Intraoperative radiotherapy

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Summary

- Intraoperative radiotherapy (IORT) is a method of cancer treatment in which a large single dose of radiation is delivered to the tumour or tumour bed at the time of surgical exposure. Although this approach has been under investigation since the early 1900s, it is still regarded as experimental in some respects.
- The rationale for the use of IORT is to improve the accuracy and level of the dose of radiation delivered to cancerous cells without increasing the damage to surrounding normal tissues.
- The primary aim of IORT is to improve locoregional tumour control. In most cases IORT has been used with curative intent, with improved local tumour control intended to translate into improved patient survival.
- In its current form IORT involves the delivery of high energy electrons, via a rigid treatment cone, to the tumour area. Normal tissues are pushed outside the cone. The area of treatment may involve unresectable tumour, proven residual disease remaining after resection, or completely resected tumour sites where local recurrence after resection is likely. IORT is delivered both alone and in conjunction with preoperative or postoperative external beam fractionated radiation, and with chemotherapy.
- Late stage cancer patients, with either primary or recurrent tumours, are the primary focus of IORT treatment. With better IORT treatment outcomes in patients with favourable surgical margins, there is some trend towards the use of IORT in earlier stage patients.
- IORT is primarily employed for the treatment of intra-abdominal and pelvic tumours; pancreatic, rectal and gastric carcinomas in particular. IORT has lesser applications for the treatment of tumours at other abdominal sites such as the cervix, biliary tract and prostate; and non-abdominal sites including the lung, head and neck, and extremities.
- The majority of data available for IORT focus on the assessment of the safety and feasibility of including IORT in conventional treatment regimens. The quality of data on the efficacy of IORT is generally poor, with few randomised controlled trials, typically small series, and limited outcome measures.
- The data available suggest limited efficacy in terms of an effect on overall patient survival. For some cancers there is evidence of a significant effect on local tumour control. This is considered to improve patient quality-of-life through prevention of the pain and discomfort associated with local disease progression. There is limited quantification of quality-of-life improvement in the literature.
- The complications arising from IORT use can be significant. Complications need to be considered in the context of late stage patients receiving treatment and failure to achieve locoregional tumour control.
- IORT may be delivered in non-dedicated facilities where patient transport is required between surgical and radiation facilities, or in dedicated facilities where surgery and radiation can be performed in a single unit. Although the potential for wound infection and patient trauma is greater in non-dedicated facilities, the literature suggests that problems with infection control are the major drawbacks of these facilities.
- The dedicated facility proposed by the Royal Prince Alfred Hospital, Sydney (NSW), which would involve the attachment of a radiation suite to two surgical theatres, potentially offers efficiencies in IORT scheduling and delivery.
- The number of patients available for treatment at the proposed facility would depend not only on the incidence of different tumour types, but also on the number of patients with appropriately staged, non-metastatic disease, and on referral patterns.
- The facility at the Royal Prince Alfred Hospital would predominantly treat patients with pelvic tumours with curative intent. A subset of patients, with unresectable pancreatic cancer and metastatic melanoma with abdominal metastases, would be treated with palliative intent.
- Details of the equipment required for the establishment and operation of the Royal Prince Alfred Hospital facility appear consistent with those described in the literature. The costs associated with the facility are difficult to assess as few economic data are available for IORT. Further economic analysis is required to determine the cost-effectiveness of this technology.

- The Royal Prince Alfred Hospital possesses the requirements for the implementation of this complex and multidisciplinary technology. The design of the proposed facility, and focus on the treatment of pelvic cancers, are in accordance with the literature on IORT planning.
- The main issues to decide are the extent to which a largely experimental technique should be supported within the State's health care system, the number of cases the facility would treat and the associated referral requirements.
- Should the facility be established, it would be important for there to be systematic collection of clinical and economic data and follow-up of patients, with a particular focus on quality-of-life outcomes.

Introduction

This report has been prepared at the request of the NSW Health Department, following a proposal to establish an intraoperative radiotherapy (IORT) facility in the State. The report is also intended as source material for a broader review of radiotherapy services being undertaken by the Australian Health Technology Advisory Committee. A preliminary review of the status of this technology has been prepared. Some areas which may require further consideration have been identified. Overall, this report seeks to examine the role of IORT in preventing local tumour recurrence or progression, and to evaluate the evidence available for its effectiveness in improving local tumour control and patient survival. Discussion of alternative local control techniques is included where appropriate.

The rationale for IORT, procedural details, potential advantages and disadvantages are covered in the first section of the report. Applications of IORT and available clinical data are reviewed, with particular emphasis on the use of this technology in the treatment of pancreatic and rectal cancer. Consideration is then given to the potential use of this technique in the context of services in New South Wales, with particular reference to the proposal for a facility at the Royal Prince Alfred Hospital, Sydney. In conclusion, some suggestions regarding potential use of this technology are made.

In preparing this preliminary overview of IORT, use has been made of major references identified in the *Medline* literature between 1990 and 1994, and earlier trials cited in those references. Emphasis has been given to reports of randomised controlled trials and Phase I/II trials with detailed reporting of treatment outcomes. This overview has also drawn on a submission by the Royal Prince Alfred Hospital to the NSW Health Department.

The principle of IORT is to deliver a large single dose of radiation directly to the tumour or tumour bed, and potential areas of local regional spread, at the time of surgical exposure. The first reported use of this technique was in 1909, with orthovoltage X-rays used to treat patients with gastric and colon carcinomas.[1,2] Up until the 1960s IORT was used primarily as a palliative treatment for advanced cancer, and to give high doses to deep-seated tumours.[3] Its use was not widespread due to the greater interest during this period in the refinement of high energy photon technology for the treatment of cancer.[2] In the late 1960s, Professor Abe at the Kyoto University, stimulated a new interest in IORT with the use of high energy electrons as the radiation beam. Following encouraging early results with this technique for the treatment of locally advanced abdominal tumours,[4] IORT was introduced as an experimental modality in an American university hospital in 1976.[3] This technique, with electrons delivered via linear accelerators, is currently employed in over 100 American hospitals,[5] in a large number of Japanese hospitals, and in various centres in Europe and China.

Rationale for IORT use

Limitations of existing cancer treatment techniques

For the majority of tumour sites, surgical resection is regarded as the principal curative treatment modality. Surgery however, does have a number of limitations particularly for patients where the tumour is not well-confined and exhibits either nodal involvement or locoregional extension. Even in cases of well-defined tumours the possibility always exists that microscopic disease remains behind after a potentially curative operation. The high rates of local tumour recurrence following curative surgery for pancreatic, rectal and gastric cancers highlight the limitations of surgery as the lone treatment technique.

The goal of definitive radiotherapy is to produce local tumour eradication without unacceptable complications. Used postoperatively, external beam radiation therapy is intended to prevent local recurrence of the tumour through destruction of suspected or known residual disease. The major limitation of external beam radiotherapy (EBRT) is that cancerocidal doses of radiation cannot be given because of the similarity in radiosensitivity of normal tissue and malignant tumours. The high rates of local recurrence following external beam irradiation of cancers in the abdominal region is a consequence of the limits placed on this technique by the radiosensitivity of abdominal tissues.

The importance of local tumour control

One of the most challenging problems facing surgeons and radiation oncologists is the local and regional recurrence of cancer after treatment.[6] Failure to achieve local tumour control leads to considerable pain and discomfort,[2] with an associated reduction in patient quality-of-life and survival, and an increase in the use of medical resources. Local failure also leads to an increased risk of developing distant metastatic disease. Attempts to improve the therapeutic ratio of tumour treatment have focused on modifying the aggressiveness or the efficiency of the treatment (and thus potentially enhancing local tumour control) without significantly increasing the complication rate.[7]

Attempts to improve the local control and cure rates for surgery through the development of more radical resection procedures have either been of limited benefit or have resulted in high rates of morbidity. In the case of EBRT of tumour sites, attempts to improve local tumour control rates through the use of higher dose radiotherapeutic regimens have resulted in unacceptable damage to surrounding tissues.

Other techniques have subsequently been developed which are specifically designed to improve locoregional control. These include intraoperative radiotherapy, interstitial and intracavitary brachytherapy alone or with EBRT or surgery, hyperthermia with radiation therapy, focused radiotherapy (radiosurgery), particle irradiation, and different routes of administration of treatment regimens such as intra-arterial chemotherapy with radiation therapy.[8,9] These techniques aim to deliver a higher biologically-effective dose of radiation to the tumour than to surrounding normal tissues, thereby increasing the potential for tumour control and improved survival, with fewer complications.

Procedural details for IORT

Preoperative examination of potential intraoperative radiotherapy (IORT) patients is carried out in accordance with standard protocols. In selecting patients for IORT treatment, particular attention is paid to the tumour stage and the absence of clinically evident metastatic disease. For those patients selected as suitable for IORT treatment, the procedure begins with the surgical exposure of the tumour and its evaluation for resectability. Depending on the tumour site and histology, the surgical procedure may entail complete resection, tumour debulking or biopsy only. Intraoperative radiation may therefore be required to treat a complete tumour mass, microscopic residual disease, or a completely resected field with a high risk of local tumour recurrence.[6] Where resection is performed, the areas of potential residual disease are subjected to frozen section histologic review to determine the extent and site of the residual tumour.[10]

An appropriately sized and angled sterile cone is subsequently selected by the radiation oncologist to encompass the region to be treated by radiation and to minimise radiation scatter to adjacent tissues. In some instances the area to be treated is marked with either radiopaque sutures or surgical clips to aid in cone placement or field definition for subsequent postoperative radiation treatment.[6] The patient is then removed from the operating suite to the radiation bunker. In some instances the operation is performed in a dedicated radiation bunker; but at most centres using IORT, transport of the patients is required (often over considerable distances within the hospital). This requires careful draping of the surgical wound, transfer of the patient to portable anesthetic equipment, and considerable hospital planning to ensure patient safety.

The final placement of the rigid cylinder or treatment cone in the anatomical cavity permits visualisation of the treatment area, defines the area which will receive the radiation beam, and allows normal tissues to be pushed outside the treatment field.[11] Where this movement of normal structures is not anatomically feasible (such as movement of the duodenum when treating the pancreatic head), custom-fabricated sterilised lead blocks can be used to shield these tissues from radiation damage.[6] The treatment or applicator cone is then used to link the patients to the linear accelerator. Radiation is delivered in the form of high energy electrons. The electrons permit a homogenous dose of radiation to be delivered to the selected treatment field and limit normal tissue damage due to their acute dose fall off at a known tissue depth.[11] The dose and energy of the electrons to be delivered to the treatment field vary according to the tumour site, the amount of residual disease and whether IORT is to be used alone or in combination with external beam radiotherapy (EBRT).[12] Orthovoltage X-ray therapy has been used where electrons are not available, but this is less than ideal.

During the delivery of the radiation dose, all personnel are absent from the room, with the patient monitored remotely. IORT takes approximately six minutes to administer,[13] and can be interrupted at any time if the patient's safety is at risk. Following irradiation, the patient is transported back to the operating room for the construction of anastomoses and completion of surgery. Anastomoses are not performed prior to IORT. This facilitates adequate exposure of cancerous tissue to IORT and avoids delay in anastomoses healing as a result of IORT exposure.[14] The addition of IORT to the surgical procedure extends the total treatment time by anything between 25 and 60 minutes.[15,16] The time taken is dependent both on the tumour site and whether the facility is dedicated or non-dedicated.

Potential advantages and disadvantages of IORT

Proponents of the intraoperative radiotherapy (IORT) technique have proposed a number of theoretical and practical advantages to its inclusion in conventional treatment programs. The proposed advantages are given in Table 1.

The potential disadvantages of IORT suggested in the literature appear to be primarily radiobiological and practical. These disadvantages are also detailed in Table 1. The disadvantages of this technique in terms of complications and treatment outcomes are considered later in the report.

