REVIEW

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Prospects and Disadvantages of Intraoperative Radiotherapy: A Systematic Review

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Abstract

Objectives: The primary objective of this systematic review was to evaluate the efficacy, safety, and limitations of intraoperative radiotherapy (IORT) across different cancer types, with a focus on breast and head and neck cancers. The aim was to compare IORT with other radiotherapy techniques and assess its benefits and drawbacks in oncological settings. **Methods:** Eligibility criteria included clinical trials, meta-analyses, and systematic reviews involving at least 15 participants, focusing on the efficacy and safety of IORT in comparison to other radiotherapy methods. The literature search was conducted in Web of Science, Scopus, and PubMed databases using predefined keywords. A total of 60 studies were initially identified, with 44 meeting the inclusion criteria. The risk of bias was assessed using standardized tools, including the Cochrane Risk of Bias Tool for randomized studies. A qualitative synthesis was performed, integrating data on local control (LC), overall survival (OS), recurrence rates, and treatment-related complications. **Results:** Of the 60 studies identified, 46 were included in the final analysis. These studies focused on various cancers, with a particular emphasis on breast cancer and head and neck cancer. The synthesis revealed that IORT offers several benefits, such as reduced treatment time and better local control in specific patient populations. However, there were inconsistencies in outcomes depending on the radiation technique used, and long-term follow-up data were often lacking. **Conclusion:** The evidence is limited by study heterogeneity, potential bias, and the absence of long-term data in some cases. While IORT demonstrates promising results, particularly in terms of reducing treatment duration and preserving healthy tissue, further high-quality studies are needed to strengthen the evidence base and clarify the long-term outcomes of IORT in different oncological settings.

Keywords: Radiation- surgery- breast cancer- radiation exposure during surgery- lumpectomy

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Introduction

Intraoperative radiation therapy (IORT) is a new treatment method in the medical field that is a type of targeted radiation that is used to target a tumour after surgical treatment. IORT is good in that it can deliver a high dose of radiation directly to the tumour site in any part of the body, whether it is breast, skin, spine, brain, or other organ cancer [1]. The method of intraoperative radiotherapy is useful because when used, it reduces the risk of local recurrence and then increases the possibility of tumour metastasis. Furthermore, healthy tissues do not receive large doses of radiation due to the fact that the doctor directs the radiation beam to a specific and necessary tissue [2]. According to Lalchandani et al. [3], it is known that only about 20% of men with oncology undergo intraoperative therapy, the rest were women with the age of 60 years and more. The use of IORT is convenient in many cases, such as colorectal cancer or rectal cancer. Also, intraoperative radiotherapy in association with chemotherapy and external beam radiation therapy significantly improves the outcome and increases the chances of survival and even leads to significantly more control of the disease. In addition, IORT also controls the disease course well in soft tissue sarcoma and especially in breast cancer [4]. Numerous works on radiation therapy show sufficient safety and efficacy in the treatment of breast cancer. According to the results of the TARGeted Intraoperative RadioTherapy (TARGIT-A) study from 2020, IORT has been used much more frequently in the last 20 years for early-stage breast cancer [5].

Several techniques that are at the forefront of radiation therapy are intensity-modulated radiation therapy (IMRT), image guided radiation therapy (IGRT), magnetic resonance (MR) radiation therapy and particle therapy. According to Boldrini et al. [6], these techniques improve the outcome of patients over 45 years old with breast and pancreatic cancer. But they also have some limitations, such as inoperable or borderline resectable cancers. Today, one of the more popular IORT techniques is intraoperative electron beam radiotherapy [7]. Kaiser et al. [8] said

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that in IORT, treatment is carried out by electron beams that are produced with different ranges with the help of mobile accelerators. In addition, electron therapy allows correcting the treatment result due to the possible detection of tumour extent.

Intraoperative radiotherapy has many promising aspects. Firstly, IORT uses the administration of a single fraction of radiation, so that no interfractional changes occur, which greatly simplifies the whole process [9]. Secondly, radiation therapy during surgery bridges the gap between surgery and intrinsic radiation therapy. Moreover, IORT reduces toxicity on the body systems, which will eliminate side effects after radiation. Also, the use of applicator, in order to protect normal tissues from unnecessary radiation dose [10]. Furthermore, the time needed for treatment during IORT is much shorter than other external beam techniques [11]. Asha et al. [12] also noted in their work that intraoperative radiation therapy controls the efficacy depending on the radiation dose, reduces the risk of local adverse effects in inoperable tumours, in addition, the risk of cancer recurrence is reduced.

In general, IORT is a safe method of treatment in combination with surgery. Prospects and advantages are the reduction of treatment time, improved quality of life, rapid resumption of daily activities, no data on acute or chronic toxicity of radiation therapy. But at the same moment, Berger et al. [13] pointed out that it is necessary to understand and study the negative side effects, which unfortunately is not popular enough at the moment. Tuschy et al. [14] showed in their study on 208 patients that the frequent side effects were suppuration, palpable seroma, grade 1-2 erythema and mastitis. Repeat surgical wound revision was necessary in only 1.4% of cases. But it seems that IORT can still lead to serious local complications that only additional surgical intervention can eliminate. Tang et al. [15] pointed out that more study of intraoperative radiotherapy is needed in order to understand the proper dosing and to study all possible side effects.

