Prophylactic radiotherapy against heterotopic ossification following internal fixation of acetabular fractures: a comparative estimate of risk

Short title: Radiotherapy for HO prophylaxis

Full paper

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Abstract

Objective

Radiotherapy (RT) is effective in preventing heterotopic ossification (HO) around acetabular fractures requiring surgical reconstruction. We audited outcomes and estimated risks from RT prophylaxis, and alternatives of indometacin or no prophylaxis.

Methods

Thirty four patients underwent reconstruction of acetabular fractures through a posterior approach, followed by 8 Gy single fraction. Mean age was 44 years. Mean time from surgery to RT was 1.1 days.

The major RT risk is radiation-induced fatal cancer. The International Commission on Radiological Protection (ICRP) method was used to estimate risk, and compared to a method (Trott & Kemprad) specifically for estimating RT risk for benign disease. These were compared to risks associated with indometacin and no prophylaxis.

Results

Twenty eight patients (82%) developed no HO; 6 developed Brooker Class I, none developed Class II - IV HO.

The ICRP method suggests a risk of fatal cancer in the range of 1-in-1000 to 1-in-10,000; the Trott & Kemprad method suggests 1-in-3000. For younger patients this may rise to 1-in-2000; for elderly patients it may fall to 1-in-6000. Risk of death from gastric bleeding or perforation from indometacin is 1-in-180 to 1-in-900, in older patients. Without prophylaxis risk of death from re-operation to remove HO is 1-in-4000 to 1-in-30,000.

Conclusions

These results are encouraging, consistent with much larger series, and endorse our multidisciplinary management. Risk estimates can be used in discussion with patients.

Advances in knowledge

Risk from RT prophylaxis is small, it is safer than indometacin, and substantially overlaps with the range for no prophylaxis.

Introduction

Heterotopic ossification (HO) can develop around surgically reconstructed acetabular fractures or hip replacements and is an important cause of morbidity. Radiotherapy (RT) has an established place in prophylaxis against HO [1-10]. We have developed a systematic multidisciplinary approach to the management of patients with traumatic acetabular fractures. The fractures are reconstructed surgically, and when a posterior surgical approach to the acetabulum has been used, this is followed by RT prophylaxis. This development has been prompted in part by the rising numbers of traumatic acetabular fracture patients presenting here, especially since our centre's designation as a major trauma centre in 2012. Most of these fractures are the result of road traffic accidents (RTAs), which are the commonest cause by far [11].

Operative fixation of displaced acetabular fractures with open reduction and internal fixation has become the standard surgical management approach to these fractures [12], and overall, outcomes are improving [13]. HO is a particular complication of posterior acetabular fractures, and a posterior surgical approach is an important additional risk factor [14]. However, this may be the optimum approach to reduce displaced fragments and achieve the best possible anatomical restoration.

The most common symptoms and signs of HO are decreased range of movement and pain. More severe HO can lead to loss of joint mobility with decreased function, and the hip may even become ankylosed. In these circumstances, it is occasionally necessary to remove heterotopic bone, although full excision of the abnormal bone is extremely difficult and associated with unacceptable complications such as poor abductor function and abnormal gait. This is a clinical outcome worth avoiding whenever possible.

HO is most commonly quantified using the Brooker classification system [15]. This scores severity from zero to IV, where class IV represents ankylosis of the joint, and correlates well with functional outcome [16]. The incidence of HO ranges from 2% to 59% [13-15, 17], with severe HO rates of 15%, 21% and 38% in three series of patients following surgical reconstruction of acetabular fractures where prophylaxis was not used [7, 8, 18]. A meta-analysis of 3670 fractures found an overall risk of 26%, with significant HO (Class III or IV) occurring in 6%; in the majority (2173 patients), prophylaxis was either not used or not documented [17]. However, the risk of grade III & IV HO is higher with the Kocher-Langenbeck (posterior) surgical approach: this was specifically reported in the meta-analysis, which suggested a risk of severe HO of 12% [17]. This may be the most relevant figure for comparison with our results.

Patients with fractures resulting from RTAs may have a number of other associated injuries. Some of these, including head injuries, may further add to the risk of developing HO [19]. Such injuries also add to the complexity of management. Ventilated patients, for example may be considered more appropriate for post-reconstruction prophylaxis using indometacin rather than radiotherapy. An additional issue is that many RTA patients are relatively young, raising the question of risk versus benefit from the use of prophylaxis involving ionizing radiation.

