Session 3: Intra-operative radiotherapy – creating new surgical boundaries

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Abstract

In patients with advanced and recurrent colorectal cancer, surgical resection with clear margins is the greatest challenge and is limited by known anatomical constraints. Preoperative or intra-operative assessment of the limits of surgical dissection may help to explore the possibility of improving resectability through either targeted external beam radiotherapy or intra-operative radiotherapy. Professor Chang reviews the evidence base and potential advantages and disadvantages of this approach, whilst the expert panel agree a consensus on the evidence for assessment and therapy of such patients.

Intra-operative radiotherapy (IORT) is not a new concept. It was introduced in the 1970s and 1980s as a technique to improve local control in locally advanced and unresectable tumours. It is typically combined with pre- or postoperative external beam radiotherapy (EBRT). Today it is used in conjunction with preoperative and, at times, repeat preoperative pelvic radiation therapy which is then followed by IORT.

There are advantages of giving a higher effective dose directly to the at-risk target in a single fraction, usually 10–20 Gy; there are reports of giving up to 30 Gy [1]. However, there are toxicity limits once you exceed 20 Gy [2,3]. Effectively what we are delivering is two to three times the external beam dose by delivering it directly to the tissues. Furthermore, the depth of penetration is between 0.5 and 1.0 cm. This is a major advantage here in that nontarget irradiation can be avoided.

There are a number of ways to deliver IORT. Conventional linear accelerators are stationary, and the same devices used for the delivery of EBRT in radiation suites can be installed in the operating room (OR). This used to be our standard approach at The University of Texas, MD Anderson Cancer Center; however, it is cumbersome and occupies OR space. Furthermore, radiation is delivered to through collimators and can only target tissues that are directly in line with the radiation source.

Nowadays there are mobile systems that have a lower energy and lower depth of penetration. One of the major advantages in the case of a mobile device is that shielding of the OR is not necessary.

At MD Anderson, we utilize an intra-operative high-dose brachytherapy delivery system using a Harrison–Anderson–Mick applicator. The advantage of this approach is that we can deliver radiation to target areas that are not in the direct line of sight from an external source, for example along the anterior pelvis in the supine position or against the prostatic bed during sphincter-preserving proctectomy. We can even use in in combination with minimally invasive surgery. Figure 1 shows a patient who underwent a robotic multi-visceral resection with IORT being delivered through a Pfannenstiel incision.

When to utilize IORT?

IORT is indicated for borderline-resectable tumours and tumours where the resection margin is predicted to be close – for both primary and recurrent cancers. It is useful when the resection margins, despite multivisceral or extended resection, are threatened. This is where we can start to think about some of the new frontiers, to utilize this as a method to improve resectability and for...
organ preservation. That is, to avoid multivisceral resection, such as of the bladder or prostate or sacral bone, in situations where we know that the reason for considering multivisceral resection is close proximity or adherence of the tumour, not infiltration by the tumour. Could IORT be an alternative to preoperative external beam therapy? That is an even more controversial issue that depends on the intent and goal of radiotherapy.

One of the only randomized trials to test the question of intra-operative radiation has been conducted by a French multi-institutional group. Patients were randomized to EBRT ± IORT. It showed no difference in local control or disease-free survival among patients who received IORT vs standard EBRT alone [4]. But one has to remember that in a study like this a number of these patients actually did not have fixed tumours. Many T3, rather than T4, tumours were included and the baseline recurrence rate was low. This study also treated the presacral plane.

So, in terms of improving local control in standard tumours, I think we have done a good job of doing that already thanks to the work of many of the people in this room. There is probably no role for IORT in the routine setting.

The data from Erasmus further confirms that the primary determinant of outcome is the completeness of resection (Table 1) [5].

However, amongst patients with close resection margins, local control rates were much better with IORT (10 Gy) than without: 50% with IORT and no durable local control without. Now we are starting to identify a population of patients in whom IORT can make a difference.

What about patients who have already been preoperatively or previously irradiated? Figure 2 shows data from Dr Haddock at the Mayo Clinic in 51 patients who had been previously irradiated either as adjuvant therapy for the original operation or as neoadjuvant therapy for their recurrence [6]. Again, stratification is based on the completeness of resection.

