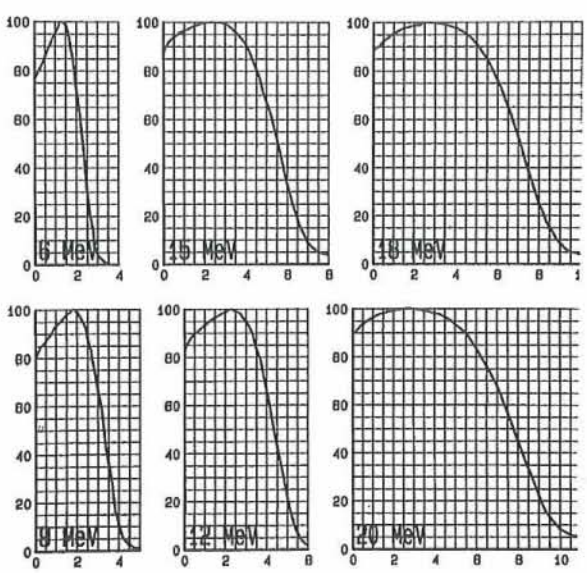
ment programs, that belong to the pre high-energy electron beam era (5). The attraction for IORT-like experiences was discontinued during the years in which refinement in high energy photon technology applied to cancer treatment achieved the maximum development.

In the late 60's, Professor Abe in Japan contributes to the evolution of IORT by incorporating the use of high energy electrons as the optimal radiation beam to be employed in IORT. (Figure 1). The technique was explored in conjunction with surgery in tumors of multiple sites and histological subtypes. Large single doses, in the range of 26 to 40 Gy were given as the sole radiation therapy component of the combined treatment. Gastric cancer was identified as a tumor site that might benefit from the use of IORT following gastrectomy in the experience of Kyoto University in which a control surgical arm was available. This group is the first reporting long term surviving patients with proven microscopic residual disease after surgery (6, 7).

Figure 1



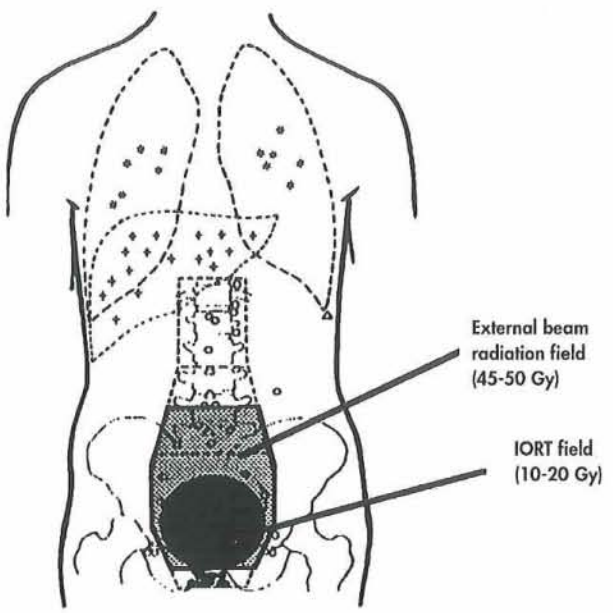
Depth dose curves for electron beams of 6, 9, 12, 15, 18 and 20 MeV, using a custom design IORT cone of 8 cm in diameter and at a source tumor distance of 116 cm. Notice the final fall off in the dose deposit of this radiation type.

In the late 70's and 80's the western clinical experience was developed, bringing to IORT several aspects of major importance such as: animal research that has investigated extensively normal tissue tolerance to IORT alone is integrated in multidisciplinary treatment protocols as a quality radiation boost, not compromising the conventional combined management with surgery and external beam radiotherapy (9) (Figure 2); IORT is studied in carefully designed Phase I-II trials in single institution and cooperative group protocols, generating information of excellent quality on feasibility (10); human normal tissue tolerance (11) and local control rates (12). Expert groups in the US have investigated IORT in intra-abdominal tumors in which the therapeutic index is easily improved by protecting most normal tissues from the IORT component of the treatment (13). European investigators have expanded the use of IORT to other sites of the anatomy, like intrathoracic and extremity locations (14, 15, 16).