This study aims to systematize information about IORT for future work and the use of intraoperative radiotherapy in different types of cancer. The main tasks of the study include the analysis of the efficacy, safety, and limitations of IORT across different cancer types; comparison of IORT with other radiotherapy techniques; assessment of its advantages and drawbacks; and evaluation of the IORT's impact on treatment outcomes, including local control, overall survival, recurrence rates, and treatment-related complications.

Materials and Methods

Eligibility Criteria

This review included studies focusing on IORT across various types of cancers, with an emphasis on breast and head and neck cancers [16]. The inclusion criteria were clinical trials, meta-analyses, and systematic reviews with experimental and control groups consisting of at least 15 participants. Eligible studies examined the efficacy and safety of IORT in comparison to other radiotherapy techniques, explored the compatibility of IORT with surgical methods, and analyzed both the advantages and limitations of IORT in different oncological contexts. Studies with design flaws, unsupported personal opinions, commercial content, or conflicts of interest were excluded.

Information Sources

The literature search was conducted in three major databases: Web of Science, Scopus, and PubMed. The search aimed to identify relevant studies published up until the search date. The search terms included "tumours," "therapy methods," "treatment," "irradiation," "radiation therapy during surgery," "breast," and "radiation treatment." A total of 60 publications were initially identified, of which 44 were selected for detailed analysis based on predefined eligibility criteria.

Search Strategy

A structured search strategy adhering to the PRISMA guidelines was applied across the selected databases. The initial search used general terms like "tumours" and "radiation therapy," which were subsequently narrowed using specific terms such as "IORT," "breast cancer," and "head and neck cancer." Boolean operators and database-specific filters were employed to refine the search, ensuring that the most relevant and up-to-date studies were captured.

Selection Process

The selection process involved multiple phases. First, titles and abstracts were screened to remove irrelevant studies. Next, full-text articles were reviewed based on the inclusion and exclusion criteria. The screening and selection were performed independently by two reviewers to minimize bias, with disagreements resolved through consensus or third-party adjudication. A total of 44 studies were included in the final synthesis.

Data Collection Process

Data were extracted using a standardized form that included key study characteristics such as the study design, sample size, patient population, type of cancer, type of IORT technique, and outcomes like local control (LC), overall survival (OS), and recurrence rates. Data extraction was performed by two independent reviewers to ensure accuracy and completeness.

Data Items

Key data items collected included study design (randomized controlled trial, cohort study, systematic review), patient characteristics (age, cancer type, stage), intervention details (type of IORT technique), comparison methods (IORT vs. other radiotherapy), and outcomes (LC, OS, recurrence rates, complications). Any missing or unclear data were addressed by contacting the authors of the original studies, where possible.

Study Risk of Bias Assessment

The risk of bias for each included study was assessed using standard tools such as the Cochrane Risk of Bias Tool for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies. This assessment

considered factors such as randomization methods, allocation concealment, blinding, and completeness of outcome data. Studies with high risk of bias were critically reviewed to determine the extent to which bias might influence the findings.

Effect Measures

For clinical trials, the primary effect measures were relative risk (RR) or odds ratio (OR) for binary outcomes like local control and recurrence, and hazard ratio (HR) for time-to-event outcomes such as overall survival. Continuous outcomes, such as radiation doses, were reported as mean differences or standardized mean differences, depending on the data available.

Synthesis Methods

A narrative synthesis of the results was conducted due to the heterogeneity in study designs, patient populations, and interventions. Where possible, meta-analyses were performed to pool results from studies with comparable designs and outcomes. Subgroup analyses were conducted to explore the effects of different IORT techniques and cancer types on outcomes. Heterogeneity was assessed using the I^2 statistic.

Reporting Bias Assessment

To assess reporting bias, funnel plots were created for outcomes with sufficient studies. Additionally, Egger's test was used to detect small-study effects. Any asymmetry in the funnel plots or significant results from Egger's test were explored further to assess the likelihood of publication bias.

Certainty Assessment

The certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. This considered factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall certainty of the evidence was categorized as high, moderate, low, or very low, depending on the presence of these factors.

Results

Included Studies

See Table 1.

Intraoperative radiotherapy for breast cancer

IORT consists of the direct delivery of precisely calculated radiation doses to selected target volumes within the open surgical field during surgery. This is achieved by being able to mobilize and move organs at risk away from the area of radiation exposure, thus reducing the likelihood of damage to healthy tissues and organs [17]. This technique has begun to be widely used in the context of the most common cancers, which is primarily breast cancer in women. The treatment of early breast cancer has undergone a significant transformation over the past decades [18, 19]. From radical mastectomy, which involved complete removal of the breast, medical practice has moved to lumpectomy, where only the tumour along with a small amount of surrounding tissue is removed, and this procedure is accompanied by adjuvant radiotherapy (RT). Studies have shown that both radical mastectomy and lumpectomy with RT show similar results in terms of LC and OS [20]. Trivially, radiation fields covered the entire breast and patients received daily treatment for 3-6 weeks. This approach, although effective, has its drawbacks, in particular the long treatment time and the risk of affecting healthy tissue.