Table 1: *Potential advantages and disadvantages of IORT*

Advantages	Disadvantages
IORT is not precluded by previous treatments—offers hope of local tumour control and palliation to patients who otherwise have failed all conventional treatment	Requires surgical procedure with associated risks of general anesthesia, surgical complications and postoperative pain.
Does not preclude postoperative external beam radiotherapy (EBRT)	Pretreatment planning is difficult due to requirements for selection of beam energy, cone size and angle, and source–tumour distance immediately prior to actual patient irradiation.
Does not interfere with chemotherapy	Is expensive in terms of equipment, and in terms of personnel and scheduling requirements
Spares skin and subcutaneous tissue	Ties up a machine for considerable lengths of time due to scheduling of IORT, operating times and unexpected delays during anesthesia and surgery. Alternatively requires a dedicated machine with large amounts of non-useful time.
Provides a means by which to decrease the toxicity of radiation by effectively shielding normal tissue from the radiation (by moving them out of the treatment field) and thereby permitting higher radiation doses to the tumour, areas of residual disease or high risk zones for recurrence	Use of single dose necessitates careful selection of proper dose level
Optimises definition of the treatment field—allowing exact borders, confining radiation mostly to tissues at risk, and allowing predictable depth of treatment and uniform dosimetry	Tumour volume which can be eliminated by single dose of irradiation is relatively small. If electrons are used, the exact definition of the field is difficult due to scatter.
Improves the ratio of local tumour control to radiation induced complications.	A single large dose of radiation is biologically equivalent to a higher dose delivered by conventional fractionation—but increases the potential extent of damage to unprotected normal tissues.
Believed to provide more than twice the biologic effect of the same dose delivered in the form of fractionated radiation	

Source: Owens et al.[6]

Applications of IORT

Aim of IORT

In most cases, patients are treated with intraoperative radiotherapy (IORT) with curative intent. The improvement in local tumour control resulting from IORT treatment is intended to translate into improved patient survival. Benefits in terms of palliation derived from improved local tumour control or tumour response appear not to be the principal focus of IORT treatment in clinical trials, as evidenced by the lack of reporting of palliative outcomes. The exception is the palliative treatment with IORT of patients with unresectable pancreatic cancers. In these patients pain relief is quantified and considered an important outcome of treatment.[17]

Role of IORT within existing treatment programs

IORT + postoperative EBRT

As Table 1 indicates, in radiobiological terms there are certain disadvantages associated with the use of a single fraction of high dose radiation. Although there is a degree of controversy over the radiobiological merits of high versus low dose, and single versus fractionated delivery of radiation to tumour sites,[7] the results of some early clinical trials which used IORT as the sole radiation treatment following surgery, indicated that a single dose was not sufficient to eliminate all cancer cells.[18]

Although IORT is still given as the sole radiation dose for some tumour sites, the most common strategy for its use is as a boost dose to postoperative external beam radiotherapy (EBRT). The use of IORT as a boost radiation dose permits the advantages of external beam fractionated radiation to be maintained, allowing a wide area surrounding the tumour or tumour bed to be irradiated, and also enabling a precise and greater overall dose to be delivered to the surgical area itself.[19] In theory this combination of radiation treatments should enhance local tumour control without increasing normal tissue damage.[3]

IORT + preoperative EBRT

IORT has also been incorporated into protocols based upon preoperative rather than postoperative EBRT. These preoperative radiation protocols are designed to reduce tumour bulk and facilitate tumour resection, with the best possible surgical margins in patients with initially unresectable or difficult to resect tumours.[20] The addition of IORT is intended to reduce the potential for local recurrence resulting from microscopic residual disease following resection.

IORT + chemotherapy

Since the curative capacity of IORT is restricted to improvements in local tumour control, chemotherapy is generally maintained within a multimodality treatment program in order to control systemic failures. The maintenance of chemotherapy in IORT treatment protocols is also potentially important in translating improved local control rates into improved patient survival.

IORT + radiation modifiers

IORT has also been explored in conjunction with a range of radiation modifiers including chemotherapeutic agents, radiation sensitisers and hyperthermia.[19] The potential benefits of these combined treatments in terms of improved tumour cell destruction have yet to be examined in large Phase I/II trials.

IORT + previous treatment

For patients who have failed all conventional treatment attempts and have experienced a recurrence in a previously irradiated field, the potential for further treatment with fractionated external beam irradiation is limited by normal tissue tolerance. IORT can be used as an extension of treatment in such patients. Further surgical exploration, tumour debulking or tumour resection is followed by a single high dose of radiation to a defined area with previously irradiated normal tissues excluded from the treatment field. This approach offers some hope of local control and palliation in patients presenting with recurrent disease who have retained sufficient resilience and fitness to cope with the stress of exploratory surgery and a high dose of radiation.

Tumour types and stages treated with IORT

IORT is primarily used for the treatment of locally advanced, non-metastatic cancer. Patients with documented distant metastases are excluded from IORT treatment on the grounds that IORT cannot control metastatic disease and that their life span is not adequate to evaluate treatment related benefits or complications.[21] Tumour Stages I–IV (based on various tumour classification systems) have been treated with IORT. However, the majority of trials have restricted IORT treatment to Stages II to IV. Both recurrent and primary site cancers are considered suitable for IORT.

The extent of disease treated with IORT ranges from unresectable tumours, to known residual disease remaining after resection, to completely resected tumour sites where local recurrence following surgery is the primary source of disease progression.

Due to the advanced stage of most cases considered for IORT treatment, there is a considerable proportion of patients who are originally selected for treatment but excluded at the time of surgery. Reasons for exclusion from IORT treatment include the presence of an early stage tumour with complete surgical excision, benign histology, or more commonly, a tumour which is too extensive, the presence of extensive regional metastases which were not detected prior to surgery or a patient who is medically unstable in the operating room.[22]

The original focus of IORT treatment in the 1970s and early 1980s was on the treatment of those intra-abdominal and pelvic tumours such as carcinoma of the pancreas, stomach, rectum, and retroperitoneal sarcomas, which are difficult to treat with conventional radiotherapy due to the radiosensitivity of surrounding tissues. The establishment of the feasibility and safety of IORT for the treatment of tumours at these sites has led, in some institutions, to a growth in the range of tumour types considered for IORT programs. Table 2 details the sites for which IORT data are available.

There is some variation between countries in the frequency with which various tumour sites are treated with IORT. The focus of IORT programs in the two largest centres—the United States and Japan—has remained primarily on pelvic and abdominal tumours, with the slight differences reflecting cancer incidence statistics in these countries. Japan has a strong interest in IORT treatment of gastric cancer and there is interest in the United States in the treatment of pancreatic carcinomas. Other centres such as the University of Navarra in Pamploma, Spain, have developed IORT programs with equal focus on abdominal, extremity and intrathoracic tumours.[19]

Table 2: *Tumour sites treated with IORT*

Tumour site (commonly treated)	Tumour site (infrequently treated)
Rectum	Lung
Pancreas	Biliary tract
Cervix	Prostate
Para-aortic lymph nodes	Bladder
Stomach	Extremities (soft-tissue)
Retroperitoneum (soft-tissue sarcomas)	Extremities (osteosarcomas)
	Head, neck and brain

IORT clinical data

The clinical data available for intraoperative radiotherapy (IORT) vary considerably in quantity and quality. This section of the report outlines the type of data available for IORT treatment, the limitations of the data in providing evidence for the efficacy and therapeutic advantages of IORT over existing treatments, and a site-specific summary of IORT clinical results, including complications.

Data type

IORT dosimetry

Some data available for IORT come from animal studies (predominantly conducted in dogs) and focus on the dose sensitivity of normal tissue structures to single dose IORT treatment alone or in combination with external beam radiotherapy (EBRT).[23,24] The data have provided dosimetry parameters for clinicians to use in the treatment of humans with IORT.

Many of the early human IORT trials were an extension of animal studies and tended to focus on establishing the safe and optimal dose of radiation to be delivered to human tumours. Trials to determine the appropriate dose of IORT to be given within a multimodality program (usually including external beam irradiation and chemotherapy) have predominantly been conducted in human rather than animal subjects.

Safety and feasibility

The majority of Phase I/II trials conducted with IORT in individual institutions, or as part of cooperative group studies, have centred on determining the clinical safety, and particularly the technical feasibility, of incorporating IORT in the management of different tumour types. For a number of non-abdominal tumour sites, the clinical data available are largely restricted to assessment of these two factors. The complications associated with IORT treatment have remained an important focus of IORT clinical research with a recent extension to the examination of the effect of IORT on immunological parameters.[25,26]

IORT treatment outcomes

Discussed below are some of the major limitations of the IORT data. These limitations have prevented IORT from making the transition from an experimental to a proven and established treatment modality.

Paucity of randomised controlled trials

To date, the complete results of only four randomised controlled trials (RCTs) have been published. While other RCTs are reported to be underway, and the preliminary results of a small number of RCTs were delivered at the 1992 IORT conference in Munich,[27] for many tumour sites there exists no randomised trial data available for the assessment of IORT efficacy. All currently published RCTs (for unresectable[28] and resectable pancreatic cancer,[29] stomach cancer[30] and retroperitoneal soft-tissue sarcoma[31]) have been conducted at the National Cancer Institute in the United States. Unfortunately, these trials have extremely small patient numbers in each treatment area (thus limiting statistical significance on most measurable outcomes and the power of the overall study), and provide outcome measures for IORT and conventional treatment which tend to differ from the majority of results produced in non-randomised trials. Exaggeration or masking of the clinical benefits of IORT is thus possible with these data.

Lack of adequate study controls

The majority of trial data available for IORT is from non-comparative Phase I/II studies. These studies, focusing mostly on the feasibility of IORT use, cannot provide a firm indication of the possible benefits of IORT compared with existing treatments. Some trials have attempted to discuss their results in relation to historical controls from the same institution[22,32,33] or from previously reported trial data.[34,35] Without adequate detailing of relative population characteristics (including prognostic indicators), or regard for the possible impact of other medical technologies on patient outcomes, these comparisons are difficult to interpret.

The results from many non-randomised comparative Phase I/II trials have been equally inconclusive in assessing possible IORT efficacy. In some cases the non-IORT comparison group has comprised those patients excluded from IORT treatment due to early stage tumour diagnosis, or more commonly due to the advanced stage of disease or medical contraindication to surgery.[36,37] Comparisons are thus being made between quite different patient populations.

Trials in which non-randomised concurrent controls have existed (patients being treated at the same time with existing treatment protocols) have tended to be the most informative of the Phase I/II studies.[38,39] Results of these trials have generally included prognostic comparisons of experimental and control groups, and have enabled the possible influence of other medical technologies on patient outcome to be avoided. Unfortunately, the statistical significance of differences demonstrated in these trials cannot be confirmed due to the non-random allocation of patients to different treatment groups.

Small sample size

For some of the more commonly IORT-treated abdominal cancer sites such as the pancreas and rectum, patient numbers in non-comparative and comparative (non-randomised) Phase I/II clinical trials have been reasonable. In rectal cancer studies, patient numbers have ranged from 30 to 50 and for pancreatic cancer have ranged from 30 to 80, with comparative studies tending to have larger sample sizes. Gastric cancer trials have tended to have 40–50 patients in non-comparative studies, and close to 200 patients in non-randomised comparative trials conducted in Japan and China. For other abdominal tumours such as gynecological and retroperitoneal soft-tissue, the patient numbers in published trials are smaller, with closer to 20 patients per trial. These small patient numbers makes the reporting of percentage outcomes problematic and cross-study comparisons increasingly meaningless. The effect of small sample size on restricting result interpretation is also significant for some of the more recently treated non-abdominal tumour sites.

Since the treatment outcomes for recurrent versus primary and resectable versus unresectable patients are predictably different, the tendency within IORT studies to include these different subgroups of patients leads to a further reduction in the number of patients of each type who can be compared across trials. Overall, limited sample size has placed restrictions on any direct (via RCTs) or indirect (via Phase I/II trial comparisons) assessment of the therapeutic advantages of IORT.

Sources of trial variability

The considerable variation between IORT trials (sources of variation are listed in Table 3 on the next page) has made comparison between IORT trials difficult, and consequently comparison between the treatment outcomes of IORT and conventional therapies is highly problematic.

The other significant form of variation which makes interpretation of IORT results difficult, is the difference within a single trial between the types of treatment given to patients. Although in some trials where these treatment variations are due to the recurrent/primary or resectable/unresectable nature of the disease there is separate reporting of treatment outcomes, in others a single result is reported with no distinction made for variations in treatment. The optimal treatment protocol for IORT and the possible benefits of IORT are consequently more difficult to assess.