Improved treatment precision

Despite the advances in diagnostic imaging, and the ability to integrate them in expert systems for radiation therapy treatment planning (17), the optimal way to

Figure 2



Idealized integration of external beam irradiation fields with and IORT boost in the high risk area of resected rectal cancer.

identify areas of unresected tumor, resected but residual or high risk for recurrent area, is determined at the time of surgical exploration. In certain anatomical areas, such as the posterior spaces of the large cavities (thorax, upper abdomen and pelvis), no alternative technique can compete with an IORT electron boost in the definition of the treatment zone and the homogeneity of the radiation dose deposit. Electron beams, depending upon the energy, can accurately deposit the prescribed dose in different tissue thickness, determined in each individual case as required following surgical manipulation (Figures 3A, B).

IORT brings to radiation therapy strategies a highly desired treatment component: a precise and accurate boost, that will decrease the incidence of marginal tumor recurrences. The local control rates reported in IORT trials have consistantly been high, confirming the concept that precision is an immediate benefit from the incorporation of IORT in cancer treatment (1).

Improved treatment tolerance

The tolerance of normal tissues limits the ability of physicians to cure cancer patients in modern multidisciplinary oncology. Major efforts are dedicated to improve tolerance of normal tissues and to decrease toxicity and complications related to cancer treatment. When external beam radiation therapy is a component of treatment trials, the dose-limiting structures and organs have compromised for decades the treatment strategies designed and results obtained in tumor sites located in human anatomical zones containing sensitive tissues (upper abdomen, pelvis, etc...).

IORT can deliver a component of the planned radiation therapy program, while protecting normal sensitive structures in critical anatomic zones (small bowel, large bowel, ureters, bladder, etc...), which will allow to decrease a certain degree the external beam irradiation total dose. A prospective randomized trial performed at the National Cancer Institute (NCI) in patients with retroperitoneal sarcomas, in which large abdominal areas were treated by combination of high dose external beam radiotherapy (split-course) and surgery, versus intermediate doses of external irradiation, surgery and IORT boost to the tumor bed area, showed a statistical significant difference in decreased toxicity rate (enteritis) among patients treated with IORT. Infield local control rate was superior in IORT patients. This is the confirmatory trial that has established the firm benefit of IORT in terms of treatment tolerance improvement in aggresive combined approach of tumors located in «dose-limited» anatomical areas (18).

Improved treatment intensity

Results in clinical oncology with classic cancer treatment modalities (surgery, radiotherapy and chemotherapy) will improve with our ability to increase treatment intensity. Many modern treatment developments have been searched with the urgency of using «old» (but well known) therapy tools in an innovative way to increase antitumor efficacy. Large surgical resections

Figure 3A

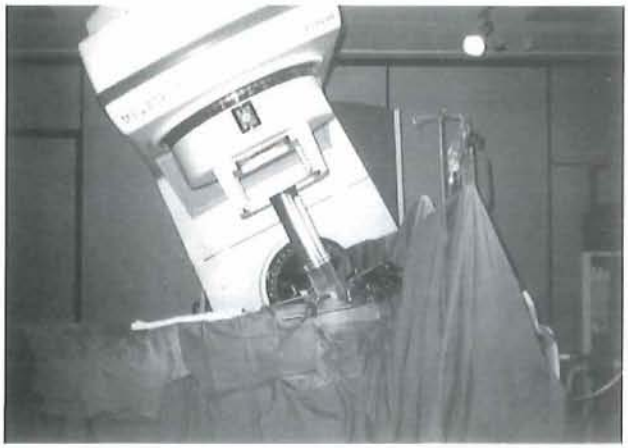
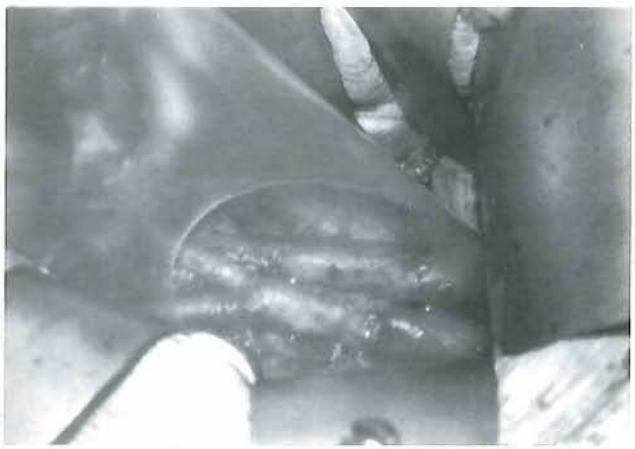