However, studies have shown that most early recurrences occur in the area of the original tumour [21]. This prompted the medical community to develop techniques that would limit irradiation to only the part of the breast surrounding the area of the original lesion. Partial breast irradiation (PBI) has emerged as an answer to these challenges. This approach involves focusing radiation therapy on a specific area, which reduces the risk of damage to healthy gland tissue, lungs, and heart. It can also reduce the potential toxicity and side effects of treatment [22]. Patient selection for PBI is critical because not all breast cancers are suitable for this technique. Several professional societies have developed criteria for patient selection, among them the American Society of Breast Surgeons (ASBrS), the American Brachytherapy Society (ABS), the National Surgical Adjuvant Breast and Bowel Project (NSABP)/Radiation Therapy Oncology Group (RTOG), and the American Society for Therapeutic Radiology and Oncology (ASTRO) [23]. IORT is the latest approach to APBI [24]. This technique involves the application of a high dose of radiation directly during breast-conserving surgery in low-risk patients. The advantages of IORT include a shorter treatment duration because radiation is delivered once during surgery, reducing the need for subsequent proton therapy sessions [25].

Two large-scale randomized, controlled trials, TARGIT-A and ELIOT, compared IORT with conventional WBI [26, 27]. The aim was to evaluate efficacy in terms of LC and OS in low-risk patients. The ELIOT study was a large-scale randomised controlled equivalence study that aimed to evaluate the efficacy and safety of intraoperative radiotherapy compared to standard whole breast irradiation [26]. The study enrolled 1,305 women aged 48 to 75 years who had breast cancer with tumours up to 2.5 cm in size and underwent lumpectomy. The participants were randomly assigned into two groups: one group received IORT and the other group received standard WBI.

The IORT procedure involved the use of electrons with energies ranging from 6 to 9 MeV, allowing a dose of 21 Gy to be delivered directly to the tumour site during surgery. This approach significantly reduced treatment time and minimized the impact on surrounding healthy tissue. Additional adjuvant lymph node adjuvant radiotherapy was administered only to those patients with four or more positive axillary lymph nodes, which increased the risk of recurrence [26]. After five years of follow-up, it was found that the risk of breast tumour recurrence was 4.4% in the IORT group compared to only 0.4% in the WBI group, indicating a statistically significant difference (p=0.0001). Despite this difference,

Table 1. Included Studies and Participants

Study Type	Source	Total Participants	IORT Context
Review	F.W. Hensley [1]	Not applicable (Review)	Physics of IORT
	L. Boldrini et al. [6]	N/A (State of the art)	MR-guided IORT for pancreatic cancer
	C. Cavedon et al. [9]	N/A (Review on treatment planning)	Treatment planning advancements in IORT
	D.L. Casey et al. [10]	N/A (Review)	IORT role in early-stage breast cancer
	W. Asha et al. [12]	N/A	Management of early-stage breast cancer using IORT
	A. Pilar et al. [17]	N/A (Review)	Techniques and results of IORT
	D. Romero [25]	N/A (Review)	APBI as an alternative to WBI in breast cancer treatment
	N. Denaro et al. [31]	N/A (Systematic review)	Follow-up in head and neck cancer
	L. Hilal et al. [33]	N/A (Review)	IORT for head and neck cancer
	Y. Li et al. [46]	N/A (Review)	Current radiotherapy for recurrent head and neck cancer
Modeling Study	A. Esposito et al. [2]	N/A (Modeling study)	Dose distribution in pelvic and abdominal IORT
Clinical Study	P. Lalchandani et al. [3]	56	Impact of IORT in underserved breast cancer patients
	M.J. Silverstein et al. [4]	1000	IORT for 1000 breast cancer tumors
	J. Burgos-Burgos et al. [11]	N/A (Evaluation of toxicity)	Toxicity after hypofractionated IORT in breast cancer
	L. Berger et al. [13]	N/A	Major complications after IORT in early breast cancer
	B. Tuschy et al. [14]	N/A	Short-term complications of IORT in early breast cancer
	A. Tang et al. [15]	204	Health care system approach and outcomes of IORT
	K. Hsieh et al. [35]	N/A	Proton therapy reirradiation in head and neck cancer
	Y.H. Zeidan et al. [37]	54	IORT for advanced cervical metastasis
	S.B. Freeman et al. [38]	N/A	Management of advanced cervical metastasis using IORT
	D.J. Perry et al. [39]	34	HDR-IORT for recurrent head-and-neck cancer
	S. Nag et al. [40]	38	Electron beam IORT for recurrent head and neck malignancies
	L.M. Scala et al. [43]	109	HDR-IORT for recurrent head and neck cancer
	T. Toita et al. [44]	45	IORT for head and neck cancer
	Y.H. Zeidan et al. [45]	N/A	IORT for parotid cancer
	J.M. Jiang et al. [50]	120	Predictors of financial toxicity in radiation therapy patients
	J. Klein et al. [51]	68	Financial toxicity and survival in lung cancer patients
Randomized Clinical Trial	J.S. Vaidya et al. [5]	3451	Long-term outcomes of TARGIT-IORT in early breast cancer
	M. Clarke et al. [20]	10,801	Effects of surgery and radiotherapy on early breast cancer
	H. Bartelink et al. [21]	5,318	Whole-breast irradiation with/without boost for breast cancer
	F.A. Vicini et al. [22]	4,216	Accelerated partial breast irradiation for early breast cancer
Randomized Controlled Trial	U. Veronesi et al. [26]	1305	ELIOT trial comparing IORT with external radiotherapy
	R. Orecchia et al. [27]	1305	Long-term outcomes of ELIOT trial for breast cancer
	J.S. Vaidya et al. [28]	3451	Insights from the TARGIT-A trial in breast cancer
	J.S. Vaidya et al. [29]	120	Insights from the TARGIT-A trial in breast cancer
Prospective Study	C. Neumaier et al. [30]	355	TARGIT-E study on IORT for elderly breast cancer patients
Phase 2 Clinical Trial	J.A. Vargo et al. [32]	62	Reirradiation with SBRT in recurrent head and neck cancer
Study Design	J. Kaiser et al. [8]	N/A (Study design for breast cancer treatment)	IORT using electron radiotherapy for breast cancer
Consensus Statement	C. Shah et al. [23]	N/A (Consensus statement)	Consensus on accelerated partial breast irradiation
Guideline	M.J. Page et al. [16]	N/A (Guideline)	PRISMA 2020 guideline for systematic reviews
Cost-effectiveness analysis	M.D. Alvarado et al. [49]	N/A	IORT cost-effectiveness in early-stage breast cancer
Retrospective Evaluation	M. Niewald et al. [52]	65	IORT combined with EBRT for soft-tissue sarcomas
Radiation Protection Study	A. Soriani et al. [54]	N/A	Radiation protection for IORT accelerators
Web Resource	Memorial Sloan Kettering Cancer Center [47]	N/A	Radiation therapy for cancer