Table 3: *Sources of cross-trial variation*

Source	Comments
Surgical procedures	Tendency to incorporate IORT into different surgical procedures for the same tumour site
Radiation therapy procedures	Variations in IORT dosage, number of treated fields, sequence of IORT and EBRT
Tumour staging	Some trials fail to report results separately for different tumour stages
Mix of recurrent/primary patients	Problem where there is single reporting of trial results
Mix of resectable and unresectable patients	As above
Outcome measurements	Variations in the number of outcome measures reported and in the time period for which measures are taken

Quality of data available for IORT complications

Although the reporting of complications arising from IORT has been widespread, the quality of the data is limited in some respects. One of the greatest difficulties in assessing the specific complications to arise for IORT treatment is the inclusion of IORT in multimodality treatment protocols and the difficulty in distinguishing treatment-specific effects. The advanced disease stage of the patients included in IORT trials has also made the distinction between disease progression, surgical complications and radiotherapy complications difficult. Finally, for some of the newer tumour sites to be treated with IORT (such as thoracic tumours), the monitored period following IORT treatment has been relatively short and has not included documentation of the possible late complications of IORT.[40]

Site-specific trial data

A detailed analysis of the intraoperative radiotherapy (IORT) clinical data has been undertaken for the two tumour sites (rectum and pancreas) which have been most extensively studied and which would be included in the IORT program at the Royal Prince Alfred Hospital, Sydney (NSW). For the other commonly studied sites, assessment is limited to a brief discussion of the quality of evidence and the main indications from the data. An attempt has been made to access all current IORT trial data. Some early 1980 IORT reports which focused primarily on assessing safe dosage levels have been excluded as they did not contribute significantly to the assessment of the efficacy of IORT.

Pancreas

Unresectable pancreatic cancer

Due to the often ill-defined symptoms of pancreatic cancer in the early stage of the disease, definitive diagnosis does not occur until there has been considerable local disease progression and often metastasis. As a consequence, over 80% of patients with pancreatic cancer have tumours which are classified as unresectable at the time of diagnosis.[17]

Existing treatment programs

Palliation is the primary aim of treatment in patients with unresectable pancreatic cancer where local disease progression is associated with jaundice, anorexia, obstruction and in particular, epigastric or back pain.[17] Palliative bypass surgery associated with injection of the celiac ganglia with ethanol or phenol is one method employed for alleviating symptoms.[17]

External beam irradiation and precision high dose radiation, used alone or in combination with chemotherapy, are intended to reduce or control the extent of local disease and associated symptoms.[17] Attempts to deliver higher doses of radiation to the pancreas without damaging the particularly dose-sensitive tissues located in the abdominal region have involved the use of interstitial brachytherapy with implantation of iodine-125. Although this technique has produced good local tumour control and associated palliative benefits, it has also been associated with significant mortality and morbidity.[41,42]

The alternative strategy for controlling local disease progression and providing palliation has been the use of IORT. As surgery (laparotomy or bypass surgery) is a standard procedure for patients with unresectable pancreatic cancer, the use of IORT on this patient group does not require an additional operation. Unresectable cancer of the pancreas is the disease that has most often been treated with IORT in Western institutions.[17]

IORT treatment protocol

With the development and refinement of IORT treatment protocols, this technique is now incorporated into a multimodality treatment program consisting of bypass surgery followed by IORT, external beam radiotherapy (EBRT) and chemotherapy.

Clinical data

The clinical data available for IORT treatment of unresectable pancreatic cancer are fairly comprehensive. The types of trials so far conducted are summarised in Table 4 on the next page.

The paucity of trials with adequate controls means that data on conventional treatment outcomes also should be included in Tables 5 and 7, and in Appendix 1. The additional data allow an indirect assessment of IORT efficacy, but their usefulness is limited by an overall lack of reporting of palliative or local control outcomes in conventional treatment trials.

Table 4: *Unresectable pancreatic cancer trial types*

Trial type	Number of trials	Mean no. of patients
Randomised controlled trial	1	22
Phase I/II comparative	4	76
Phase I/II	12	30

Results

Median survival time

Although a comprehensive meta-analysis of clinical trial results was not possible due to the non-randomised nature of the trials, a mean value (and standard deviation) for the median survival time of patients treated with various techniques has been calculated. The data used in these calculations are given in Appendix 1.

Table 5: *Median survival time following IORT or conventional treatment of unresectable pancreatic cancer*

Treatment	Median survival time (mean and SD in months)
EBRT alone	6.7 (1.0)
IORT alone	4.9 (1.0)
IORT + EBRT	9.4 (1.8)
EBRT + 5-FU	10.6 (1.4)
IORT + EBRT + 5-FU	12.2 (2.8)

Note: EBRT = external beam radiotherapy, IORT = Intraoperative radiotherapy, 5-FU = 5-fluorouracil

Local tumour control

For unresectable pancreatic cancer, local tumour control is generally taken to mean that the primary lesion in the pancreas is controlled with no increase in tumour size or involvement of regional lymph nodes. The data available on local control rates are largely restricted to trials involving treatment with IORT plus postoperative EBRT and chemotherapy using 5-fluorouracil (5-FU). A mean value for the percentage local control in a one year period has been calculated from Table 16 as 72% (one year mean value) for treatment with IORT plus EBRT and 5-FU. The sparse results for local control rates from other treatment protocols are also shown in Table 6 (extract from Tables 16 and 17, Appendix 1).

Table 6: *Locoregional control following conventional treatment of unresectable pancreatic cancer*

Treatment	% Local control	Author and study type
EBRT	76 (2y)	Moertel et al. 1981
EBRT (4000 rad) + 5-FU	74	RCT
EBRT (6000 rad) + 5-FU	73	
EBRT + 5-FU	48 (1y)	Roldan et al. 1988
	20 (2y)	Phase I/II Comp. NR
EBRT + IORT	80 (1y)	Willech et al. 1988
		Phase I/II

Note: Comp. = comparative study, EBRT = external beam radiotherapy, IORT = Intraoperative radiotherapy, NR = non-randomised, RCT = randomised controlled trial, 5-FU = 5-fluorouracil

Pain relief

The proportion of patients experiencing pain relief following treatment is reported in the majority of trials involving IORT. The mean and range of percentage pain relief values derived from available IORT data are 80% and 50–90% respectively. Due to the reporting of single pain relief figures in comparative trials of IORT alone or IORT in combination with other treatments, a percentage pain relief value for all treatment protocols incorporating IORT is reported.

Discussion

The principal argument for the use of IORT in the treatment of unresectable pancreatic cancer is that it provides rapid and effective pain relief. The results from a range of trials employing IORT in various treatment protocols indicated that around 80% of patients experience pain relief following IORT treatment. Unfortunately, the definition of what constitutes pain relief for measurement purposes, and the length of time for which palliation is obtained in these patients, are rarely described in the clinical literature. Only three papers of those examined defined what constituted pain relief (being patient opinion in one case,[43] and the need for none or only mild pain killers in the other two.[44,45] The paper by Willich et al.[45] reported that 90% of patients were free of pain without drugs or using nonopoids 10 days after the IORT, and more than 85% maintained a pain-free state over the following four months. The study by Hiraoka noted that in all patients experiencing pain relief following IORT, the pain was recurrent in later stages of tumour progression.[43] The pain relief levels in the Willich et al. study indicated a similar decline four months after IORT. The long-term palliative effects of IORT treatment are thus not established.

A recently published pilot trial in which unresectable patients were treated with EBRT and a simultaneous multidrug regimen[46] found that in almost all patients, treatment was accompanied by a 50–100% reduction in tumour volume, with associated relief of refractory pain. This less invasive, alternative technique requires further consideration.

As Table 5 indicates, there are no strong arguments for the use of IORT for the improvement in the median survival time of patients with unresectable pancreatic cancer. Although these figures are not definitive, treatment of patients with EBRT and chemotherapy alone appears to be as effective as the more extensive and invasive multimodality protocol of IORT with EBRT and chemotherapy (5-FU).

On the issue of local control, the lack of reporting of this outcome in conventional treatment trials makes outcome assessment difficult. The non-randomised comparative study conducted by Roldan et al.[39] found a local control rate of 72% for IORT with 5-FU compared with only 48% for EBRT with 5-FU for a one year period, but further trials would be needed to confirm this result. Although not statistically significant due to small patient numbers, the reduction in time to local disease progression associated with the addition of IORT to EBRT protocols[28] may, with further investigation, provide an additional rationale for the use of IORT in the treatment of unresectable pancreatic cancer.

Complications

The most frequent complication of the combination of IORT and EBRT in the treatment of pancreatic cancer is injury to the superior parts of the digestive tract.[47] Due to the proximity of the pancreas to the radiation-sensitive digestive system, gastrointestinal bleeding, gastric outlet obstruction, gastric ulceration and duodenal damage are among the complications which arise after combined radiotherapy treatment. These complications, although significant, need to be considered in the light of the radiation damage occurring with the use of EBRT alone, and the chronic pain and extremely dismal prognosis if unresectable pancreatic cancer is left untreated.

Conclusions

The indications for the use of IORT in pain relief for unresectable pancreatic cancer patients appear encouraging. However, in the absence of evidence for sustained pain relief and the likely need for a return to conventional pain control methods as the disease progresses, IORT treatment may be an expensive and potentially risky means by which to provide palliation. Better definition and analysis of pain control, and further investigation of the role of IORT in delaying disease progression, would strengthen the case for the use of IORT in the treatment of these patients.

Resectable pancreatic cancer

Less than 20% of patients have potentially resectable pancreatic cancer at the time of diagnosis.[17] The encouraging results from IORT treatment of unresectable patients led clinicians to experiment with the use of IORT following radical surgery. With high rates of local recurrence (50–90%)[10] and overall poor survival (a median survival time of 12 months)[17] in patients undergoing resection, it was hoped that IORT would improve both these treatment outcomes. The addition of IORT was also seen as a potentially safer way of improving treatment quality than more radical surgical techniques (involving extended lymphatic resection) which are associated high mortality and morbidity.[48,49]

To date, the trials for resectable pancreatic cancer have focused on establishing the feasibility and safety of combining IORT in a curative capacity, with various surgical protocols including regional pancreatectomy. A randomised controlled trial conducted by Sindelar et al.[29] in 1986, and a further trial in which 17 of 20 patients were randomised,[34] provide the best evidence in terms of possible efficacy of IORT for patients with resectable pancreatic cancer. A standard protocol for IORT treatment of these patients does not as yet exist. In most cases treatment is restricted to pancreatectomy plus IORT without EBRT.

Discussion of clinical results

Due to the small number of trials so far reported and the variability in protocol design, trial results for IORT treatment of resectable pancreatic cancer are not presented separately. The list of articles to which this discussion refers are given in Appendix 1.

Local control

Local disease progression in resectable patients is taken as any failure within the retroperitoneum, or on the peritoneal surfaces. The results from the two Sindelar studies indicate a significant improvement in local control rates with the use of IORT compared with surgery alone (80% versus 0%),[29] and surgery with EBRT (56% versus 25%)[34] for a one year period. The local control rate from surgical treatment alone against which IORT is compared in the 1986 trial corresponds with previous surgical trial results reported by Merrick and Dobelbower in 1990.[17] Overall indications are that IORT does improve local control in this group of patients. Studies by Sindelar et al.[29] and Hiraoka[43] also suggest that there is a trend towards delayed disease recurrence following IORT treatment. This has obvious significance for improving patient quality-of-life.

Survival

The indications from the Sindelar studies are that improved local control does not translate to improved patient survival (12 months versus 10 months).[29,34] Results from non-randomised comparative studies suggest some improvement in patient survival following IORT treatment compared to surgery alone, but only for particular stages of disease.[38,43,50] Survival also seems highly dependent on the extent of tumour resection.[38,43] The role of IORT in improving patient survival requires further investigation and needs to be considered in the light of a median survival time of 22.8 months in the 1993 study by Foo et al. using surgery with EBRT and 5-FU on similarly staged patients.[51]

Complications

The complications experienced following IORT treatment of patients with resectable pancreatic cancer need to be considered in the light of the highly technical nature of the surgical process in pancreas resection. Clinical results indicate that, although postoperative complication rates were high (up to 55% following regional pancreatectomy and IORT),[34] these rates were comparable with those associated with treatment by surgery alone. The high rate of infectious complications with combined treatment[10,34] could be a result of the addition of radiotherapy to the surgical process. The only evidence for specific radiation damage from IORT appeared in a study by Abe et al.[52] where patients were treated with very high doses (25–40 Gy) of IORT compared with other trials (10–20 Gy).

Conclusions

At this stage, IORT does not appear to have an established role in the treatment of resectable pancreatic cancer. In the absence of evidence for the translation of improved local control into improved survival, possible quality-of-life improvements resulting from better local control will need to be documented.