The particular issue of risk from RT prompted us to review our overall management approach. The first step was to audit the outcome of patients treated with our multidisciplinary approach using post-operative RT, to ensure that our results matched other larger series. We also reviewed the published information on efficacy of the two established methods of prophylaxis, RT and indometacin. We then sought to consider the potential risks of RT prophylaxis, and to estimate the risks compared to the alternatives of indometacin treatment and no prophylaxis. We present and discuss these estimates of risk.

Materials and Methods

Audit of HO outcomes

The review of outcomes was registered with the Audit Department. Data was obtained and analysed in accordance with hospital guidelines. Between 1997 and 2012, 57 patients had radiotherapy for heterotopic ossification prophylaxis in our centre. Of these, 39 patients had undergone surgery for posterior fractures of the acetabulum. Thirty one were treated from 2005 onwards, averaging just under 4 per year, although this number appears to be rising, possibly related to major trauma centre designation.

In affected patients, HO increases post-operatively, typically reaching its maximum by about 12 weeks following surgery [6, 8, 18]. Thirty-four of the 39 patients had plain X-rays taken 12 weeks or more after surgery, and so were suitable for evaluation. The remaining 5 were lost to follow up, which is a hazard with RTA patients who may not live locally. Twenty five patients (73%) were male and 9 (27%) female. The mean age was 44 years (Figure 1). Road traffic accidents were the cause of the trauma in 85%. One fracture was the result of a rugby injury, one patient fell from scaffolding, one tripped and fell, and in two the cause of the trauma was not recorded. Twenty five (74%) sustained 1 or more other injuries, including 2 with head injuries.

All 34 patients had major fractures with or without dislocation requiring surgical reconstruction, aimed at restoring anatomical integrity. This allows early mobilisation, reducing morbidity and speeding discharge, and also improves the long term outlook [18, 20]. Surgery was carried out as soon as the patient was stable following the injury (mean 6 days, range: 0-17 days). In all patients a posterior Kocher-Langenback approach was used to provide optimal access for the reconstruction, and since it is this group who have a particularly high risk of developing HO, RT was given postoperatively. The mean time from surgery to RT was 1.1 days (range 1 – 5). Presence and severity of HO were assessed using the Brooker grading system [15] on the latest plain (AP) pelvis radiograph. The average time to the latest follow up plain radiograph was 110 weeks (range 13 – 534 weeks). None of the patients was pregnant when treated.

Five additional patients were originally intended to have RT: 4 had other injuries sufficiently serious to preclude RT, and the fifth could not be treated with RT within 96 hours, was treated with indometacin instead, and did not develop HO. Where RT prophylaxis is not possible, and provided there are no contraindications, we use indometacin 25mg three times a day for 6 weeks as an alternative.

The remaining 18 patients (of the 57) had all developed HO and received RT following excision or revision surgery. Three received radiotherapy following surgery to remove heterotopic bone which had formed around traumatic femoral fractures; 14 were treated following revision hip replacement and one after revision total knee replacement, where HO had developed after the original procedure. They will not be considered further here.

Radiotherapy Technique

Radiotherapy was planned from CT using ProSoma virtual simulator software (OSL, Shrewsbury, UK), except for the first few patients for whom a conventional simulator was used. The CT demonstrates the surgical reconstruction, and is therefore routinely passed to the hospital PACS system for review by the surgical team. The axial CT can also show the position of the ovary in premenopausal women, allowing confirmation that treatment avoids the ipsilateral ovary.

Anterior and posterior opposed fields are used, with the central axis closer to the medial field border to reduce divergence medially. The target includes the acetabular fracture, the musculature proximal to the greater trochanter including gluteus minimus [21], the lesser trochanter, and the muscle tissue lateral to the femur, excluding the skin laterally. Multi-leaf collimator shielding is used to reduce the volume treated, and especially to minimise dose to the pelvic contents and external genitalia. Similar fields are reported in other studies [10, 22]. Figure 2 shows an example of a case in which RT prophylaxis was not given as the result of severe additional injuries. The distribution of the HO is useful in identifying the target volume for treatment. HO can also develop in the musculature lateral to the greater trochanter [22]. The area posterior to the hip joint and neck of femur is also at risk. Indeed, a previous report described a technique to shield the femoral head in the hope of reducing late arthritis [22]. However, HO developed in 48% of shielded hips, compared to 20% of those not shielded, so this is not recommended.