APBI, accelerated partial breast irradiation; WBI, whole breast irradiation; HDR-IORT, high-dose-rate intraoperative radiation therapy; ELIOT, ELectron IntraOperative RadioTherapy; SBRT, stereotactic body radiation therapy; EBRT, external beam radiation therapy.

five-year survival rates were similar between both groups, indicating that both techniques are effective in terms of overall survival. Further analysis of distant recurrence and survival outcomes in the ELIOT study showed that the higher recurrence rate in the IORT group persisted after 10 and 15 years. Specifically, the 10-year recurrence rate was 8.1% in the IORT group versus 1.1% in the WBI group, and the 15-year recurrence rate was 12.6% versus 2.4%, respectively. However, these increased recurrence rates did not affect the overall survival of the patients [27].

Due to its single-session treatment method, which eliminates the need for many hospital visits and lessens the financial strain on patients and healthcare systems, IORT has been linked to lower overall healthcare expenses in terms of cost-effectiveness. Conversely, WBI necessitates several sessions spread over several weeks, which raises the direct medical expenses. According to quality-of-life evaluations from these trials, patients having IORT reported a quicker return to normal life and fewer interruptions to daily activities than patients undergoing WBI. Furthermore, IORT was associated with a decreased prevalence of radiation-induced skin toxicity, exhaustion, and emotional distress – all of which are prominent in WBI because of cumulative side effects and protracted exposure. However, because of its proven long-term safety and effectiveness, especially in lowering recurrence rates, WBI continues to be the standard of therapy for many patients, even though IORT has benefits in terms of convenience and short-term adverse effects.

The TARGIT-A study was another important clinical trial that aimed to compare the effectiveness of intraoperative radiotherapy and whole breast irradiation in patients with breast cancer. This study used the same radiation technique as the other cohort studies to maximize comparability of results. The study was designed to determine whether IORT is as effective as standard WBI in terms of local control and overall survival. The trial enrolled 3451 patients who underwent lumpectomy for the treatment of early-stage breast cancer. Participants were randomly assigned into two groups: one group received IORT using the Intrabeam® device, and the other group received standard WBI. Eligibility criteria included women aged 45 years or older, with early-stage clinically negative node-negative ER+ invasive ductal carcinoma who were undergoing breast-conserving surgery (BCS).

Patients could receive IORT at the time of lumpectomy or as an adjuvant procedure after confirmation of the pathological diagnosis after the first surgery. In 15.2% of patients, adjuvant WBI was required after IORT because of definitive pathology that showed positive lymph nodes, positive surgical margins, or high-risk biologic tumour. This indicated that additional radiation was necessary to ensure complete removal of cancer cells and reduce the risk of recurrence. Compared to IORT or WBI alone, the combined radiation exposure raises the risk of treatment-related toxicity, which includes increased rates of skin reactions, fibrosis, and lymphoedema. Additional radiation therapy may also influence overall quality of life and lengthen recovery time, resulting in increased fatigue and possible delays in returning to regular activities. Notwithstanding these obstacles, the combination of adjuvant WBI and IORT may enhance long-term therapy success by lowering recurrence risk and improving local control in high-risk patients. The mean follow-up period in this study was 8.6 years. During this time, the breast tumour recurrence rates after five years were as follows: 2.11% for the IORT group compared to 0.95% for the WBI group. Thus, the study showed that IORT may be as effective a treatment option as standard WBI for certain patient groups [5]. An additional analysis of a cohort of patients published by Vaidya et al. [28], suggested the possibility of the existence of an abscopal effect in patients who received IORT during lumpectomy. The abscopal effect is a phenomenon in which treatment of one tumour can lead to the reduction or disappearance of other tumour foci in the body. This opens new perspectives for the use of IORT as an effective treatment modality that may have additional benefits beyond the directly irradiated region.