Rectal/colorectal cancer

Primary advanced stage rectal cancer

Surgical resection is the standard initial treatment for patients with resectable carcinoma.[36] Recurrence rates after curative surgery depend on the extent of disease at the time of diagnosis and can be as high as 50%.[53] In patients with early stage tumours, postoperative radiotherapy and chemotherapy have been used as adjunct treatments with improvements in local tumour control and patient survival.[54,55]

In more advanced stages of rectal and colorectal cancer where there is extension of the tumour through the bowel wall or attachment to pelvic side walls, the possibility of a curative surgical procedure with no microscopic or gross surgical margins is limited.[20] Treatment of these more advanced patients with surgery and postoperative EBRT[56,57,58] indicated that radiotherapy could not compensate for incomplete resection. Local control rates were considerably worse for patients with gross disease than for those patients with only microscopic residual disease. The subsequent strategy for improving local tumour control was to treat primary advanced rectal cancer patients with preoperative rather than postoperative external beam irradiation. This had the effect of significantly improving the rate of complete tumour resectability (through tumour shrinkage), but left local recurrence rates quite high (19–55%).[59,60,61,62] In a further effort to improve local control and patient survival by increasing the radiation dose to the tumour bed, IORT was added to existing treatment protocols.

Clinical data

Clinical data for IORT treatment of advanced stage primary rectal cancer are restricted to the results of Phase I/II non-comparative studies. In order to provide an indirect assessment of the possible efficacy of IORT, the results from previous non-IORT trials have been included in Table 7. The results of three IORT trials are included in this table.[21,35,36] Results for percentage pelvic control and survival are presented with a breakdown of figures on the extent of tumour resection and the amount of residual disease. Two other trial results are available for IORT but the number of patients is less than 10 in one study,[63] and in the other, the results for recurrent and primary advanced patients are not separately reported.[64]

Discussion

Due to the reporting of results in terms of the extent of surgical resection and the amount of residual disease remaining after resection, comparison of outcomes from different treatment protocols is somewhat complex. In the Tepper et al.[35] and Gunderson et al.[21] trials, the results for local control and survival were improved relative to previously treated patients at these institutions (historical controls treated with preoperative EBRT plus surgery). Indirect comparisons made from data in Table 7 suggest that the addition of IORT to preoperative EBRT procedures improves both local control and survival, but that this improvement appears to be highly dependent on the extent of tumour resection. The results for patients with complete resection are encouraging and suggest a role for IORT in the treatment of this subset of patients. The results for patients with microscopic or gross residual disease particularly in terms of disease-free survival do not support a role for IORT in the treatment program. The high rate of distant metastases (33–41.9%) reported in a number of IORT trials[21,35,63] indicates that effective systemic therapy is also required to improve the survival of advanced stage rectal cancer patients.

Complications

The addition of IORT to the preoperative EBRT and surgical treatment of primary advanced rectal cancer patients does not appear to increase the complication rate associated with treatment (compared with historical controls).[35] The complications appear to be primarily concentrated in the small bowel with no reports of motor or sensory neuropathy.

Conclusions

The results available to date, particularly for patients with complete resection, suggest a role for IORT in curative treatment of primary advanced stage rectal cancer. Some authors have suggested that IORT treatment be restricted to those rectal patients who do undergo complete resection but further studies may be necessary to confirm the ineffectiveness of this treatment for patients with microscopic residual disease. Improved local control in the absence of improved patient survival, in complete or incompletely resected patients, may have an important impact on patient quality-of-life.

Table 7: *Summary of clinical data for IORT and conventional treatment of primary rectal cancer*

			% Pelvic control				% Survival			
References	Treatment	No. of patients	Overall	Complete	Micro	Gross	Overall	Complete	Micro	Gross
Allee 1989 (57)	S + postop EBRT	63	58	–	70	43	26 (dfs) (5y)	–	45 (dfs) (5y)	11(dfs)
Schild 1989 (58)	S + postop EBRT	17	24	–	30	14	24 (dfs) (5y)	–	30 (dfs) (5y)	14 (dfs)
Gosshein 1981 (56)	S + postop EBRT	31	–	–	84	50	–	–	–	–
Dosoretz 1983 (60)	Preop EBRT + S	25	–	62	–	–	28 (5y)	–	43 (5y)	–
Stevens 1983 (61)	Preop EBRT + S	72	–	68	–	–	10 (dfs) (5y)	–	–	–
Emamai 1982 (59)	Preop EBRT + S	44	–	81	–	–	41 (3y)	–	69 (dfs) (3y)	–
Mendenhall 1987 (62)	Preop EBRT + S	23	30.5	45	–	–	9 (5y)	–	–	–
Tepper 1989 (35)	EBRT + S + IORT	31	85	95	90	–	52 (4y)	–	–	–
Gunderson 1991 (21)	EBRT + S + IORT	20	80	–	–	–	50 (3y)	–	–	–
Willett 1991 (36)	EBRT + S + IORT	42	77	88	69	50	43 (dfs) (5y)	53 (dfs) (5y)	47 (dfs) (5y)	17 (dfs)

Note: dfs = disease-free survival, EBRT = external beam radiotherapy, IORT = intraoperative radiotherapy, micro = microscopic, postop = postoperative, preop = preoperative, S = surgery

Recurrent rectal cancer

Local failure after curative treatment for rectal or colorectal cancer is accompanied by chronic pelvic pain and rectal bleeding.[65] The treatment options open to recurrent rectal cancer patients depend considerably on the 'extent and location of the recurrence, the type of previous surgical procedure, and whether or not adjuvant radiation therapy was previously given'.[65] Re-resection is potentially curative for small anastomotic recurrences or isolated perineal recurrences.[66] For recurrences in the central pelvic region which have invaded the pelvic side walls, sacrum or anterior structures such as the prostate or bladder, re-resection alone is rarely curative.[36] Where patients have undergone previous radiotherapy the complication, local failure and operative mortality rates are increased.[65] The use of external beam irradiation in a curative capacity has been restricted to patients who have not previously been treated with radiotherapy. The principal use of radiotherapy for recurrent rectal cancer has been in the palliative treatment of patients with poor prognosis. Pain relief has been found in up to 90% of patients with symptomatic pelvic recurrences treated with external beam irradiation.[67,68]

IORT treatment for patients with recurrent rectal and colorectal cancer has been introduced with the intention of restricting the need for such extensive surgical procedures, improving local disease control and potentially improving patient survival. The major focus of outcome reporting following IORT treatment of these patients has been disease-free survival rates. Only a small number of Phase I/II non-comparative studies have so far been conducted. A collaborative multicentre trial is currently underway in the United States with locally advanced and recurrent patients randomised between postoperative external beam irradiation and IORT.[69]

The treatment protocol employed in existing trials has generally consisted of surgery, preoperative or postoperative radiotherapy with or without chemotherapy and IORT. The variability of treatments administered within a single trial is a consequence of the variability in previous treatments administered to patients. There is conflicting evidence on whether the sequence of administration of EBRT affects overall treatment outcomes.[65,70]

Clinical data

The clinical data available for IORT treatment of recurrent rectal and colorectal cancer is given in Table 8. Results for local tumour control and disease-free survival are presented for each trial with a breakdown of figures on the basis of the extent of tumour resection.

Discussion

The absence of direct comparisons of IORT with conventional treatment protocols makes the assessment of the benefits of IORT for recurrent rectal cancer patients extremely difficult. The variations in treatment outcome on the basis of the location of the rectal recurrence also makes indirect cross-trial comparisons of different treatment strategies problematic. Results available for the curative treatment of recurrent patients with surgery with or without EBRT are variable, with local control rates ranging from 61% down to 39%.[65] Long-term survival rates of around 5% are reported in the early literature for patients with recurrent disease,[21] but more recent studies indicate that disease-free survival rates in patients treated with standard techniques vary 5–38% for five years.[65]

When overall results (complete resected patients plus partially resected patients) are considered for IORT trials, the treatment outcomes of local control and disease-free survival are not impressive. However, when these parameters are considered on the basis of the extent of surgical resection, the results for those patients undergoing complete resection appear encouraging. In relation to local disease control, the results in these patients are very encouraging and could have significant quality-of-life benefits given the symptoms associated with local disease progression.

Some caution is needed in interpreting the survival results due to the differences in time periods for which rates are given. Although the 5-year disease-free survival for the completely resected patients in the Willett et al. trial[69] was 54%, the projected 5-year disease-free survival for the patients in the Abuchaibe et al. trial[65] is only 17%, which is not significantly different from survival rates achieved in conventional treatment programs. An important result from the IORT trials is the high percentage of patients developing distant metastases (close to 50%).[21,63,65] The possibility that many recurrent patients have microscopic disseminated disease at the time of diagnosis would prevent IORT treatment from having a significant impact on disease-free or overall patient survival. Finally, IORT treatment of recurrent patients needs to be considered in the light of the possibility that it may add to the already substantial complications resulting from treatment of this patient group. Indications are that the complications arising from existing IORT protocols are substantial and involve a number of patients experiencing delay in soft-tissue healing,[21,69,71] hydronephrosis[65] and serious pelvic pain.[65,69,71]

Conclusions

IORT may have a role to play in the curative treatment of patients with recurrent rectal cancer who are able to undergo complete resection but further studies are required. Future trials should investigate and quantify the effect of IORT on the time to local disease progression as this could be a significant contributor to patient quality-of-life in the absence of overall improved survival.

Table 8: *Local control and survival in patients with recurrent rectal cancer treated with IORT*

Reference	No. of Patients	% Local control			% Survival		
		Overall	Complete	Partial	Overall	Complete	Partial
Tepper 1989 (71)	22	30	80	25	25 (4y)	–	–
Gunderson 1991 (21)	50	–	68	–	–	–	–
Willett 1991 (69)	30	26	62	18	19 (dfs) (5y)	54 (dfs)	6 (dfs)
Abuchaibe 1993 (65)	27	26	50	16	26 (dfs) (2y)	50 (dfs)	13 (dfs)
Lanciano 1993 (63)	33	28	77	10	–	88 (2y)	48

Note: dfs = disease-free survival

Gynecological cancer

Standard surgical treatment for cervical cancer includes radical hysterectomy, lymphadenectomy or exteneration.[76] Conventional radiotherapeutic treatment consists of a combination of EBRT to the pelvis and intracavitary brachytherapy.[76,77] It is this latter treatment regimen which is most frequently reported in the medical literature for patients with early and intermediate stage cervical cancer.

The inclusion of IORT into the treatment program for patients with cervical cancer has occurred for a number of reasons and has involved treatment of a range of patient types. In the initial stages, IORT was introduced for the treatment of primary patients with known or suspected para-aortic metastases from gynecological malignancies.[76,78] Previous external beam treatment of these patients had resulted in significant complications in the gastrointestinal tract.[80,81] In more recent times IORT has been used in combination with surgery, preoperative or postoperative pelvic irradiation with or without chemotherapy for the treatment of residual disease remaining after surgery for primary cervical cancer. The other significant use of IORT has been in the treatment of patients with recurrent gynecological cancer (usually involving para-aortic or pelvic side wall recurrence), who would normally be considered untreatable or difficult to approach with second line radical treatment.[78,82,83,84,85,86]

A summary of the results from Phase I/II clinical trials describing IORT treatment of gynecological cancer is given in Appendix 2. The trials predominantly describe the treatment of patients with uterine cervical cancer. Although some endometrial and ovarian cancer patients are included, results for these patients are not reported separately.[82,85] Only results from a single pilot study of IORT treatment of five patients with ovarian cancer are currently available.[87]

Discussion of clinical data

Treatment of locally advanced primary residual disease

Only the results of a preliminary study[82] are available for the treatment of this patient group. With a short follow-up time no survival data are available and the local control rate at one year was only 3/8 (37.5%).

Treatment of para-aortic nodes in primary patients.

IORT treatment of advanced stage patients with para-aortic nodal involvement does not appear to improve patient survival compared with external beam treatment (25% with IORT compared with 23–29% for EBRT). Given the suggestion that distant metastases and para-aortic nodal metastases develop simultaneously,[52] the potential for IORT to improve survival in these patients is probably limited. It should be noted, however, that a small proportion of patients with para-aortic modal involvement have been cured with EBRT,[88] so IORT may have a role in the treatment of a small subset of these primary patients. The complications associated with para-aortic lymph node resection, exposure and IORT treatment of the para-aortic field were significant in the Goldson et al.[76] and Konski et al.[78] studies due to the close proximity of the ureter to the para-aortic nodes and the potential damage of IORT to the underlying pelvic nerves.

Recurrent gynecological cancer

A number of trials to date have focused on the treatment of patients with recurrent gynecological cancer with maximum debulking surgery, IORT and in some patients (depending on prior treatment) additional EBRT.[78,82,83,84,85,86] Given that the overall 5-year survival for patients with pelvic side wall recurrences of cervical cancer treated with standard radiation therapy, depending on the extent of disease, is in the 2–30% range,[83] the survival rates for IORT treatment appear comparable although only one figure is currently available for 5-year survival following IORT.