Figure 3B



A. View of cone positioning in the abdominal area. Notice the extensive use of surgical retractors.
B. Detail image of the anatomic area treated with IORT. The para-aortic space is directly exposed to the electron beam while the retractors have mobilized all the small bowel and other structures out of the field.

with functional reconstruction (19), high dose chemotherapy with marrow of peripheral stem cell support (20), intra-arterial drug delivery (21), simultaneous chemo-radiation (22), IORT and other sophisticated radiation boost systems (brachytherapy and stereotactic radiosurgery) (23, 24), are examples of increasing treatment intensity strategies with recently reported encouraging results.

While waiting for the arrival of the important achievements of immunology and molecular biology into clinical applications, groups devoted to cancer treatment and care have the committment to refine techniques using the available means to improve results. In this context, any radiation therapy treatment component that can include an IORT boost will be the most intense alternative possible in many areas of human anatomy.

Present clinical results

(Table I)

The data that supports the expansion of this technique at an institutional level, and its indications within malignant diseases and tumor sites, is frequently updated. A brief reference will be made to the most consolidated clinical experiences in the late eighties. In the US the National Cancer Institute completed three Phase III trials in unresectable and resectable pancreatic cancer (25, 26) and retroperitoneal sarcomas (18). The three trials have in common to compare surgery plus external irradiation (and 5-Flurouracil in the pancreas trials) with or without an IORT boost to the tumor or tumor bed area. The results described evidences of local tumor control promotion in the three trials, but with no differences in overall survival. A fourth Phase III trial designed for gastric cancer failed to be completed (27). Recent reports have analyzed the Mayo Clinic and Massachussets General Hospital experience in unresected pancreatic and primary or recurrent colorectal cancer. Treatment strategies and results have been very similar in both institutions. Median survival time for patients with unresectable pancreatic cancer have been in the range of 9 to 12 months, with unusual survivors of more than 3 years (28, 29). These results have been confirmed in a Phase I-II trial performed in a cooperative group frame (RTOG) concluding that IORT is a feasible, safe and quality radiation boost for the management of unresectable pancreatic cancer (30). Recurrent colorectal cancer is in most cases an incurable clinical event. IORT has been used in the rescue treatment of these patients and the data from expert groups has consistantly shown high pelvic control rates (in the range of 60 to 70%), median survival time of 20 months (twice the value observed in surgical series) and long term survivors (unusual finding in surgical series) (31, 32). Although modest, these results clearly improved previous data using surgery alone or combined with conventional external beam radiotherapy, but more importantly they show excellent figures in local control and survival in selected patients amenable for good surgical resection. In locally advanced primary colorectal cancer the results are difficult to overcome regarding loco-regional disease control. No recurrences have been reported in the IORT zone, and although survival is still modulated by tumor stage, it is expected that a frequent component of failure (pelvic) will no longer contribute to disease progression, which might impact in long term survival rates (33, 34). A Phase III trial has been activated in Radiation Therapy Oncology Group, in an effort to address the value of IORT in both primary and recurrent colorectal cancer (35).