The ELIOT and TARGIT-A studies had significant differences regarding the methods used for intraoperative radiotherapy of IORT. The ELIOT study used electron beam therapy, whereas TARGIT-A used low-energy X-rays, which is an important aspect affecting the results and technical features of the procedure. As noted by Vaidya et al. [29], the technique of electron beam IORT requires a much greater degree of opening of the breast tissue. This is due to the need to place a metal shield on the chest wall and accurately aim the electron beam through the opening onto the breast tissue. This amount of dissection can create greater tissue hypoxia, which is known to reduce sensitivity to radiation and may affect treatment efficacy.

On the other hand, the Intrabeam® technique, which was used in the TARGIT-A study, allows direct contact between the applicator and the surrounding breast tissue after lumpectomy. This technique ensures that radiation is delivered directly to the target tissue, potentially increasing treatment efficacy and providing a full dose to the target area. This technique does not require major surgical access and may provide better local control than electron beam therapy. However, differences in techniques may partially explain the worst local control with electron IORT [30]. Vaidya et al. [29] showed schematically how intraoperative radiotherapy is performed in breast cancer (Figure 1).

Intraoperative radiotherapy for head and neck cancer

Head and neck cancer (HNC) is an equally important problem. HNC is a significant public health problem, as most cases are diagnosed at loco-regionally advanced stages due to non-specific early symptoms. Despite advances in radiation therapy and surgery, approximately 40% of patients experience recurrence after initial treatment, making it particularly challenging to treat. The relevance of HNC research stems from the need to develop more effective and less toxic treatments, such as IORT, which has the potential to improve local tumour control and patient survival while minimizing side effects and financial burden (Figure 2).

Locoregional recurrence of head and neck cancer often requires repeat surgery and/or repeat radiotherapy for effective disease control [32]. However, re-irradiation

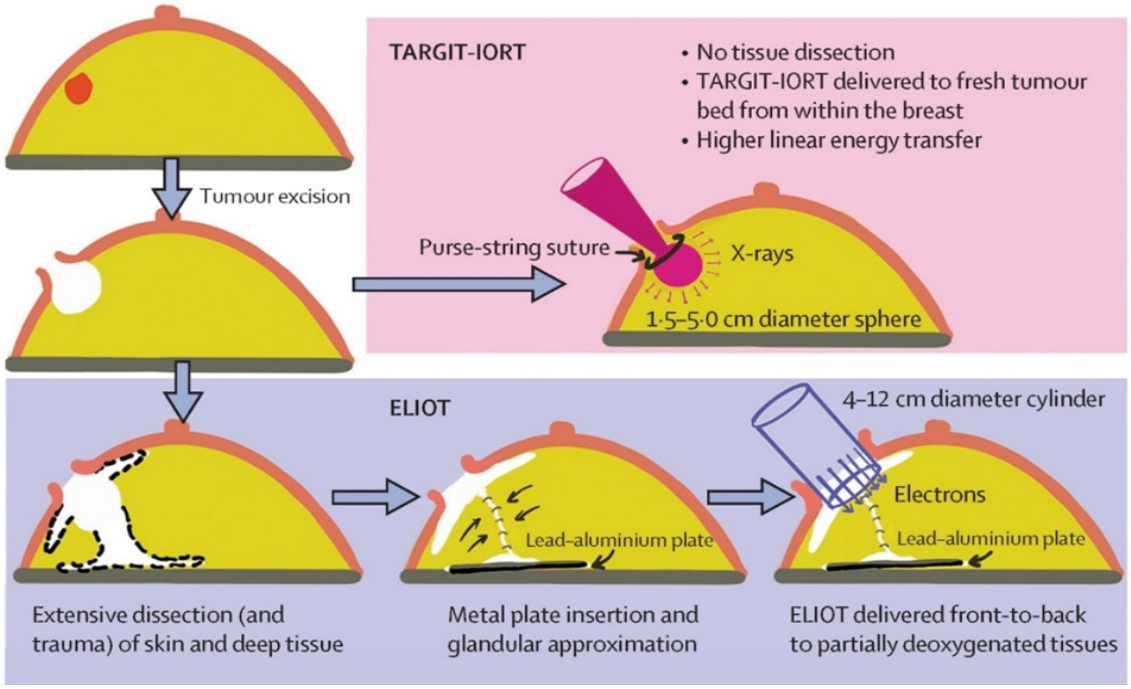

Figure 1. IORT Versus Standard Irradiation: the ELIOT study design Source: compiled by the author based on Vaidya et al. [29].

with EBRT is associated with a high risk of serious toxicity, including potentially fatal treatment-related complications. IORT has emerged as a promising modality, demonstrating improved surgical outcomes in patients previously treated with EBRT. The use of IORT in the primary setting effectively optimizes local tumour control, providing more targeted and intensive therapy directly at the time of surgery. This increases the likelihood of eradicating residual cancer cells and reduces the risk of recurrence [33]. Treatment of recurrent HNC is challenging, especially in cases where the patient has already received radiation therapy [34]. According to the 2024 National Comprehensive Cancer Network (NCCN) guidelines, surgery remains the mainstay of treatment