Figure 3 shows the RT planning images for a patient who had reconstruction of posterior wall fractures from an RTA. Treatment was planned and delivered the day after surgical reconstruction, which has the advantage that the fracture is stabilized and any traction has been removed. The field shown in Figure 3 is defined as the 50% isodose, and must make some allowance for variation in set up on the linac. Our standard practice is to perform an electronic portal image of the anterior field before treatment, and to correct a discrepant position with an action level of 0.5 cm. Testicular shielding has been recommended by some [23], but we prefer to avoid placing uncomfortable bulky additional shielding between the legs, which could adversely affect patient positioning.

A standard single dose of 8 Gy (central axis mid plane) is delivered with a linear accelerator, with energy of 6, 10 or 15 MV, with one of the higher energies preferred for larger patients. At the beginning of the prophylactic RT programme, a dose of 8 Gy, rather than 7 Gy, was chosen in order to harmonise with other single fraction treatments, especially those given for bone metastases, for which 8 Gy is a widely used and evidence-based dose. We prefer to plan and treat the patient the day after surgical reconstruction to minimize the delay (see below). Typically, the patient is more comfortable and confident in moving from bed to scanner and treatment couch following reconstruction. RT is more traumatic prior to the fracture being reconstructed, and timing of surgery is sometimes unpredictable. We therefore prefer to give early RT post-operatively; the reverse is true

for revision hip replacement prophylaxis, when pre-operative RT is more comfortable and convenient for the patient.

Although non-union can occur with RT, this is less relevant where internal reconstruction has been performed, and can also occur with indometacin [23, 24]. RT does not affect healing of other fractures, unlike systemic indometacin [24].

Estimates of risk

We sought to estimate the risk of fatal complications from 3 potential treatment strategies, namely RT prophylaxis, prophylaxis with indometacin, and no prophylaxis. The most important risk associated with RT for HO is fatal radiation-induced cancer. However, a risk of death is also associated with indometacin therapy, even of short duration, particularly from gastro-intestinal complications. In addition, there is a (small) risk of death associated with re-operation in patients who go on to develop severe HO. We have not attempted to address non-fatal side effects, nor to estimate effects of HO on quality of life.

Estimating risk from RT

A method to estimate the risk of fatal radiation-induced malignancy over the lifetime of the patient is provided by the International Commission on Radiological Protection (ICRP) [25]. It is based largely on epidemiological studies of individuals exposed to whole body low dose irradiation, particularly survivors at Hiroshima and Nagasaki, and provides an estimate of global population risk, irrespective of age. However, this is designed explicitly for use in protection. Although not intended for application to the risks from therapeutic exposure, it does provide a methodology which considers different tissues and different volumes of tissue. The method involves calculating the mean organ dose for relevant organs at risk, multiplying this by an organ weighting factor [25], summing these and finally multiplying by the recommended risk factor. We assumed 8 Gy exposure to 2% of the bone marrow and bone surface and 1% of the skin and muscle, with ICRP tissue-weighting factors of 0.12 for marrow and 0.01 for these other tissue. The risk factor is normally quoted as 5% per sievert (Sv) [25]. However, this applies to the whole population, including children, and the ICRP suggests a risk factor of 4.1% per Sv for an adult population. However, the ICRP method is explicitly *not* intended for prediction of risks from therapeutic radiation [25], and moreover, it is thought to over-estimate the risk, possibly by as much as 1 – 2 orders of magnitude [26, 27]. We have not attempted to model scattered doses [28].

Another approach is to consider the number of cases of malignancy in patients treated with RT, for either malignant or benign tumours, although most series relate to treatment of malignancy. Case reports of malignancy related to RT for HO prophylaxis, whilst important, do not provide estimates of incidence since no denominator of unaffected cases can be provided.

Trott & Kemprad [26] developed a procedure specifically for estimating cancer risks after radiotherapy of non-malignant diseases by using direct evidence derived from epidemiologic data in patients who were treated using irradiation in the past. They included allowance for field size and modifying factors, such as risk genes like retinoblastoma, to produce risk estimates relevant to clinical situations such as RT prophylaxis against HO.