As with treatment of primary patients with pelvic and para-aortic nodal involvement, the likely presence of distant metastases will prevent any substantial improvement in patient survival with IORT treatment. The local control rates described by Garton[83] and Calvo[82] are encouraging for patients with recurrent disease, although no known comparative figures are available. Although improved local control may play a role in improved quality-of-life, attention must be given to the considerable complications (particularly ureteral stricture and pelvic pain) which accompany IORT treatment of patients with recurrent cancer.

Gastric cancer

As with many tumour sites, patient survival after curative gastric surgery is dependent on the extent of initial disease, with lower survival rates occurring in those patients with regional lymph node involvement or extragastric tumour extension.[30] Overall one of the main reasons for the limited success of gastric cancer surgery is the high incidence of metastases to the lymph nodes along the gastric and common hepatic arteries and around the celiac axis.[90] Radiotherapy has been used as a locoregional adjuvant treatment but has not played a major role and is associated with considerable gastrointestinal complications.[93] IORT was first used in the treatment of gastric carcinoma in the late 1970s in patients with unresectable metastatic disease.[94] The safety, feasibility and palliative effects of IORT were noted in this preliminary study. The first major clinical report of IORT treatment of gastric cancer with curative intent came in 1981 from Abe in Japan.[4] Promising results for the advanced stage patients in this study led to the establishment of Phase I/II,[95] and later an RCT,[30] at the National Cancer Institute in the United States.

In general, the quality of data available for gastric cancer is good with one published RCT,[30] two RCTs underway,[96,97] one non-randomised comparative study with large patients numbers,[90] and other Phase I/II trials.[32,93,95] Patients with tumours of all stages have been included in clinical trials and IORT has been used in patients in a curative capacity. The vast majority of patients treated have had primary (rather than recurrent) resectable tumours. A list of published data (some of which were not obtainable for this report)[98,99,100] and a table of summary data is included in Appendix 3.

Discussion of clinical data

The majority of trials (randomised controlled trials and non-randomised comparative Phase I/II trials) have compared the survival and tumour control rates resulting from surgery alone with those from surgery with IORT. EBRT has been included along with surgery for patients with advanced disease in one trial,[30] and in conjunction with surgery and IORT in two recent trials.[32,93]

Survival

The results from comparative non-randomised IORT studies suggest a survival advantage for treatment with surgery plus IORT over treatment with surgery alone for certain tumour stages. In the Abe 1989 study,[90] the addition of IORT did not improve the 5-year survival of patients with Stage I/II disease but it did significantly improve survival in patients with later Stage III and IV disease with lymph node involvement or tumour penetration through the gastric wall. Preliminary results for the Jiang 1992 randomised study[96] also indicate significantly improved survival for Stage III patients. Early results from the Kramling et al. randomised trial[97] show slightly improved survival in the IORT group (staging not specified). The Sindelar et al. 1993 RCT,[30] which involved primarily advanced stage patients, did not however, find a difference in survival rates between control (surgery with or without EBRT) and experimental (surgery with IORT) groups. Small patient numbers, the randomisation of five-sixths of early stage patients to the control group and the long-term nature (seven years) of the survival figures may explain the lack of survival difference between treatment arms in this particular study. A significant finding in both the Sindelar et al.[30] and Abe et al.[90] studies was a salvage rate of close to 20% for IORT treatment of late stage patients. The final results from the Jiang et al.[96] and Kramling et al.[97] randomised controlled trials should assist in clarifying the suggested efficacy of IORT in the treatment of gastric cancer.

Local control

Reporting of local control rates following IORT treatment is uncommon but the results from the Sindelar 1993[30] randomised study suggest a significant local control advantage with IORT treatment. Locoregional (intra-abdominal including peritoneum) disease failures occurred in only 44% of IORT patients compared with 92% of control (surgery or surgery with EBRT) patients. In those patients experiencing disease failure, 100% were locoregional in the control group but only 50% in the IORT group (the remainder in the IORT group being distant metastases). Local control rates reported for late stage patients in the Calvo et al. study[93] are within the range of that reported for IORT treatment in the Sindelar et al. trial. Indirect comparisons of IORT control rates with conventional treatment outcomes is limited by a lack of analysis of locoregional progression patterns in other trial literature.[93]

Complications

The rate of treatment complications reported in the Sindelar et al. randomised trial[30] were high for both experimental and controls groups (56% and 72%). Close to 50% of the complications in each group were gastrointestinal although the types of complications varied between treatment protocols. Acute and chronic enteritis were particularly significant in the control group but not in those patients treated with IORT. No patients in the Sindelar et al. study developed complications which could be directly attributed to IORT. In the Abe et al. study,[90] IORT was not associated with increased infection rate, delayed wound healing or noticeable pancreatic damage. Results from the Kramling randomised trial[97] indicate a slightly higher morbidity and mortality associated with the addition of IORT to surgery. The results available for the combination of surgery, IORT and EBRT in the Calvo study[93] indicate some serious treatment complications, including vertebral collapse which may be attributed to IORT.

Conclusions

Treatment outcomes in terms of local control and survival appear encouraging for the use of IORT in the treatment of gastric cancer. The availability of reasonable data allows a more accurate assessment of possible efficacy.

Retroperitoneal soft-tissue sarcomas

Retroperitoneal soft-tissue sarcomas are uncommon tumours (about 1000 cases per year in the United States)[31] which are usually locally advanced at the time of diagnosis. With resectability rates of around 50%[101] and subsequent recurrence rates of over 70%[101] even after complete resection, the prognosis for patients with these tumours is poor. The addition of adjuvant postoperative external beam irradiation has been limited by the radiosensitivity of tissues and structures in the intra-abdominal and pelvic region. Preoperative radiotherapy to improve the resectability rate of retroperitoneal soft-tissue sarcomas has also been attempted. IORT has been added to both preoperative and postoperative radiotherapy protocols in an effort to improve local control rates and patient survival. It is being employed in a curative capacity for both primary and recurrent patients. Although data from a single randomised controlled trial is available for IORT treatment of these pelvic tumours,[31] the rarity of this tumour has resulted in small patients numbers in all trials and a compromising of data quality. Varied reporting of treatment outcomes and inclusion in results of non-IORT-treated patients[102] makes results interpretation difficult. A summary of the trial results are presented below with summary data from conventional treatment protocols included for indirect comparison. Detailed IORT and conventional trial results are presented in Appendix 4.

Table 9: *Local control and survival in patients with retroperitoneal soft-tissues sarcomas treated with IORT or conventional treatments*

	% Survival (5y)	% Local control	
Treatment	**Range**	**Range**	**Mean**
Surgery alone	25–50 (CR) 5–20 (PR)	10–30 –	– –
Surgery + EBRT	23–54	20–83	40
Surgery + IORT + EBRT or EBRT + IORT + EBRT	33–48.5	50–80	5

Note: CR = complete resection, EBRT = external beam radiotherapy, IORT = intraoperative radiotherapy, PR = partial resection

Local control

Indirect comparison of IORT with conventional treatment trials indicates an improvement in local control rates with the inclusion of IORT. Direct comparison of local control rates in the randomised control trial published by Sindelar[31] confirms the improvement in local tumour control provided by IORT. In this randomised study, 16 of 20 patients treated with surgery and high dose EBRT experienced local recurrence compared with only six of 15 patients treated with IORT. The high rate of local recurrence amongst the EBRT control group in the Sindelar study (compared with other EBRT trials) is of some concern, but the overall indications are for improved control with the addition of IORT.

Survival

As with other tumour sites treated with IORT, improved local control does not appear to translate into improved survival in patients with retroperitoneal sarcomas. This was confirmed in the randomised study by Sindelar et al.[31] which gave median survival times of 52 and 48 months for control and experimental groups respectively. The higher rate of distant metastases in IORT compared with the control group in Sindelar's randomised trial suggests that death due to local disease progression is being replaced by death due to distant metastases. In terms of patients' quality-of-life, this failure to translate improved local control into improved survival does not rule out the use of IORT for these patients.

Complications

Complications associated with IORT use such as hydronephrosis and sensory neuropathy occur in retroperitoneal patients treated with IORT, although their incidence is not high.[102,103] Most notable is the reduction in the number of patients experiencing radiation enteritis after IORT treatment compared to treatment with high dose EBRT (20% versus 50% for chronic enteritis and 7% versus 60% for acute enteritis).[31]

Conclusion

The evidence for improved local control and reduced radiation enteritis associated with the replacement of high dose EBRT protocols with low dose EBRT plus IORT programs indicates a role for IORT treatment in this small subset of cancer patients. In the likely absence of improved survival in future trials, measurement of quality-of-life effects would be beneficial.

Other tumour sites

A summary of the data available for less frequently treated and documented tumour sites is given in Table 10. Appendix 5 lists the references available for IORT treatment of these tumour sites.

Overall indications from clinical data

Surgical margins

The extent of residual disease remaining after tumour resection appears to be the most significant factor in determining the success of IORT treatment, both in terms of local control and patient survival. For this reason some authors have suggested a shift in the focus of IORT treatment to those patients where near complete surgical resection can be achieved.[63,65,104]

Local control versus distant metastases

At a number of tumour sites, success in terms of improved locoregional control is not being translated into improved patient survival due to an accompanying higher rate of death due to distant metastases. Although it is argued that local tumour control reduces the risk of developing distant metastases,[105] his may only apply to a subset of tumour types (Guiney, personal communication). For other tumour types the presence of undetectable microscopic metastatic disease at the time of initial diagnosis means that attainment of local tumour control will not necessarily prevent the subsequent development of distant metastases. Given the advanced stage of disease (whether primary or recurrent) in patients considered for IORT treatment and the likely presence of microscopic metastases, the likelihood of improving patient survival though improved local control may be limited.

It is important to note that although this lack of survival improvement is discouraging in the context of the curative intent of IORT treatment, the quality-of-life benefits associated with improved local tumour control may be significant and should be better documented.

Complications

The clinical data pertaining to IORT-specific complications are fairly comprehensive with both specific and general reporting of treatment mortality and morbidity. The establishment of toxicity criteria has helped to encourage uniform documentation of complications.[106] The results of the Cromack et al. 1989 study[107] in which patients were identified from randomised controlled trials, provide the best comparative data for IORT and conventional treatment programs. In that study there was no significant difference in the incidence of infections, complications, the number of complication episodes (either early or late), the mortality associated with treatment or the amount of hospitalisation time due to complications. These results are confirmed by complication-specific data available for IORT and historical controls,[22] and IORT and concurrent non-IORT controls[37] as well as by the majority of general site-specific clinical trials.

Animal studies and human clinical trials have identified peripheral nerve and ureter as the two normal tissues most likely to develop an IORT-associated complication in the treatment of locally advanced pelvic malignancies.[108,109,110] This is primarily due to the technical difficulty in avoiding radiation exposure of these two structures in many pelvic cancer patients. In a recent study involving IORT treatment of colorectal cancer, 32% of patients developed peripheral neuropathy and 63% showed evidence of ureteral obstruction and hydronephrosis.[110] These figures need to be considered in the light of the advanced stage of disease in IORT patients and, in particular, the significant incidence of pelvic nerve damage and pain associated with alternative radical surgical procedures and the failure of treatment to control local progression of the tumour.[110] Other serious complications arising from the use of IORT, such as bowel hemorrhage, vascular damage occlusion and bone damage, also need to be considered in the context of the complications arising from a lack of local tumour control.[150]

Overall, the indications are that the inclusion of IORT to standard treatment protocols does not significantly impact on complication rates. Although there appears to be a higher rate of peripheral nerve and ureteral damage, there is also a significant reduction in the rate of acute and chronic enteritis with the use of combined IORT and EBRT rather than high dose EBRT alone.