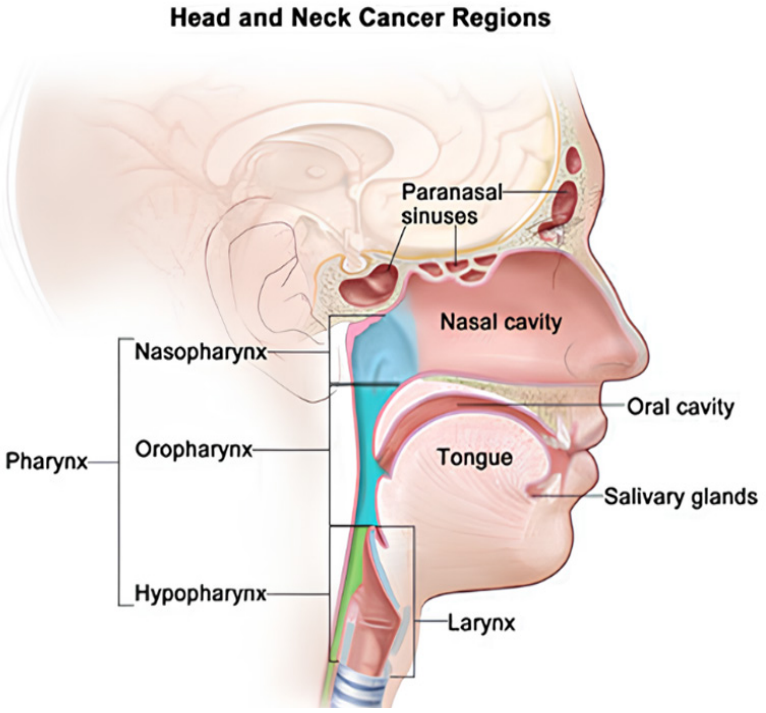

Figure 2. Head and Neck Cancer Encompasses Several Anatomical Regions that are Frequently Involved in the Pathological Process. This includes the paranasal sinuses, nasal cavity, oral cavity, tongue, salivary glands, larynx and various parts of the pharynx: nasopharynx, oropharynx and hypopharynx. Source: compiled by the author based on Denaro et al. [31].

for operable recurrences, with the possible addition of postoperative re-irradiation. However, the NCCN notes that re-irradiation should only be used for a carefully selected group of patients, given the high risk of treatment-related toxicity [35]. The main problem with re-irradiation is the limited tolerance of surrounding healthy tissues to the additional radiation dose, which significantly limits the possibility of effective treatment.

IORT is a critical treatment option for neck recurrences in patients with HNC because these recurrences often affect critical structures, such as the carotid artery, or deep tissues, making complete tumour resection difficult [36]. These complications are especially relevant after previous radiation, which can cause fibrosis. In a study by Zeidan et al. [37], the authors reported one of the largest retrospective series of neck IORT, which included 231 patients with neck metastases. Of these, 198 patients (88%) had recurrent tumours. All patients had either microscopic or macroscopic residual disease and received intraoperative electron radiotherapy (IOERT) with a mean dose of 15-20 Gy. Postoperative adjuvant radiation therapy was offered to 50 patients (21.6%). With a median follow-up period of approximately one year, the 5-year recurrence-free survival and overall survival rates were 49% and 26%, respectively, for all included patients. Since many cancer recurrences happen after the first year of therapy, a shorter follow-up duration could result in underreporting of long-term recurrence and survival results. Because early local control rates might not be a reliable indicator of long-term disease development, this shortcoming could lead to an overestimation of the initial efficacy of IOERT. Therefore, it is important to interpret efficacy carefully, and long-term follow-up research is required to ascertain the longevity of IOERT results and their actual influence on overall survival. Another significant study by Freeman et al. [38], regarding intraoperative radiotherapy to the neck, included 52 patients with recurrent tumours. IOERT with a mean dose of 20 Gy was used in this analysis. Importantly, patients were followed up for two years, providing detailed and reliable data on treatment efficacy. The results showed that two years after IOERT, local control and overall survival rates were 68% and 45%, respectively.

Intraoperative radiotherapy for other tumour localizations

IORT has also shown good results for tumour recurrence in primary localizations. Perry et al. [39] presented a study that included 34 patients, including 21% of salivary gland tumour (SGT) recurrences, as well as tumour recurrences in other primary head and neck localizations. Most patients had a history of prior external beam radiotherapy, with a mean dose of 63 Gy. Additional adjuvant EBRT was administered to 15% of patients at recurrence, with a mean dose of 50 Gy. The use of HDR-IORT with doses of 10-20 Gy resulted in 2-year local control and overall survival rates of 56% and 55%, respectively. However, in an earlier study conducted by Nag et al. [40] reported less encouraging results. This series included 38 patients, of whom 29% were treated with intraoperative electron radiotherapy due to recurrences in primary tumour localizations. Radiation dosage varied: patients with microscopically positive margins received 15 Gy and those with significant tumour remnants received 20 Gy. An essential aspect of this study was that patients did not receive additional adjuvant EBRT together with IORT, which probably resulted in less favourable outcomes. Specifically, the 2-year local control and overall survival rates in this case were 13% and 21%, respectively. Most studies of intraoperative radiotherapy for head and neck cancer recurrence find an important association between the level of local control of the disease and the status of the resection margins.

The limitations of the evidence included in this review primarily relate to potential biases, inconsistencies, and imprecision across studies. Many studies had a risk of selection bias due to non-randomized designs or small sample sizes, which limit generalizability. Inconsistencies were observed in the methods used for IORT, particularly between different radiation techniques, leading to variability in outcomes. Some studies lacked long-term follow-up, resulting in imprecise survival and recurrence data. Additionally, heterogeneity in patient selection criteria across studies may have contributed to inconsistent findings on the efficacy and safety of IORT.