The difference in risk for different age at exposure is difficult to assess, although some data are available from the National Research Council of the National Academies BEIR VII Phase 2 report [29]. This comprises data on estimates of risk of death from cancer attributable to whole body radiation exposure according to age at exposure, from birth to age 80. The most relevant data relates to risk of 'other' tumours, which excludes central pelvic and thoracic tumours, and breast cancer.

Estimating the risk from use of indometacin

Estimates of risk are based on published series of patients taking indometacin, or similar drugs, who develop complications, often concentrating on older patients who are at higher risk. We sought reports which might provide risk estimates, although have not undertaken a systematic literature review. These have been combined with surgical estimates of risk of death from the known major gastro-intestinal complications of perforation and haemorrhage.

Estimating the risk from use of no prophylaxis

Although slightly artificial, a risk of death can be considered to exist for patients who develop severe HO, since a proportion may require further surgery to reduce morbidity, carrying a risk of peri-operative death. Estimates are based on the incidence of severe HO, the proportion requiring surgery, and estimates of risk for elective surgery.

Results & Discussion

Results of clinical series

In our small series of 34 patients, plain radiographs demonstrated that 28 (82%) patients developed no heterotopic ossification. Six (18%) developed Brooker Class I HO and none developed Class II, III or IV. One of the patients with Brooker Class I HO had the additional risk factor of an associated head injury. These results compare favourably with the published risk of severe HO of 1 in 8 (12%) in patients requiring a posterior surgical approach [17], even though our series is small. As noted above, 5 patients were unable to receive RT: 2 received indometacin, one remaining free from HO, the other developing grade III HO; 3 had no prophylaxis and developed grade I, grade III and grade IV HO. This provides endorsement for the use of prophylaxis, as discussed below.

RT and indometacin as prophylaxis against HO

The clinical features of ankylosis and reduced function only appear in grade III and above. Therefore, prophylactic therapy is aimed at reducing significant HO of a higher degree [16]. Timing and dose of prophylactic radiotherapy have been established over some years, with large randomized controlled trials providing robust data. Early reports of RT as HO prophylaxis typically used modest doses such as 20Gy in 10 fractions, similar to schedules known to impair bone growth [1]. In historical cohorts, 10Gy in 5 fractions was found to be as effective as 20Gy in 10 fractions [2]. A randomised trial of post-operative RT demonstrated no difference between 10Gy in 5 fractions and 17.5Gy in 5 fractions [4], endorsing the lower dose. Subsequent

studies have shown that single fractions are just as effective, provided doses of 7 Gy or more are used [2, 3, 5, 10].

No difference in outcome was found in patients randomised to pre-operative RT (≤ 4 hours before surgery) or post-operative RT (≤ 96 hours post-op) [4]. However, delays beyond 3 – 4 days have higher rates of HO [7], with rates rising dramatically for delays of more than 3 weeks [10].

Indometacin has also been used for prophylaxis, but appears less effective. In a randomised trial, 301 patients received postoperative RT with either 5 or 7 Gy or indometacin [5]. Overall rates of HO were 30.1%, 11.1% and 16.0% respectively. Statistically 5Gy was least effective, and 7Gy and NSAID were equivalent. However, for HO grades III and IV, 7Gy was significantly more effective than NSAID, though both treatments had low rates (0% versus 1.7%). Rates of severe HO after surgery and RT of 9% compared to 18% for indometacin [6], and 4% versus 11% [8] have been reported. Sixteen patients who did not receive prophylaxis all developed HO, 38% with grade III or IV [8]. In a meta-analysis based on 5 prospective studies, describing 384 patients, the incidence of Grade III and IV HO was significantly lower in patients treated with RT (3%, 5 of 160) than those who received indometacin (9%, 20 of 224) ($p \approx 0.04$) [9].

There is evidence of efficacy of NSAIDs in preventing HO after hip arthroplasty, with a suggested reduction in risk of HO after hip arthroplasty of a half to two thirds [30, 31]. However, there are some clear reports of lack of efficacy after reconstruction of acetabular fractures [18, 31-33]. In a randomized study of a six-week course of indometacin or no prophylaxis in 107 patients, no statistically significant difference was seen in overall rates of HO (47.7% versus 56.8%) or rates of grade II or more [33]. A similar finding was reported in a further randomised trial of 121 patients [18]. Indometacin once daily for six weeks was compared to placebo in patients with displaced fractures of the acetabulum reconstructed through a Kocher-Langenbeck approach. There was no statistically significant reduction in the incidence of severe (Brooker grade III – IV) HO with the use of indometacin compared to placebo (15.2% in the indometacin group, 19.4% for placebo). Based on the results, the authors now recommend against the use of indometacin for HO prophylaxis [18, 32]. Problems of compliance with indometacin treatment have also been reported [6, 18]. Overall, these data suggest that radiotherapy is more effective than NSAID, provided doses of 7Gy or more are used.