Table 10: *Summary of IORT data for less frequently treated tumour sites*

Tumour Site	Tumour type				Treatment	Mean sample size	Study types	Data quality comments	Indications for IORT efficacy
	Resectable	Unresectable	Primary	Recurrent					
Lung	Yes	Yes	Yes	–	S + IORT + EBRT ± C	64 (Calvo) 19 (other)	Phase I/II Phase I/II NR Comp.	Lack of controls, variable treatment, short follow-up, palliative outcomes not reported	No proven benefits over interstitial brachytherapy in terms of local tumour response, control and survival
Head & neck	Yes	No	Yes	Yes	S + IORT ± EBRT	104 (Freeman) 30 (others)	Phase I/II	Range of sites treated, no comparative studies	Safe, good indications for improved local control, feasible palliative treatment
Intracranial	yes	No	Yes	Yes	S + IORT + EBRT	24	Phase I/II	Variable tumour types, some concurrent and historical controls, most trials have small patient numbers	Feasible, complications from high doses, may be beneficial for highly selected patients
Extremity soft-tissue	Yes	No	Yes	Yes	S + IORT + EBRT	24	Phase I/II	Only two trials published	Feasible, no evidence of advantage over existing techniques

Note: na = at these sites the whole organ was irradiated as resection was not desirable, C = chemotherapy, Comp. = comparative study, EBRT = external beam radiotherapy, IORT = intraoperative radiotherapy, NR = non-randomised, S = surgery

Source: See Appendix 5

Table 10: *Summary of IORT data for less frequently treated tumour sites*(Continued)

Tumour Site	Tumour type: Resectable	Unresectable	Primary	Recurrent	Treatment	Mean sample size	Study types	Data quality comments	Indications for IORT efficacy
Osteosarcomas	Yes	No	Yes	No	S + IORT ± C	23	Phase I/II	Only two trials published, used in multimodality protocol so difficult to assess role of IORT	Feasible, safety still questionable due to radiosensitivity of peripheral nerves
Biliary system	Yes	Yes	Yes	Yes	S + IORT + EBRT ± C	15 (bile duct) 15 (gall bladder)	Phase I/II Phase I/II NR Comp.	Variable treatments, some comparative studies	Indications of improved local control and survival
Bladder	na	na	Yes	No	EBRT + C + S + IORT or S + IORT + EBRT	6 (Shipley) 34 (Calvo) 117 (Matsumoto)	Phase I/II	Limited number of trials, varied treatment protocols	Feasible and safe, preliminary results for local control and disease-free survival are encouraging
Prostate	na	na	Yes	No	S + IORT + EBRT	21	Phase I/II	Only one trial published	Suggestion of achievable local control with minimal morbidity
Paediatric	Yes	No	Yes	No	Variable depending on site	28	Phase I/II	Few studies with few patients and short follow-up times	Safe and feasible in the short term

Note: na = at these sites the whole organ was irradiated as resection was not desirable, C = chemotherapy, Comp. = comparative study, EBRT = external beam radiotherapy, IORT = intraoperative radiotherapy, NR = non-randomised, S = surgery

Source: See Appendix 5

IORT in New South Wales

In New South Wales, use of intraoperative radiotherapy (IORT) has so far been restricted to occasional cases without dedicated facilities. Patients have been moved during surgery to a radiotherapy suite and then returned to theatre. The proposal put forward by the Royal Prince Alfred Hospital, Sydney (NSW), is for a facility which would integrate surgical and radiotherapy services at the same site.

Technical requirements

Overall facility design

In establishing IORT facilities, various factors such as potential patient numbers, available funding and the proximity of radiation and surgical facilities must be taken into consideration. In the early years of IORT use in Japan and the United States, the majority of IORT programs involved the transport of an anesthetised and surgically opened patient from the operating theatre to the radiotherapy department. In the absence of evidence to support the concerns of increased wound infection rates and catastrophes during transportation,[14,37,90,106,111] many large hospitals overseas have continued to operate their IORT programs in this manner. The main drawbacks of patient transportation have been logistical, with complex planning and scheduling required, and a pressure in many centres to perform IORT procedures outside standard working hours.[16,112]

Other options for IORT facilities, all of which are employed in various overseas hospitals, include:

- installing a dedicated radiation machine in a surgical suite;
- modifying an existing radiation therapy suite to meet operating room standards;
- constructing an operating theatre close to the radiotherapy department.

The option put forward in the 1993 Royal Prince Alfred Hospital report on IORT[113] is that of installing a dedicated machine in a surgical suite. The dedicated linear accelerator, contained in a shielded bunker, would be linked by a sterile corridor to an operating theatre complex which would allow access to the IORT machine from two different operating theatres.

As the report emphasises, 'this option has the advantages of convenience and control as the whole procedure is carried out in sterile conditions and the patient remains in the operating theatre at all times'. This type of IORT facility also offers the best potential for maximising use of this specialised facility and for avoiding the possible disruptions to facility scheduling within the radiation oncology department arising as a consequence of the degree of uncertainty in scheduling patients for IORT treatment. Although patients can be selected as appropriate for IORT treatment from preoperative assessment, the actual decision on whether to proceed with IORT cannot be made until the patient is in the operating theatre and the surgeon and radiation oncologist have directly examined the tumour and surrounding tissues.

There are two principal advantages of the Royal Prince Alfred Hospital proposal over the option of incorporating a complete operating theatre into a treatment bunker. Firstly, the Royal Prince Alfred Hospital proposed facility would permit the IORT treatment of non-scheduled patients by simply moving them from the operating suite in to the bunker as required. More particularly, by not tying up a linear accelerator with patients who at the time of surgery are not amenable to IORT treatment, the IORT machine could be more efficiently utilised.

Radiotherapy machine

Linear accelerators (linacs) are used almost exclusively in overseas institutions for the generation and delivery of high energy electrons during IORT treatment. Machines used include both standard linacs operating in the electron mode, and dedicated linear accelerators which are designed specifically for radiotherapy using electron beams.[114] The proposed machine for the Royal Prince Alfred Hospital IORT facility is a Siemens Mevatron ME Medical Accelerator—a high energy linear electron accelerator designed for specialised electron beam radiotherapy. As the hospital's report[113] and the IORT literature suggest,[114,115] there is obvious space saving (due to wall mounting) and reduced shielding requirements associated with the use of such machines. These dedicated machines also have multidirectional head rotation which facilitates alignment of the machine with the surgically placed applicator cone, and are lower in cost that conventional linacs.[114] The obvious limitation of a dedicated machine is that its use is restricted to patients in the IORT program as a consequence of the need to maintain sterile conditions in the radiotherapy suite.

In relation to requirements for the generation of high energy electrons, the majority of IORT patients would be treated with electron energies ranging from 6–15 MeV (6–9 MeV for microscopic residual disease and 12–15 MeV for gross residual disease after surgery).[11] However, the proposed use of the machine for the treatment of unresectable pancreatic cancer may require generation of electrons in the 18–20 MeV range.[11,39,116,117,118] As depth of penetration of electrons is important for unresectable cancers in the pelvic region, the ability to generate higher energy electrons would be an advantage (Sandeman, personal communication).

Additional capital/equipment requirements

Apart from the linear accelerator, the establishment of an IORT program requires the purchase of a range of additional equipment ranging from a specialised operating table to permit movement of the patient for positioning under the IORT machine, to close circuit television equipment for remote monitoring of the patient during the administering of the radiation. The equipment requests made in the 1993 Royal Prince Alfred Hospital report are consistent with well-detailed information in the literature.[12,14,112,114,119]

Staffing requirements and safety needs

The number and type of staff required for IORT treatment are documented in the current literature[11,16] and are dependent on the type of IORT facility used. More staff are required where patient transport is necessary. The Royal Prince Alfred Hospital proposal of one surgeon plus an assistant, one radiation oncologist, up to three theatre nurses, one anesthetist and an assistant, and one radiotherapist falls within the staffing guidelines available.

An increase in overall staff numbers with the addition of IORT to the existing radiation oncology program is not envisaged by the Royal Prince Alfred Hospital group in the short-term. To ensure that staff from the existing pool are available for performing IORT on those patients deemed suitable for such treatment at the time of surgery, careful rostering/scheduling will be required. Future staffing requirements would need to be considered once the workload of the facility is established.

The occupational health and safety of hospital staff is an important consideration in the proposed introduction of a new technology such as IORT. The remote administering of this type of radiation treatment precludes radiation exposure of treatment staff, and there is no risk to the attending nurse of exposure to radiation as might be the case with interstitial or intracavitary brachytherapy.[111]

Program planning and staff training

A point frequently stressed in the literature on IORT is the multidisciplinary nature of this treatment, with requirements for close cooperation between surgical, radiation oncology and radiotherapy departments. The development of an IORT program is most often undertaken by groups or institutions with expertise in multidisciplinary oncology, particularly surgical and radiation oncology.[12] As a major teaching hospital and a major cancer referral centre in New South Wales, the Royal Prince Alfred Hospital would appear to possess the necessary staffing requirements for successful operation of an IORT program.

Establishment of an IORT program at the Royal Prince Alfred Hospital would require a high level of planning, staff and resource scheduling, with some physics data collection and staff training also required.[11,12] The complexity of planning is reduced in the Royal Prince Alfred Hospital proposal by the IORT facility design. However, there would still be a need for efficient scheduling of treatment to overcome the possible disruptions to the overall radiation oncology department schedule caused by the difficulty of identifying the need for the IORT bunker and radiotherapy staff until the time of surgery. As with the installation of any new linear accelerator some machine-specific physics data would need to be generated.[16,114]

Differences in the standard physical and dosimetric approaches between external beam radiotherapy (EBRT) and IORT necessitates different technical requirements from radiotherapists, physicists and radiation oncologists.[114,119] Appropriate knowledge of applicator cones, adaptor systems, IORT dosimetry, field verification and the use of matching and multiple IORT fields is required for patient safety and quality assurance.[120] Adequate exposure of the tumour site for IORT treatment also requires additional experience amongst surgical staff.[6,112] Although some detailed procedural information is available in the literature, clinical observation and experience (most likely obtained in the United States) will be necessary for radiation oncology, surgical and radiotherapy staff to adequately establish an Australian centre for IORT (Sandeman, personal communication).

Potential patient numbers

The feasibility and economic viability of an IORT facility in Sydney will depend upon the pool of patients who are potentially suitable for IORT treatment. Patient numbers will be influenced by the incidence of different tumour types, the type of referral system operating, the proportion of patients with appropriately staged, non-metastatic disease, the proportion of those patients who are actually able to undergo IORT, and whether the program strategy is for treatment of a few well-documented tumour sites or for treatment of a broad range of sites, some treated in an experimental capacity.

The 1991 New South Wales cancer incidence and mortality data for the major tumour types which would be treated in the proposed Royal Prince Alfred Hospital IORT program are given in Table 11.

The proportion of such patients who would be at a suitable stage of disease progression (usually Stages II to IV) would represent a small but unknown subset of the total patient pool. As highlighted previously in this report, the actual delivery of IORT treatment to patients can only be determined at the time of surgery, after direct examination of the tumour and surrounding tissues. Although the most common reason for exclusion from further treatment is the evidence of regional metastatic disease, another potential source of patient exclusion, particularly for patients with abdominal/pelvic tumours, is the identification of numerous sites of tumour attachment to the intestines (Guiney, personal communication). Most large American institutions reporting their program findings in 1989 and 1991 indicated that in selected series of patients, the proportion of cases who actually underwent IORT treatment was just over 70%.[14,122,123] Other institutions report IORT delivery rates of 45–54% amongst selected series.[16,22] Although these treatment figures may improve over time with better preoperative diagnostic imaging and assessment, a certain percentage of patients is always likely to be excluded after surgical examination.

The IORT facility proposed for the Royal Prince Alfred Hospital is intended to have a maximum capacity for treatment of 800 cases per annum (based on the treatment of four patients per day over 200 days per year). The 1993 report proposes that approximately 102 patients would be treated in the first year of operation, with an increase to 260 patients per annum in subsequent years. The breakdown of IORT cases by tumour type taken from the report are detailed in Table 12. These potential patient numbers were estimated from retrospective examination of patient records to determine which patients would have been suitable for IORT treatment. Because of the difficulty of predicting IORT delivery until the time of surgery, these figures could be an overestimate.

The appropriateness of these IORT patient estimates in light of the available incidence and mortality data for New South Wales would be highly dependent on the type and extent of referral of patients to the Royal Prince Alfred Hospital facility. As is outlined in the 1993 Royal Prince Alfred Hospital report, this hospital is currently a major referral centre for New South Wales, and in some cases Australia, for gastrointestinal malignancies, gynecological cancers, sarcomas of the retroperitoneum, pelvis and extremities, thoracic tumours and malignant melanoma. This existing referral system would be significant in providing an important feeder system into the IORT program, but the issue of specific referral of potential IORT patients identified at other institutions remains to be addressed.

The referral of these patients to the Royal Prince Alfred Hospital facility is likely to be influenced by the perceptions of IORT treatment amongst referring radiation oncologists and surgeons. Referral, particularly from outside the Sydney area, is also likely to be influenced by the knowledge that patients may in fact be unsuitable for IORT treatment once they have been examined surgically at the time of scheduled IORT treatment at the Royal Prince Alfred Hospital. The movement of patients from their existing treatment environment to the Royal

Prince Alfred Hospital when IORT treatment cannot be guaranteed, may be considered inappropriate by some referring centres. The surgical examination of patients at their initial treatment institution before transfer to the Royal Prince Alfred Hospital for further surgery and IORT is also considered inappropriate (Guiney, personal communication). Certainly in the early stages of the program, interstate referral is likely to be small. A further issue for consideration is the likely need for the Royal Prince Alfred Hospital to provide post-IORT treatment such as external beam irradiation to patients specifically referred to the hospital for IORT treatment.