A number of obstacles must be overcome in order to successfully use IORT in clinical practice, including the requirement for specialised training, specialised infrastructure, and efficient multidisciplinary team collaboration. Surgeons, medical physicists, and radiation oncologists need to have specialised training to guarantee precise dose administration, patient selection, and treatment planning because mistakes in these areas could jeopardise patient safety and treatment effectiveness [41]. Specialised mobile accelerators, radiation shielding techniques to prevent radiation exposure to surgical personnel, and the logistically challenging and expensive integration of IORT into operating room procedures are all examples of infrastructure requirements. Furthermore, smooth cooperation between the radiation oncology and surgical teams is essential for successful implementation, requiring clear guidelines and in-the-moment decision-making during surgery. If these issues are not resolved, IORT may only be widely used in high-resource hospitals, limiting its availability to a larger patient base.

Local control is a key indicator of treatment efficacy, determining how successful it has been in halting tumour spread within a localized area following therapy [42]. In particular, Scala et al. [43] conducted an analysis that showed that patients with negative resection margins (i.e. no residual tumour tissue) had a 1-year local control rate of 82%. In contrast, patients with positive resection margins, where residual tumour tissue was still present, had a 1-year local control rate of only 56%. This stark contrast in rates highlights the importance of complete removal of tumour tissue during surgery. Positive resection margins are a significant risk factor for recurrence, as residual tumour tissue may continue to grow and spread, even after radiation therapy has been performed. Studies also suggest that the use of IORT doses greater than 15 Gy is associated with a significant improvement in the level of local control of disease. In particular, higher doses of IORT have been found to contribute to more effective

suppression of tumour growth. In addition, several prognostic factors influence the results of local control and recurrence-free survival. One such factor is the duration of the recurrence-free period before re-irradiation, which should exceed 12 months to improve prognosis.

IORT has demonstrated encouraging outcomes for a number of cancer types, with special advantages for head and neck and breast malignancies. For breast cancer, IORT has demonstrated efficacy in reducing treatment time, offering a single-session radiation therapy that minimizes radiation exposure to healthy tissues. According to the TARGIT-A and ELIOT investigations, IORT offers comparable overall survival rates to conventional WBI while lowering the likelihood of adverse effects such fatigue and skin damage. However, even while IORT is convenient and has short-term advantages, it has greater long-term recurrence rates than WBI, especially when compared to the IORT group after a ten to fifteen-year timeframe. In head and neck cancers, IORT has demonstrated efficacy in treating locoregional recurrences, particularly when previous radiation restricts additional treatment options. It lowers the chance of recurrence by delivering high-dose radiation directly to the tumour site, greatly improving local tumour control. Even though IORT has been shown to enhance outcomes for head and neck malignancies, further research is required to understand long-term survival rates and optimise treatment procedures. All things considered, IORT has benefits for lowering treatment times and enhancing quality of life, especially for patients with head and neck and breast cancer.

Discussion

This technique has several advantages that make it important in modern oncology. Firstly, it eliminates the delay between surgery and subsequent adjuvant RT, which contributes to faster patient recovery and reduced risk of disease progression. Secondly, IORT provides improved accuracy of target delineation, as it allows the surgeon to immediately and directly observe and adjust the localization of treatment sites. Finally, the third benefit is the potential reduction in therapy toxicity.

It should be taken into account that intraoperative radiotherapy, although effective in treatment, can have a significant negative and toxic effect on patients. According to data presented in the scientific literature, the incidence of intraoperative complications associated with the use of radiotherapy ranges from 22% to 52%. These complications are observed both in cases of primary treatment and in the therapy of recurrent disease. Early studies, in particular, those conducted by Toita et al. [44], demonstrated a significant increase in toxicity when doses exceeding 20 Gy were applied. Among several reported complications, the incidence of carotid artery rupture ranges from 2% to 5%, reaching up to 10% in previous series. This complication is one of the most fatal complications associated with treatment. The incidence of fistulas and abscesses ranges from 4% to 15%. Wound-related toxicity ranges from cellulitis to flap necrosis and ranges from 0% to 12%. Osteoradionecrosis is recorded at an incidence of 0% to 13% [45]. A study by Li et al. [46] reported treatment-related neuropathy with an incidence of 1% to 3%, which is usually treated with symptomatic analgesia. However, in a Memorial Sloan Kettering Cancer Center study [47] involving 57 patients with recurrent tumours, the incidence of neuropathy was as high as 26%, the incidence of trismus was 24%, and the incidence of fibrosis was 29%. Similar rates of trismus and fibrosis (28% and 23%, respectively) were reported in 34 patients with recurrent disease. It is worth noting that the aforementioned studies used different toxicity scales and median follow-up variables. Taken together, IORT in experienced centres demonstrates an acceptable toxicity profile and does not increase perioperative mortality.

IORT has several compelling advantages besides reducing radiation exposure to normal tissue. One of the key advantages is its cost-effectiveness, which affects both healthcare costs and reduces the financial burden on patients. This treatment method avoids prolonged daily radiation treatment, which usually lasts for days or even weeks. Such prolonged therapy can cause significant financial problems for patients due to transport costs and lost work time. The difference from daily radiotherapy, which is the standard of care in many treatments, makes intraoperative radiotherapy particularly attractive for patients with head and neck cancer [48]. This method provides reduced financial and time costs for patients because it does not require daily visits to the treatment facility for radiotherapy sessions [49]. A recent study by Jiang et al. [50] found that the baseline financial cost was 52% among a group of patients from less affluent populations, who usually have inadequate access to medical care and simultaneously received chemoradiotherapy before any other cancer therapy. This rate increased by at least 25% during the course of treatment. A study by Klein et al. [51] found a correlation between financial burden and worse progression-free survival rates among patients with lung cancer. This indicates that financial difficulties may negatively affect the effectiveness of treatment and overall survival of patients.