This approach of using RT as prophylaxis against HO in high risk surgical cases appears to be uncommon in the UK. In an informal survey, with responses from 30% of UK centres, no other centre is using RT is this way. One centre reported using RT as HO prophylaxis after repair of fractures around the elbow, and 47% have used RT after revision hip surgery when HO is known to have occurred.

Overall, the results of this small series, especially the complete absence of any patients with severe HO, compare favourably with large published series [2-10, 13-15, 17]. They provide a context for estimates of risk and endorse our multidisciplinary approach of meticulous surgical reconstruction and post-operative RT. Where this is operationally or clinically impossible, indometacin 25mg three times a day for 6 weeks has been used, but is not favoured in older patients.

Estimate of risk from RT

In this context, the major risk from RT is malignancy. The ICRP methodology [25], with a risk factor of 4.1% per Sv for an adult population, provides an upper limit for the risk of fatal radiation-induced malignancy over the lifetime of the patient. Using this method, the estimated risk from RT for HO prophylaxis at the hip is around 0.092%, or 1 in 1092 (Table 1). For practical purposes of patient information, rounding to a risk of 1 in 1000 is appropriate. This risk is delayed by an average of approximately 15 years [34, 35]. However, the ICRP method is explicitly *not* intended for prediction of risks from therapeutic radiation [25]. It provides an estimate of global population risk, irrespective of age. It is also thought that the method may over-estimate the risk, possibly by as much as 1 – 2 orders of magnitude [26, 27]. Assuming the more conservative level of over-estimate reduces the risk of RT-related death to 1 in 10,000, although it may be even lower. These figures provide estimates of the likely upper and lower limits of risk (Figure 3).

Another approach is to consider the number of cases of malignancy in patients treated with RT, for either malignant or benign tumours, although most series relate to treatment of malignancy. Although rare, the incidence of radiation-induced sarcoma (RIS) after RT, using high cancer treatment doses rather than low prophylaxis doses, has been estimated to be around 0.1% (i.e. 1 in 1000) [36], although may be half that, 1 in 2000, in patients treated with megavoltage RT [36]. This is consistent with a report [37] of soft tissue sarcomas (n=20) and osteosarcomas (n=27) arising in 38,000 patients treated with orthovoltage radiotherapy for a variety of benign and malignant conditions, including retinoblastoma, over 50 years. Ten of these arose in individuals treated as children. Interestingly, and relevant to the issue of HO prophylaxis, no cases occurred with doses less than 30Gy.

There are two reports of radiation-induced sarcoma post HO prophylaxis. One patient received 2 x 7 Gy and developed sarcoma after 18 years [38] and the second had a single 7 Gy and developed sarcoma after 11 years [39]. These reports are important but do not provide estimates of incidence since no denominator for unaffected cases is provided.

The method of Trott & Kemprad [26], developed specifically for estimating cancer risks after radiotherapy for benign disease, is highly relevant. The main tissues at risk are the bone, muscle and other soft tissue, and bone marrow. Taking the risk for radiation-induced sarcoma after treatment of benign disease as 1 in 100,000 [26], with the risk for induction of leukaemia as 1 in 3125 (assuming 2% of the bone marrow exposed), and the leukaemia risk estimate as 0.2% per 1 Gy whole marrow exposure [26]), gives an estimated risk of 1 in 3000. This risk estimate falls within the range estimated above, using the ICRP methodology. Were there to be a small incidence of severe HO requiring surgery, the additional risk associated with surgery makes a negligible difference to these estimates.