Table 11: *New South Wales cancer incidence and mortality data, 1991*

Tumour site	Incidence	Mortality
Rectal	1,131	498
Cervical	361	105
Stomach	585	472
Pancreas	493	449
Biliary System	171	147
Melanoma	2,010	307

Note: Figures for sarcomas are not available due to the recording of data on the basis of tumour site rather than type

Source: Coates et al.[121]

Table 12: *Breakdown of IORT cases of the proposed facility by tumour type (estimated)*

	Patient numbers (p.a.)	
Tumour	First year	Subsequent years
Rectal	50	100
Gynecological	30	70
Stomach, pancreas, biliary	10	30
Thoracic	2	10
Melanoma	5	30
Sarcomas	5	20
Total	**102**	**260**

Source: Houghton et al.[113]

IORT program strategy—tumour types and treatment outcomes

According to the report from the Royal Prince Alfred Hospital, the proposed program strategy would be to treat predominantly those tumour types for which there are reasonable clinical data available (rectal, gastric, pancreatic and sarcomas) but also to treat tumour types for which there is presently only limited (thoracic and biliary cancer) or no available evidence (metastatic melanoma). (See Table 12.)

Patients at the Royal Prince Alfred Hospital with metastatic melanoma are routinely operated on in order to remove abdominal metastases. IORT would be added to this procedure in an attempt to limit the recurrence of these tumours and minimise pelvic pain resulting from local disease progression. Concerns have been raised by other cancer treatment agencies over the intention of the Royal Prince Alfred Hospital to treat with IORT the abdominal metastases of metastatic melanoma patients due to the absence of clinical data for IORT treatment of such cases. Concerns have also been raised over the intention to treat the positive para-aortic nodes of cervical cancer patients. The difficulty of surgically accessing these nodes and the potential damage to the radiation-dose-sensitive ureters and major blood vessels, are issues which some Australian clinicians consider significant.

The proposed strategy for IORT use at the Royal Prince Alfred Hospital is as an adjunct to conventional treatment with curative intent. The intended outcome of IORT treatment is improved local tumour control with prevention or delay of pain associated with local tumour growth, improvement in patient quality-of-life and possible improvement in patient survival. For abdominal tumours in particular, failure to control the tumour at the primary site is considered the worst case scenario, and is associated with pain which is clinically the most difficult to treat. For patients with metastatic melanoma and unresectable pancreatic cancer, IORT would be delivered with palliative intent.

The curative focus of the IORT program proposed for the Royal Prince Alfred Hospital is in accordance with the program strategies described by overseas centres. In the absence of evidence for improved patient survival following IORT treatment, the Royal Prince Alfred Hospital program would need to demonstrate other benefits resulting from local tumour controls such as improved quality-of-life. Theoretically, that there would be benefits from local control in terms of improved quality-of-life are evident, but in the absence of good documentation of these benefits, the addition of IORT to conventional curative treatment is more difficult to justify clinically. Better documentation of the benefits arising from palliative IORT treatment would also be warranted as would an appropriate clinical comparison of IORT and other palliative techniques.

Economic factors

The issue of the cost-effectiveness of IORT has not to date been investigated. The absence of well-designed clinical trials examining the efficacy of IORT has prevented an examination of the important issue of whether IORT can reduce the health care costs associated with the treatment of cancer. Overall, the economic data available for IORT are limited to the results of two independent American surveys conducted in 1986 and published in 1989 covering 33 facilities in the United States.[124] This survey examined the major costs associated with the establishment of an IORT facility, the procedure charges associated with IORT delivery (such as physician fee and basic physics costs), the number of patients required to make a facility economically viable, and the additional treatment costs created by IORT. While the establishment costs and billing charges are difficult to translate into the Australian context, the latter two details may be of interest to the financial planning and management of the Royal Prince Alfred Hospital facility.

In relation to the IORT break-even analysis, while only 15 patients per year would be required to make a non-dedicated facility economically viable, for a dedicated facility with a linear accelerator to be viable, 238 patients per year would be required. The proposed treatment figure of 260 patients per year made by the Royal Prince Alfred Hospital seems to be of the right order for a dedicated facility (with consideration being given for likely differences in equipment and procedural costs between countries and across time periods). On the issue of additional costs associated with treatment of patients with IORT, the most complex analysis compared average billed charges before and after the introduction of IORT with cases matched for sex, age, and medical condition. This analysis, although not conclusive, suggested that in terms of length of stay, requirements for supplies and other special procedures, there were no significant additional costs associated with IORT.[124]

The 1993 IORT report by the Royal Prince Alfred Hospital provides detailed estimates of the capital costs associated with the establishment of the facility (including building works and equipment requirements), and the total recurrent costs (including salaries and wages, goods and services, and repairs and maintenance). These estimated costs are presented in Tables 13 and 14. In relation to salaries and wages, no overtime for existing medical, nursing or other staff is predicted at the Royal Prince Alfred Hospital, with overtime limited to physics and electronic technical staff. Costs associated with repairs and maintenance of the dedicated IORT are predicted to be minimised by employing existing electronic engineering staff, and by using a dedicated machine with the same basic components as the existing accelerator used in the Royal Prince Alfred Hospital Radiation Oncology Unit. Other costs are not detailed in the Royal Prince Alfred Hospital report, but should be given consideration in costing the establishment and operation of an IORT facility. These include costs associated with staff training, cost of keeping staff on stand-by for scheduled IORT treatments which are not undertaken, additional preoperative and postoperative assessment (particularly with diagnostic imaging) of patients treated in a clinical trial setting, effect of IORT on hospital stay and effect of IORT on requirements for other palliative treatments (such as bypass surgery and pain management drugs). The cost of providing additional treatment (such as external beam irradiation) and general patient care to cases referred to the Royal Prince Alfred Hospital specifically for IORT treatment would also need to be considered, particularly if this source of referral to the Royal Prince Alfred Hospital became significant.

Table 13: *Capital cost estimates of the proposed IORT project at the Royal Prince Alfred Hospital*

Capital cost item	**Cost ($)**
Building works	830,000
Equipment	
ME linear accelerator	1,100,000
Operating table	100,000
Spare parts including PCBs for console	60,000
Cooling unit	17,000
CCTV equipment	11,000
Support service equipment	16,000
Equipment total	*1,304,000*
Total	**2,134,000**

Source: Houghton et al.[113]

Table 14: *Recurrent cost estimates of the proposed IORT facility*

Recurrent cost item	**Cost ($ p.a.)**
Salaries and wages	5,000
Goods and services	2,000
Repairs and maintenance (based on probable costs)	27,000
Total	**34,000**

Source: Houghton et al.[113]

Discussion

While intraoperative radiotherapy (IORT) may have been in use for many years, it is still experimental in many respects. The quality of the data on the efficacy of IORT is poor, with no curative role for this technology yet established. For some cancers there is evidence of a significant effect on local tumour control with the suggestion that IORT may be a worthwhile intervention in terms of patient quality-of-life. This role is not well-defined with no direct measurement of quality-of-life provided in the clinical literature. Nor are there good comparisons with other approaches to treatment. At present, concurrent analysis of local control and complication rates is the only possible means by which to gauge the likely effect of IORT on quality-of-life. Important issues to decide are the extent to which a largely experimental technique should be supported within the State's health care system, the number of cases it would treat, the associated referral requirements and expected impact on health status. If the technology is introduced, the following points would need to be considered.

Need for a well-established IORT centre

There are obvious disadvantages to the ad hoc unmonitored, unreported treatment of patients with IORT in non-dedicated facilities requiring patient transport between surgical and radiation departments. There are a considerable number of facilities in the United States but very few report their clinical findings in the scientific literature. This suggests that most facilities are currently using unchecked, a still experimental treatment modality. Two Sydney hospitals are currently planning to undertake IORT in non-dedicated facilities and without established IORT programs. There are strong arguments for the establishment of a dedicated facility to be operated as part of an organised and monitored IORT program, if the technology is to be used in the State. Despite some reservations amongst clinicians in New South Wales and Victoria regarding the merits of IORT, there seems a definite consensus that IORT should not be allowed to develop ad hoc in non-dedicated facilities in Australia.

Need for clinical trials

Although IORT is used on a widespread basis in the United States and has been part of radiation oncology programs since the 1970s, the absence of good randomised controlled trials for this technology requires that it still be viewed as an experimental modality. This applies particularly to the less well-studied non-abdominal tumour types.

The proposed IORT program for the Royal Prince Alfred Hospital, Sydney (NSW), should be conducted within the context of close clinical monitoring and reporting of results as part of clinical trials. This requirement for procedural, outcome and complication reporting is especially vital for patients with metastatic melanoma, since no overseas clinical data are available for the IORT treatment of these patients. Good monitoring of Royal Prince Alfred Hospital patients as part of prospective clinical trials with a focus on local control and quality-of-life outcomes would provide Australia with world leading clinical data on the efficacy of IORT use. It would also be highly desirable to link clinical trails to economic studies, including measurement of the quality-of-life of patients.

Need for appropriate patient selection

With the establishment of the safety and feasibility of IORT for the treatment of a number of abdominal tumours there has been a tendency to use IORT for a whole range of tumour sites including tumours such as soft-tissue sarcomas of the extremities where there are already good results in terms of local control from the use of brachytherapy.[125] It is suggested that any IORT program established in New South Wales should not be directly tied to fulfilling patient quotas so as to prevent the recruitment of patients with inappropriate tumour types and possibly even tumour stages.

Establishment of an adequate referral base

Transfer of appropriate patients to the Royal Prince Alfred Hospital for IORT treatment will require knowledge of, and support for, the proposed clinical benefits of IORT by other medical centres. The dissemination of knowledge through some form of clinician education program would greatly assist in maximising the benefit to patients of a specific IORT treatment facility. In addition, given that good diagnosis would be needed to assess patients eligible for this technique, it will also be important to train radiation oncologists and other clinicians to identify those patients who are appropriate for IORT treatment. With a certain degree of scepticism prevailing amongst radiation oncology and therapy specialists over the benefits of IORT compared with existing treatment protocols it would be essential to have adequate reporting of treatment outcomes to encourage and sustain referrals to the Royal Prince Alfred Hospital centre.

Addendum

After completion of the text of this report, advice was received from Dr Harvey Wolkov, Radiation Oncology Centre, Sutter Memorial Hospital, Sacramento, California. He comments that:

- Clinical studies suggest an improvement in local control, and possibly survival, in patients who have locally advanced gastric carcinoma with evidence of nodal involvement or extragastric extension.
- Intraoperative radiotherapy (IORT) is the standard of care at several institutions in Japan in all patients with locally advanced gastric cancer. In the United States IORT is considered investigational in these patients.
- For advanced primary colorectal carcinomas there appears to be improved local control and a trend towards improved survival in patients with recurrent or locally advanced primary colorectal cancers, providing that gross resection can be performed.
- The role of IORT in the management of pancreatic carcinoma is largely palliative in nature.
- Patients with retroperitoneal sarcomas demonstrate improved local control and decreased chronic intestinal complications with the combined use of IORT and external beam radiotherapy (EBRT). There does not appear to be a survival advantage with IORT over EBRT alone. Further evaluation of IORT combined with preoperative versus postoperative EBRT, with or without aggressive chemotherapy, appears to be justified in advanced primary and recurrent retroperitoneal sarcomas.
- IORT has also been used in tumour sites such as lung, esophagus, bladder, prostate, brain and in pediatric malignancies. However, its role remains to be defined. Future directions will probably involve the use of radiation dose modifiers such as hypoxic cell sensitisers noted to improve the biological effectiveness of IORT.
- With respect to the economic aspects of this technology, it is hard to justify a dedicated IORT facility. However, there are clear clinical advantages to having IORT in a pre-existing operating room.

Appendix 1

Summary of studies on IORT and conventional treatment of primary advanced resectable and unresectable pancreatic cancer

Resectable

The IORT specific references examined for resectable pancreatic cancer are listed below:

(29) Sindelar et al., 1986
(43) Hiraoka et al., 1989
(34) Sindelar, 1989
(126) Abe et al., 1991
(127) Glaser et al., 1992
(50) Gotoh et al., 1992
(128) Grab et al., 1992
(10) Evans et al., 1993

Unresectable

Table 15 summarises the data available for IORT treatment (either alone or in combination with conventional treatments) for unresectable pancreatic cancer.

Table 16 summarises the data available for conventional treatment (EBRT ± chemotherapy) of unresectable pancreatic cancer.