Although intraoperative radiotherapy has emerged as a promising treatment option for HNC, some key aspects have been identified that require further research. Firstly, the efficacy of IORT requires detailed evaluation in the case of randomized phase III clinical trials. Given the limited number of centres with IORT facilities, multicentre cooperative groups are recommended. The second important aspect is the need for clear professional standards that detail the process of IORT application and ensure effective coordination between surgical and radiation specialists. This is relevant to ensure uniform treatment methodology, which improves the quality and efficiency of therapy.

The third problem that requires further research is the use of low molecular weight additives for radiosensitisation of tumour cells and protection of normal tissues in patients with HNC. The development of new methods to integrate such additives into the IORT process may significantly improve therapeutic outcomes, reduce side effects, and increase the overall level of treatment efficacy. Recent studies in oncology provide critical

indications regarding the potential use of intraoperative radiotherapy in the treatment of head and neck cancer. In particular, the implementation of a treatment planning system for intraoperative electronic radiotherapy represents a significant potential for improving clinical outcomes. This system allows precise distribution of radiation dose to target tissues and minimizes the impact on surrounding healthy structures. Reducing doses to normal tissues helps to reduce side effects and increases the efficacy of therapy, making it more appropriate for patients with complex head and neck cancers [52].

Ensuring radiation safety in the operating theatre during IORT is one of the key issues in modern oncological practice [53]. According to recent studies conducted by Soriani et al. [54], the average radiation doses from IORT at a distance of 1 m from the patient are about 6 microsieverts per hour, which requires compliance with strict radiation protection standards. The basic radiation safety requirements in operating theatres are usually met by shielding aimed at reducing the radiation exposure to the environment and medical personnel. This includes the use of various structural shielding methods, as well as the possibility of using mobile shielding walls to minimize the risk of radiation exposure to staff. For example, a study conducted in Poland by Hensley et al. [1] demonstrated that effective radiation shielding can be achieved by using a mobile lead shield with dimensions of 1 cm*140 cm*150 cm placed between the accelerator and the operating room. Despite the obvious advantages of mobile screens in minimizing the effects of radiation exposure on personnel and the environment, the use of these screens can face criticism from regulatory authorities. One of the main aspects of the criticism is the potential difficulty in ensuring that the correct positioning and correct use of mobile screens in medical settings is monitored.

The future direction of development in this area may be the improvement of interlocked systems that automatically regulate the activation of ionizing radiation only when the mobile screens are properly positioned and provide the maximum level of protection for staff and patients. This approach will enable effective implementation of IORT technologies with strict radiation protection standards, a critical aspect in medical settings where staff safety and patient safety is a high priority. Intraoperative radiotherapy opens new perspectives for personalized cancer treatment, where each case can be customized during the surgery itself. It may become standard practice in cancer surgery, offering significant advantages over conventional treatments, such as shorter overall treatment time and improved outcomes.

In conclusions, the need for IORT is bound to grow, and as a result, there will also be a need for automation of the radiotherapy process, which should stimulate the introduction of fast but accurate Monte Carlo dose calculation algorithms fast enough for regular use in clinical settings. Finally, patient safety requires the integration of multiple functions into a comprehensive system to simplify the monitoring of the treatment process. As seen in this study, IORT for neoplasms of the breast, bowel and other body systems, is an advanced technique that allows radiation treatment to be delivered directly during surgery. Radiotherapy also minimizes treatment time and improves the quality of life of patients, reducing the need for additional radiation therapy sessions after surgery. A major positive aspect is the increase in efficacy, as the use of IORT reduces the risk of recurrence, as the radiation treatment targets potentially remaining cancer cells.

An analysis of studies on the use of IORT in patients with breast tumours, such as TARGIT-A and ELIOT, showed that intraoperative radiotherapy does not always have clear advantages over standard irradiation methods. The five-year recurrence risk was 4.4% with ELIOT and 1.1% with standard techniques. After 10 years, the recurrence rate was 8.1% in the IORT group and 1.1% in the WBI group, and after 15 years it was 12.6% and 2.4%, respectively. However, patients with IORT had less systemic toxicity and survival rates were similar for all radiotherapy modalities. For head neoplasms, the risk of recurrence after IORT was 40%. Therefore, further research on dosages and therapies should be continued. However, successful implementation of this technology requires access to specialized equipment and highly qualified medical staff, as well as careful monitoring of possible complications such as radiation toxicity and risk of damage to surrounding healthy tissue. Further improvements in technology and the development of standards to optimize procedures and minimize potential risks are important.

Author Contribution Statement

YK: conceptualisation, methodology, data collection and analysis, writing (original draft preparation, review, editing).

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Ethical standards

Ethical approval of the study was obtained from the Health Research Ethics Commission of the Kazakh-Russian Medical University with No. CD-35. This study does not require informed consent.

Competing interests

The authors declare no conflict of interest.

Availability of data, code, and other materials

Data can be accessed by reaching out to the corresponding author.

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