The median IORT dose was 20 Gy, but up to 30 Gy. There is potential for increased toxicity, but this is perhaps acceptable with dose tailoring. The authors concluded that re-irradiation with EBRT and IORT appeared to improve local control, but there was no comparison with a non-IORT irradiated group within this study [6].

Expert centres like the Mayo Clinic have been among the pioneers of IORT, yet this study highlights the challenges in studying this question. Because we have a very heterogeneous population of patients it is very difficult to make direct comparisons. Even so it is possible to start thinking about some of these questions.

Table 2 shows data from Heidelberg where patients received either pre- or postoperative EBRT [7]. Among 97 patients with recurrent rectal cancer, 54 also received EBRT. Some patients received IORT alone. Patients were stratified by completeness of resection (R0, R1 or R2). Among those patients who had R1 resection, the combination of IORT with EBRT was associated with a significant improvement in disease control when compared with IORT alone, but it is unclear what the effect was on the R2 patients.

So this again begs the question: can we enhance our local control achieved with standard treatments by adding IORT? It also suggests that IORT alone is probably insufficient for such complex disease.

A systematic review and meta-analysis conducted by Alex Mirnezami in collaboration with our group (at MD Anderson), Paris Tekkis and others [1] again highlights the challenge. Twenty-nine studies were included in this review, yet only about six studies were available for meta-analysis. But what we can conclude, whether we are looking at local control, disease-free survival or overall survival, is that there is an apparent benefit of
There is a tremendous heterogeneity in this literature and it therefore has to be taken with a grain of salt. However, the summary statistics show a benefit.

The primary toxicity of IORT appears to be wound related with an increased risk of wound toxicity with the addition of IORT.

A study from Memorial Sloan Kettering Cancer Center reviewed outcomes among 300 patients who underwent IORT, mostly for recurrent disease. The patients were categorized as negative margins, positive margins and close margins [8]. Their outcomes were stratified according to the resection status. In combination with IORT, these data suggest that while we can get improved results in patients with recurrent cancer it is unclear whether we can correct for potential deficiencies at the time of surgery. That is, with a close margin, can we get the outcomes with IORT to be as good as for patients with a negative resection margin status?

So what do we do at MD Anderson?

Here are data (Fig. 4) from 100 consecutive patients treated with IORT at MD Anderson. R0 resection was achieved for 54% of the patients and 46% were resected with R1, none were R2 [9]. Most of these patients had recurrent disease and most required multivisceral resection. With respect to either local recurrence or survival, the addition of IORT corrected the gap in outcomes. This would suggest that IORT was able to correct a close resection margin to improve resectability.

The follow-up data compare outcomes with and without IORT stratified by R0/R1 resection status [9]. The addition of IORT was associated with improved

Table 1 Erasmus data for 5-year local control and overall survival based on completeness of resection and whether IORT was given.

| Pathology status, n (%) | IORT* | Local control (%) | Overall survival (%) |
|------------------------|-------|-------------------|---------------------|
| R0, 85 (69%)           | No    | 71                | 56                  |
| R0, 19 (15%)           | Yes   | 72 (NS)           | 66 (NS)             |
| R1/R2, 8 (7%)          | No    | 0                 | 0                   |
| R1/R2, 11 (9%)         | Yes   | 58 ($P = 0.016$) | 38 ($P = 0.026$)    |

R0, complete resection; R1/R2, microscopic/macroscopic residual tumour; IORT, intra-operative radiotherapy; NS, not significant.

*IORT added for patients with margins ≤ 2 mm, after 1997 [5].