In gastric cancer, the most recent update from the original japanese experience at Kyoto University is still showing differences in favor of combination of surgery and IORT compared to surgery alone in Stages II, III and IV (36). The analysis of the Phase I-II trial performed at the University Clinic of Navarra, combining gastrectomy plus an IORT moderate boost dose (15 Gy) and upper abdominal nodal and gastric bed irradiation (46 Gy), has shown absence of loco-regional recurrences in primary treated patients (37).

Results in other tumor sites, such as extremity bone and soft sarcome (38, 39) have shown high local control rates (including large lesions and proven residual tumor), when used in conjunction with extremity preservation surgical technique. Mature results in retroperitoneal sarcomas are available (40).

Some pilot studies have explored feasibility, tissue tolerance, and local control rates in lung (41) and head and neck (42) cancer, and miscellaneous disease site indications (43, 44, 45). The clinical data generated in these studies suggest high local control rates (in general related to tumor burden and treatment intensity), but acceptable technical feasibility and tissue tolerance. Peripheral nerves have proven to be dose-limiting structures in clinical trials for the combination of IORT boost and external beam irradiation, and particular caution has to be undertaken to the dose selection process if nerves ought to be included in the IORT field (46, 47).

Table I

LOCAL CONTROL AND SURVIVAL IN RECENT IORT REPORTS

AUTHOR (REF.)	TUMOR SITE	LOCAL CONTROL RELAPSES/TOTAL	SURVIVAL AND COMMENTS (YEARS, FOLLOW-UP)		
Sindelar (25)	pancreas	1/16	0%	(2)	Phase III. Resected
Sindelar (25)	pancreas	?/16	0%	(2)	Phase III. Unresected
Gunderson (28)	pancreas	3/42	8%	(2)	Unresected Disease
Tepper (30)	pancreas	?/51	9%	(2)	RTOG Phase I-II
Willett (31)	colorectal	11/30	19%	(5)	Recurrent Disease
Willett (31)	colorectal	8/42	43%	(5)	Primary Disease
Gunderson (34)	colorectal	9/51	42%	(5)	Primary & Recurrent
Calvo (37)	gastric	5/48	39%	(5)	Primary & Recurrent
Calvo (38)	sarcomas	2/38	69%	(5)	Ewing & Osteosarcoma
Gemer (39)	sarcomas	5/28	–		Extremity Lesions
Willett (40)	sarcomas	3/12	64%	(4)	Sensory Neuropathy
Kinsella (18)	sarcomas	3/15	50%	(5)	Phase III. Enteritis
Juetter (41)	lung	1/21	–		90% Responders
Rate (42)	head & neck	20/47	61%	(2)	Recurrent Disease
Calvo (43)	miscellaneus	1/25	45%	(5)	Upper Abdomen

Future developments and research

The future of IORT depends closely upon the acceptance of the technique by surgeons and radiation oncologists. Successfull programs would be based on an excellent coordination between both specialties, including an adequate space design that will facilitate the consolidation of the program. Dedicated linear accelerators, or surgical rooms close by the radiation treatment area, are the most convenient arrangements to asure adequate patient accrual for this program. Patient selection process for IORT trials has become important, due to the fact that IORT is able to promote high local control figures in disease situations in which the risk zone is easily encompassed by a reasonable size IORT treatment cone and most normal tissues can be protected rom the radiation beam. In the long term, primary tumors of intermediate stage, are the most likely situations in which survival benefits can be expected from promoting high local control rates.

Recurrent disease, unresectable tumors and/or macroscopic malignant residue, are situations that require further research. The use of radiation modulators, such as compounds with sensitizing properties (48, 49) and hyperthermia (50) have been tested in conjunction with IORT, in an effort to improve local control rates.

IORT is a technique that will benefit many cancer patients. The development and consolidation of an active IORT program challenges the «team work» capacity of any institution (51). In any expert group involved in IORT the effort has proven to be worth for the good of the patients and for the quality of Oncology.

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