Table 17 summarises the raw data available for the median survival time of patients following IORT or conventional treatments. Summary mean values derived from this table are presented in Table 5.

Table 15: *Results of IORT treatment of unresectable pancreatic cancer*

Reference	Study type	Treatment	Cancer stage	No. of patients	Results		
					Median surv. (mo)	% Local control	% Pain relief
Goldson 1981 * (18)	Phase I/II	IORT	unresectable	19	5.5	–	85
Hiraoka 1989 (43)	Phase I/II	IORT	unresectable	30	4.8	–	80
Sindelar 1986 * (28)	RCT	IORT + EBRT	unresectable	10	8.7	–	–
		EBRT		12	8.1	–	–
Abe 1987 * (129)	Phase I/II	IORT	unresectable	49	5.5	–	70
	Comp. NR	IORT + EBRT		20	12.0	–	–
Willich 1988 * (130)	Phase I/II	IORT + EBRT	unresectable	15	8.0	80 (1y)	93
Matsuda 1989 (47)	Phase I/II	IORT	unresectable	24	3.0	–	86
	Comp. NR	IORT + EBRT		30	11.0	–	–
Yamaue 1992 (26)	Phase I/II	IORT + EBRT	unresectable	9	7.0	–	71
Kawamura 1992 (38)	Phase I/II	IORT	unresectable	9	5.7	–	95
	Comp. NR	IORT + EBRT		12	11.8	–	–
Gilly 1992 # (131)	Phase I/II	IORT + EBRT	unresectable	27	9.5	–	75
Shipley 1984 ^ (134)	Phase I/II	IORT + EBRT + 5-FU	unresectable	29	16.5	64 (1y)	–
Tepper 1987 * (133)	Phase I/II	IORT + EBRT + 5-FU	unresectable	63	14.2	64 (1y)	50
Gunderson 1987 (116)	Phase 1/II	IORT + EBRT + 5-FU	unresectable	52	11.0	82 (1y)	–
Roldan 1988 (39)	Phase I/II	IORT + EBRT + 5-FU	unresectable	37	13.4	72 (1y)	–
	Comp. NR	EBRT + 5-FU		122	12.6	48 (1y)	–
Tepper 1991 (134)	Phase I/II	IORT + EBRT + 5-FU	unresectable	51	9.0	–	–
Kojima 1991 (33)	Phase I/II	IORT, EBRT, 5-FU + MM hyperthermia	unresectable	9	8.3	–	80
Calvo 1992 (117)	Phase I/II	IORT + EBRT + 5-FU	unresectable	25	10	72 (1y)	88
Willich 1992 # (44)	Phase I/II	IORT + EBRT or IORT	unresectable	30	7.2	–	90
Garton 1993 (118)	Phase I/II	EBRT + C + IORT	unresectable	27	14.9	78	–

Note: * = cited in Heijmans 1986 (188), ^ = cited in Gunderson 1987 (172), # = Abstract from Willech 1992 (175), Comp. = comparative study, EBRT = external beam radiotherapy; IORT = intraoperative radiotherapy, MM = mitomycin, NR = non-randomised, RCT = randomised controlled trial, 5-FU = 5-fluorouracil

Table 16: *Results of studies on conventional treatment of unresectable pancreatic cancer*

Reference	Study type	Treatment	Cancer stage	No. of patients	Results: Median surv. (mo)	Results: % Local control
Haslam 1973 # (136)	Phase I/II	EBRT	unresectable	23	7.5	–
Mayo Clinic 1969 # (137)	RCT	EBRT + placebo	unresectable	32	6.3	–
		EBRT + 5-FU		32	10.4	–
Moertel 1981 (138)	RCT	EBRT	unresectable	25	5.7	76 (2y)
		EBRT (4000 rad) + 5-FU		83	9.8	74
		EBRT (6000 rad) + 5-FU		86	9.4	73
Sindelar 1986 * (28)	RCT	EBRT	unresectable	12	8.1	–
Roldan 1988 * (39)	Phase I/II	EBRT + 5-FU	unresectable	122	12.6	20 (2y)

Note: * = cited in Heijmans 1986 (188), # = cited in Moertel 1981 (138), RCT = randomised controlled trial, EBRT = external beam radiotherapy, 5-FU = 5-fluorouracil

Table 17: *Median survival time (months) following IORT or conventional treatment of unresectable pancreatic cancer*

EBRT alone		EBRT + 5-FU		IORT alone		IORT + EBRT		IORT + EBRT + C	
Reference	MST	Reference	MST	Reference	MST	Reference	MST	Reference	MST
Moertel 1969	6.0	Moertel 1969	10.4	Goldson 1981	5.5	Sindelar 1986	8.7	Shipley 1984	16.5
Moertel 1969	6.3	Moertel 1961	9.8	Abe 1987	5.5	Abe 1987	12.0	Tepper 1987	14.2
Haslam 1973	5.7	Moertel 1981	9.4	Hiraoka 1989	4.8	Willich 1988	8.0	Gunderson 1987	11.0
Sindelar 1986	8.1	Roldan 1988	12.6	Matsuda 1989	3.0	Matsuda 1989	11.0	Roldan 1988	13.5
				Kawamura 1992		Kawamura 1992	11.8	Tepper 1991	9.0
						Willich 1992	7.2	Kojima 1991	8.3
						Yamaue 1992	7.0	Calvo 1992	10.0
						Gilly	9.5	Garton 1993	14.9
Mean value	**6.7**		**10.6**		**4.9**		**9.4**		**12.2**

Note: C = chemotherapy, EBRT = external beam radiotherapy, IORT = intraoperative radiotherapy, MST = median survival time, 5-FU = 5-fluorouracil

Appendix 2

Summary of studies on IORT treatment of gynecological cancer

Table 18 summarises the data available for IORT treatment of primary advanced and recurrent gynecological cancer.

Table 18: *Results of studies on IORT treatment of gynecological cancer*

Reference	Patient type	Treatment	No. of patients	Results		
				% Survival	% Local control	Median survival (months)
Yordan 1988* (85)	Recurrent	S + IORT + EBRT	15 (10 recurrent)	47 (>1y)	–	–
Dosoretz 1984* (84)	Recurrent	S + IORT + EBRT	5	40	–	–
Calvo 1992 (82)	Recurrent	S + IORT	19	57 (1y)	55 (1y)	–
Garton 1993 (83)	Recurrent	S + IORT + EBRT	21 (19 recurrent)	58 (2y) 33 (5y)	71 (5y)	– –
Konski 1993 (78)	Recurrent	S + IORT + EBRT	8	25 (2y)	–	9
Martinez 1993 (86)	Recurrent	S + IORT + EBRT	26[a]	7 (4y)[a] 33 (6y)[b]	33[a] 77[a]	– –
Goldson 1989 (76)	Primary + para-aortic	S + IORT + EBRT + B	19 (16 primary)	47 (1–3y)	–	17
Konski 1993 (78)	Primary + para-aortic	S + IORT	8	25 (5y)	–	31
Calvo 1992 (82)	Primary advanced	S + IORT + EBRT ± C	8	–	37.5 (1y)	–

Note: * = cited in Garton 1993 (118), [a] = disease recurrent to previous radiotherapy, [b] = disease recurrent to previous surgery, B = brachytherapy, C = chemotherapy, EBRT = external beam radiotherapy, IORT = intraoperative radiotherapy, S = surgery

Appendix 3

Summary of studies on IORT treatment of gastric cancer

Table 19 summarises the data available for IORT treatment of gastric cancer.

References describing the IORT treatment of gastric cancer which were unattainable or detailed preliminary results are listed below.

(4) Abe et al., 1981
(94) Abe et al., 1974
(95) Sindelar, 1988
(98) Guillemin et al., 1991
(99) Gerard et al., 1991

Table 19: *Results of studies on IORT treatment of gastric cancer*

					Results		
Treatment	Trial type	Patient type	Treatment	No. of patients	% Local control	% Survival (IORT)	% Survival (other)
Abe 1989 (90)	Phase I//II NR Comp.	Stages I–IV	S	110	–	87.5 (I) (5y) 83.5 (II)	93.0 (I) 61.8 (II)
			S + IORT	101	–	62.5 (III) 14.7 (IV)	36.8 (III) 0 (IV)
Calvo 1992 (93)	Phase I/II	Stages I–IV	S + IORT + EBRT + C	48	100 (I+II) (5y) 63.2(III) 61.6 (IV)	39.0 (5y)	–
Gilly 1992 (32)	Phase I/II	Stages I–III	S + IORT + EBRT	45	–	40.0 (3y)	–
Jiang 1992 (96)	RCT	Stages I–IV	S	100	–	64.8 (III) (5y)	30.4 (III) (5y)
			S + IORT	100	–	51.4 (III) (8y)	22.1 (III) (8y)
Kramling 1992 (97)	RCT	Stages I–IV	S	30	–	83.3 (9m)	95.7 (9m)
			S + IORT	23	–	–	–
Sindelar 1993 (30)	RCT	Stages I–IV	S (± EBRT)	25	8 (5y)	18 (7y)	16 (7y)
			S + IORT	16	56.3	–	–

Note: C = chemotherapy, Comp. = comparative, EBRT = external beam radiotherapy, IORT = intraoperative radiotherapy, NR = non-randomised, RCT = randomised controlled trial, S = surgery

Appendix 4

Summary of studies on IORT treatment of retroperitoneal soft-tissue sarcomas

Table 20 summarises the data on EBRT treatment of retroperitoneal soft-tissue sarcomas. Table 21 summarises the data on IORT treatment of retroperitoneal soft-tissue sarcomas.

Table 20: *Results of studies on EBRT of retroperitoneal soft-tissue sarcomas*

	Results	
Reference	**% Survival**	**% Local control**
Cody 1982 (139)	55 (5y)	–
Tepper 1984 (140)	54 (5y)	67 (5y)
Glenn 1985 (141)	23 (5y)	31 (5y)
Sindelar 1993 (31)	–	20 (5y)

Table 21: *Results of studies on IORT of retroperitoneal soft-tissue sarcomas*

			Results		
Reference	**Treatment**	**No. of patients**	**% survival**	**Median survival time (months)**	**% Local control**
Tepper 1989 (142)	EBRT + S + IORT	20	39 (5y)	–	50 (5y)
Willett 1991 (102)	EBRT + S + IORT	17	64 (dfs) (5y)	–	75 (4y)
Calvo 1992 (143)	S + IORT + EBRT	6	33 (5y)	–	50 (5y)
Kiel 1992 (144)	S + IORT + EBRT	28	–	22	–
Gunderson 1993 (103)	S + IORT + EBRT	20	48.5 (5y)	–	80 (5y)
Sindelar 1993 (31)	S + IORT + EBRT	15	–	45	60 (5y)

Note: dfs = disease-free survival, EBRT = external beam radiotherapy, IORT = intraoperative radiotherapy, S = surgery

Appendix 5

IORT-specific references available for less frequently treated tumour sites

Lung cancer
(145) Juettner et al. 1990
(40) Arian-Schad et al. 1990
(146) Calvo et al. 1991
(15) Calvo et al. 1992
(147) Calvo 1992 (abstract)
(148) Dubois et al. 1992

Head and neck cancer
(149) Garrett et al. 1987
(150) Garrett et al. 1989
(151) Schmitt et al. 1989
(152) Freeman et al. 1990
(153) Freeman et al. 1991
(154) Rate et al. 1991
(155) Calvo et al. 1992
(156) Garrett et al. 1992
(157) Katoshi et al. 1992
(158) Prades et al. 1992
(159) Rate et al. 1992
(160) Arimoto et al. 1993

Intracranial cancer
(161) Calvo et al. 1992
(162) Matsutani et al. 1992
(163) Rube et al. 1992
(164) Sakai et al. 1992
(165) Zhong et al. 1992

Soft-tissue sarcomas of the extremities
(4) Abe et al. 1981
(166) Calvo et al. 1989
(167) Calvo et al. 1992

Osteosarcomas
(168) Abe et al. 1989
(169) Calvo et al. 1992

Bladder cancer
(170) Matsumoto 1989
(171) Shipley 1989
(172) Calvo et al. 1990
(173) Calvo et al. 1992
(174) Calvo et al. 1993

Prostate cancer
(175) Takahashi 1989
(176) Abe et al. 1991

Biliary System cancer
(177) Todoroki et al. 1980
(178) Busse et al. 1989
(179) Todoroki et al. 1991
(180) Chen et al. 1992
(181) Hultenschmidt et al. 1992
(182) Todoroki et al. 1992
(183) Todoroki et al. 1992

Paediatric cancer
(184) Calvo et al. 1989
(185) Ritchey et al. 1991
(186) Calvo et al. 1991

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