Table 2 Prognosis related to completeness of resection and EBRT/IORT.*

|               | EBRT + IORT, 3-year local control | IORT alone, 3-year local control | EBRT + IORT, 3-year overall survival | IORT alone, 3-year overall survival |
|---------------|-----------------------------------|----------------------------------|---------------------------------------|-------------------------------------|
| R0            | 83%                               | 79%                              | 72%                                  | 100%                                |
| R1            | 52%                               | 29%                              | 43%                                  | 31%                                 |
| R2            | 13%                               | 21%                              | 53%                                  | 17%                                 |
| $P$-value     | < 0.001                           | 0.028                            | 0.011                                | < 0.001                             |

EBRT, external beam radiotherapy; IORT, intra-operative radiotherapy; R0, complete resection without microscopic residual disease; R1, microscopic residual disease; R2, gross residual disease.

*Table 2, from Roeder et al. [7], is published under the terms of the Creative Commons Attribution License 4.0.
Figure 3 Meta-analysis of oncological outcomes following IORT for colorectal cancer, showing results for 5-year local control (A), 5-year disease-free survival (B) and 5-year overall survival (C). The diamond represents the overall treatment effect and squares are treatment effects for individual studies with 95% CI indicated by horizontal bars [1]. Reprinted from Mirnezami et al. [1]. Copyright (2013), with permission from Elsevier.

Figure 4 There was no difference in post-IORT overall survival in patients with positive (R1) vs negative (R0) microscopic margins [9]. (Reprinted from Hyngstrom et al. [9]. Copyright (2014), with permission from John Wiley and Sons.)
local control, with R1 patients approaching similar rates of local control as R0 patients. Similar findings have been found by Professor Harm Rutten in Eindhoven.

Positive margin patients have a high risk for local recurrence, whereas those achieving at least a 0–1 mm negative margin have similar rates of disease control with the addition of IORT. The addition of IORT seems to improve local control, although this study did not directly compare patients with IORT with those without [10].

So for patients who have a microscopically positive margin, we can see that the addition of IORT is perhaps one option that is available to improve resection outcomes. So now if we have a borderline resectable patient for whom, despite a radical extended resection, we know we are going to have a close margin, then perhaps the addition of IORT may be able to close that gap and expand our therapeutic window for surgery.

So the key questions that remain now are:

• Can IORT improve outcomes following resection of borderline resectable tumours?
• Can it facilitate organ preservation? For example, can an anterior tumour threatening the prostate or a posterior tumour abutting the sacral bone be resected using IORT in order to avoid the morbidity of exenteration or composite bone resection?
• Are there circumstances in which a single IORT fraction may be considered?

I would like to address these points briefly with this recent case, the kind of case we often see (Fig. 5). We know that despite extended resection in the lateral pelvis we are going to be dealing with a very close margin. Figure 6 shows the intra-operative photograph – not dissimilar to what you have seen. This resection resulted in a 1-mm negative margin which was treated with IORT. So we could not do anything further than what we have done in this operation without dramatically altering the resection. Yet we may be able to augment our result with the addition of IORT.

**What about the issue of a single dose?**

I just want to touch briefly upon radiation biology. There are two mechanisms of cell death – either mitotic death due to DNA injury or direct apoptosis with a high dose. The principle here is that cells that are producing DNA in S-phase are the most sensitive to radiation and not all cells will be in S-phase at the same time. So the concept of fractionation and delivery over a long course is that we are allowing an opportunity to hit the cells as they go through this cycle. But if we give radiation only once then there is going to be a population of cells that are not in the S-phase. So clearly there has to be another mechanism for those patients.

The TARGET A trial [11], with which I am sure those of you who are from London are quite familiar, is a trial that randomized women undergoing breast conservation therapy for early invasive ductal carcinoma: 20 Gy at 1-cm depth in a single intra-operative fraction with selective EBRT vs routine EBRT. There were two groups of patients in a pragmatic design. Patients received either IORT at the time of surgery or, if it was not known that they would need it, if the pathology details needed to be present and the system did not allow for that treatment at the time of surgery, patients received it at a second operation. The
wound was re-opened and radiation therapy was administered.

What we see here, if we just focus on the graphs (Fig. 7) of the patients who had pre-treatment assessment, is that patients who underwent EBRT vs single-dose IORT had local control rates that were not significantly different. In fact, the EBRT patient group actually had more deaths – although the difference was not statistically significant.

So it begs the question: if we have a situation such as that in Fig. 8 (a para-aortic recurrence) and we are going to approach this with surgery as part of a multimodality approach, there are a number of challenges with abdominal EBRT. EBRT to the abdomen may be a therapy that results in toxicity that is worse than the disease we are treating; but perhaps we can consider a multimodal treatment strategy of preoperative chemotherapy followed by lymph node dissection and high-dose IORT. Does that provide an opportunity for managing that kind of disease?

To summarize, we can rephrase the key questions:

Q1; Can IORT improve resectability of borderline resectable tumours and create new surgical boundaries?
A1; The hypothesis would be ‘yes’.

Q2; Are there circumstances in which a single IORT fraction may be considered in combination with chemotherapy?

A2; The hypothesis for that would then be ‘potentially’.

Discussion

Prof. H. Rutten: I would like to start the discussion with you about pushing the borders. We all acknowledge the need for a sufficient surgical margin, even after induction of neoadjuvant CRT [chemoradiotherapy]. With very close margins (smaller than 2 mm) IORT will help you to achieve a radical [resection] without increased [risk of] local recurrence.
So this is one of the questions I would like to discuss: is it possible that with an additional boost of radiotherapy our view on the extent of the required surgical resection in advanced and recurrent rectal cancer can be changed? Can we accept closer margins?

This is another question regarding re-irradiation for patients with locally recurrent rectal cancer, who have already been irradiated for their primary rectal cancer. There is some discussion whether it is safe to do this or not? We have pooled our data together with the Mayo–Rochester who use the same protocol as we have regarding IORT. In both institutes EBRT combined with chemotherapy is considered the optimal preoperative treatment for patients with locally recurrent rectal cancer. From these pooled data you can see that the re-irradiated patients in combination with chemotherapy have the same survival. In 217 patients who were re-irradiated [we observed the] same survival as in patients who underwent preoperative full-course CRT.

Prof. G. Chang: When you are re-irradiating them, how are you fractionating them?

Prof. H. Rutten: Fifteen fractions of 2.0 Gy or 17 fractions of 1.8 Gy once a day in combination with capecitabine 850 mg/m². This dose on the limited volume of the recurrent tumour could probably be pushed a little bit further.

If we look at R0 resected patients, the waiting time between the preoperative treatment and the surgery, when the IORT boost is applied, is not of importance. However, in R1 resected patients it is possible to reduce the local recurrence rate to a level comparable to R0 resected patients if you adhere to waiting times between 3 and 7 weeks. The effectiveness of IORT seems better.

Prof. J. Nicholls: With this we should also try and answer some of the session objectives: defining resectability in exenterative surgery [which] I think ties in a little with the use of RT [radiotherapy] to change resectability status.

Prof. H. Rutten: The first question really is, is IORT a possible approach either with a linear accelerator or high-dose brachytherapy to reduce the required surgical border and subsequently to perform less exenterative surgery?

Dr M. Hawkins: The challenge in the UK is that we do not have IORT facilities. So, [as] a way to get around that, we were considering doing stereotactic ablative EBRT as a boost. Either at the area at risk prior to the operation or we have done some cases postoperatively at the area where the surgeon indicates remaining pathology [is] at the resection margin; we think this definitely could improve local control.

Prof. H. Rutten: Would you be willing to accept a smaller surgical border when you had the possibility to give an extra boost? [For example] irradiate the prostate after obtaining a close margin instead of doing an exenterative procedure?

Dr M. Hawkins: I don’t know. [Would the surgeons] change their border if I [say] that the margin will be clear?

Dr J. Marks: I think Prof. T. Holm probably said it best – which is that he is showing a 60–70% survival if you have an R0 resection, so clearly the goal is, and will continue to be, to do en bloc resection with an R0 resection. We have been in favour of boosting the dose preoperatively, higher than 55/80 Gy, for these patients who had borders at risk to sterilize them for surgery. I think IORT is an excellent option for those patients who have something that [is] going to be stuck to the [pelvic] sidewall/bone/pelvis that you are not going to be able to resect en bloc. But in general, in our unit at least, we are not comfortable saying ‘I am willing to accept microscopic R1 lesion’ and then re-irradiating that.
Prof. H. Rutten: I [agree], an R0 resection is always the goal.

Prof. N. Mortensen: But it would be great to have this as a possibility. As you have mentioned, one of the dilemmas is invasion of the prostate. Can you do a prostatic shave? [This is] usually pretty unsatisfactory. Can you do a partial prostatectomy? We have had some combined operations where we have done that robotically. It would be great to say we can clean it up afterwards with IORT. At the moment we [are resecting] the lot out just in case. We have some patients who have had major exenterative surgery when there is nothing in the adjacent [structures].

Prof. H. Rutten: Our experience is that we do fewer sacral resections because we have the possibility of IORT. We perform frozen sections of the area at risk and if we see we have the smallest margin, we accept the margin and administer an IORT boost. This is something additional, and I think you can probably translate this biological principle into modern radiotherapy schemes.

Dr J. Marks: I think the other issue is that you end up [operating on patients] whom we might not otherwise have offered an operation to.

Prof. H. Rutten: Yes, that is true.

Audience: Can I be slightly provocative? IORT has always been centralized, obviously because of its limited availability. Isn’t the whole benefit of IORT not just [that it creates centralization instead of the IORT does something itself?]

Prof. H. Rutten: [It has] always being said that if you have a good surgeon you will have a lot of R0 resections and have a good outcome. On the other hand, we can see that we can accept the smallest margin with IORT, and don’t see an increased number of local recurrence and so there is a biological phenomenon. [Data pooled] with the Mayo Clinic showed that if you use IORT in a certain time window you can even correct for R1 resections. Prof. G. Chang [also] showed some patients with an R1 resection [who seemed to do as [well] as [those with a] R0 resection. We have a series of more than 200 patients where we can demonstrate this biological phenomenon which cannot be explained by good surgery. It is provocative, but I think there is something else going on too.

Prof. J. Nicholls: But at an individual level you cannot be sure that by giving IORT to a potentially R1 tumour, that you are not actually giving substandard local clearance in that particular case. Even though overall there may be a global difference in the two groups.

Prof. H. Rutten: Well you cannot rule that out totally, but [a trial of] randomized surgery is really not possible [as] the accrual of these kinds of patients would take too much time.

Prof. J. Nicholls: Should we move onto to defining resectability in exenterative surgery? We have three surgeons on the panel and a medical oncologists and a radiotherapist. Do the surgeons want to talk about where they think consensus might be reached on defining resectability?

Prof. R. Steele: I think it is all around R0 resection – if you can resect the tumour with adjacent organs then it is resectable if the [resection] is technically possible. I think this links with the argument around IORT – all surgeons know if you shave a tumour off it is going to come back if you don’t do something else. And whether IORT can help is still open to question. My view is that you have to do everything you can to get an R0 resection, and if that is not possible then [the tumour] is not resectable.

Prof. J. Nicholls: And that will be judged on your clinical examination and imaging pretreatment?

Prof. R. Steele: Yes.

Prof. J. Nicholls: [And also imaging] presurgery [but] after CRT?

Prof. R. Steele: Yes.

Audience: I think when talking about resectability it’s down to the radiologist, with the surgeons, to...
decide whether a tumour is resectable or not. Of course whenever we are talking about IORT to try and improve your chance of getting an R0, that again depends on which surgical team you are working with. There have been lots of surgical innovations in terms of dealing with tumours extending to the sidewall. So I think, nowadays, what was considered in that past as unresectable is now considered resectable. [With a good radiologist] you should be able to work that out without having necessarily to use radiotherapy.

Prof. G. Brown; One of the things we should consider voting on, I don’t know if it is realistic, is to say that there is a radiology assessment of what would be needed to get [an R0] resection but not necessarily a decision [about] whether it is resectable. That decision should be made by the surgeon. So what we would say is [that] in order to get R0 clearance, because [the tumour] is invading the sciatic notch, this patient would require [resection of the following] compartments, that would amount to a hemi-pelvectomy. We are not saying they are irresectable we are saying the patient would need a hemi-pelvectomy for R0. If radiologists started to do that generally, even in district general hospitals where they do not have access to exenterative surgeons, it may at least provoke the referral to the correct teams. I wonder if we shouldn’t actually set that as a standard?

Prof. R. Steele; I think that is the greatest challenge we face – [ensuring that] all patients [with] potentially resectable disease reach a unit where it is possible to do that. We can be certain in this country [that] the vast majority of [these] patients do not [reach these centres]. [This] is what we need to try to achieve.

Prof. N. Mortensen; To add to that in our small number of cases coming through in Oxford we ask for second opinions from Prof. P. Tekkis and Prof. G. Brown [as] our in-house radiologist may not be [able] to tell exactly which compartments need to be resected. I think [a] second opinion in this situation is really helpful.

Audience; I just want to echo the concept it is only possible to discuss what is and is not resectable and to discuss changing operations due to [MDT] discussions because of advances in imaging [and improved resolution]. All of these concepts go hand-in-hand and are inextricably linked.

Prof. J. Nicholls; So we have consensus that essentially the pathological anatomy is given to us by the radiologist and within the framework of that appreciation we then make a surgical decision on the extent of resectability [that can] be performed. Dr J. Marks would you agree?

Dr J. Marks; Absolutely. I would add that from the surgeon’s standpoint, that as well as [imaging], physical examination continues to be critical. In our unit [physical examination] is as important in terms of determining resectability and sphincter preservation. It is a clinical evaluation in conjunction with excellent imaging that allows you to make these type of critical decisions that push the boundaries for your patients.

Prof. J. Nicholls; Yes, along with an assessment of the general health and condition of the patient.

Summary of the key points
- An R0 resection margin is associated with best overall survival and should be the aim, even if this includes en bloc resection of adjacent organs.
- The definition of resectable disease varies between centres but requires clinical examination and high-quality imaging and radiology reporting.
- IORT may enable R0 resections without increased local recurrence where the margins are very close. The optimum time for IORT boost is yet to be confirmed but may be between 3 and 7 weeks.
- IORT may be an option to avoid en bloc resection of adjacent structures, for example if there is
minimal invasion of the prostate. Centre-specific experience has shown that fewer sacral resections are performed as a result of the availability of IORT.

- The biological process behind IORT is not well understood.
- There are some data to support re-irradiation for patients with locally recurrent rectal cancer.
- The UK does not currently have IORT facilities; stereotactic ablative EBRT as a boost may be an alternative.
- Radiologists, irrespective of whether they work in an exenteration centre, should report the structures into which the tumour invades and which compartments would need to be resected to achieve an R0 margin.
- Imaging provides the ‘pathological anatomy’ following which a surgical decision regarding the extent of resectability should be made with the findings of clinical examination and an assessment of the general health and condition of the patient.

Audience voting

**Question:** Preoperative EBRT of margins at risk should be considered equivalent in effect to IORT for centres without access to IORT in order to increase the R0 resection rate or indeed organ preservation rates in exenterative type surgery. Agree or disagree?

- **Strongly agree:** 8%
- **Agree:** 22%
- **Neutral:** 44%
- **Disagree:** 20%
- **Strongly disagree:** 6%

*Editors note:* There was no consensus on the use of EBRT. The audience required clarification of the term ‘local recurrence’ and it was felt that the distinction between EBRT and IORT was not required as these are both adjuncts. The question was rephrased to determine whether if IORT is not available is re-irradiation a sensible way to approach, i.e. can SBRT become equivalent of IORT?

**Question:** A trial is needed to test whether SBRT irradiation is equivalent in effect to IORT for centres without access to IORT to increase R0 resection rates? Agree or disagree?

- **Strongly agree:** 50%
- **Agree:** 34%
- **Neutral:** 8%
- **Disagree:** 5%
- **Strongly disagree:** 3%

**Question:** Radiological assessment of compartments that require resection should be performed to facilitate referral. Agree or disagree?

- **Strongly agree:** 61%
- **Agree:** 30%
- **Neutral:** 5%
- **Disagree:** 2%
- **Strongly disagree:** 2%

Disclosures

The authors have no conflicts of interest.

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