The motivation for attempting to estimate risk was prompted by the recognition that some of the patients requiring consideration of RT prophylaxis are relatively young (Figure 1). Specifically, in our patient group the mean age was 44, 15 (44%) were under 40, 5 (15%) were under 30, and the youngest patient treated was only 21. This led to the additional need to evaluate risk for different ages at exposure, although this is notoriously

difficult to assess. Some data are available from the National Research Council of the National Academies BEIR VII Phase 2 report [29]. The most relevant data are for 'other' tumours, thus excluding central pelvic and thoracic tumours, and breast cancer, an important risk organ for whole body exposure in women. Normalizing to our mean age of 44, the BEIR data suggest a small increase in risk for patients below 30 and a large reduction in risk for older patients. Taking a risk of 1 in 3000 as the starting point, these numbers convert to 1 in 1900 or 1 in 6400 for a patient of 20 or 70 respectively. For simplicity, these could be rounded to 1 in 2000 or 1 in 6000.

Estimating the risk from use of indometacin

Indometacin is the only drug proven to be effective against the development of HO following acetabular surgery. It is considered the gold standard NSAID for HO prophylaxis [23, 40], although other non-steroidal anti-inflammatory drugs (NSAIDs) have been used [30, 31], and may be effective after hip arthroplasty [40]. There is some evidence of efficacy, as noted above, but his has not been consistently replicated [18, 31-33].

However, indometacin also appears to be amongst the most toxic of the NSAID drugs [41]. In their meta-analysis of NSAIDs, Fransen + Neal [30] identified 5% of patients to have experienced gastro-intestinal toxicity, including 1.5% with serious toxicity. They were unable to comment on the risk of death. A separate review [42] reported that there was clear evidence that NSAIDs increase the early risk of upper gastrointestinal complications, suggesting that patients taking a short course are not be exempt. They also reported that "only" 2% of upper gastrointestinal complications were recorded as being fatal. Indometacin is also associated with a risk of non-union in fractures away from the hip [23, 24], which is relevant for patients experiencing poly-trauma such as occurs with RTAs.

Here, only risk of immediate death from intestinal perforation or haemorrhage will be considered, although other adverse effects occur and may be serious [43, 44]. In patients aged 65 and over who were admitted with peptic ulcer or upper GI bleeding following non-aspirin NSAID use, 53% had at least one serious complication and 11% required surgery [45]. The greatest risk was in the first month, a time frame analogous to HO prophylaxis. Patients of 60 and over who used NSAIDs were 4.7 times more likely than non-users to die from ulcer disease [46]. In a meta-analysis of 16 studies on serious GI complications [47], NSAID users were roughly 3 times more likely to have a serious GI complication than non-users, with increased risk in patients of 60 and over, and in the first few weeks of administration. The overall prevalence of serious gastrointestinal complications was 1 per 1000 in the first year [47].

Some of the reservations about indometacin were illustrated in a randomized, prospective double-blind placebo-controlled clinical trial of the drug after the operative treatment of acetabular fractures [18]. Overall, 53% developed HO, which was severe in 17.3%. No significant difference in the incidence of HO was found between indometacin and placebo groups. However, 20% of the indometacin patients withdrew because of side effects which were serious in 3% (one haemorrhage and one perforated ulcer). Compliance with the medication was also problematic, an issue also noted by others [6]. This, combined with the rate of complications, led the authors to terminate the study early, and recommend against the use of indometacin in HO prophylaxis. Others

have used misoprostol to aid in prevention of GI complications, although its routine use remains controversial [44].

Taking a figure of 11% of patients (≥ 65 years) requiring surgery [45], and assuming a 1% peri-operative mortality, gives an estimated mortality of 1 in 900 (Table 1). This assumes that every patient with life-threatening complications reaches the operating theatre alive. This risk is immediate and matches the figure for serious GI complications from Gabriel et al [47]. This is consistent with a risk of death of 2% in patients experiencing GI complications [42], if about half of patients taking the drugs experience these [45]. Some sources suggest that the risk in emergency surgery for perforation or haemorrhage may be rather higher, in the range 5-10% [48, 49]. Taking a 5% figure increases the risk to 1 in 180, at least in the over 60s. The additional risk associated with surgery for HO resulting from failed indometacin prophylaxis makes little difference to these estimates.

In our series, 21% of patients were 60 or over, and the oldest was a man of 72. The risk in older patients is fairly clear, and remarkably high, even with short exposure. Unfortunately, data do not appear to exist (or be available) on the risk at younger age. Qualitatively, it appears to be less, perhaps considerably less, than in older patients. Nevertheless, the efficacy of indometacin treatment may also be less than RT, and compliance remains a concern.

Estimating the risk from use of no prophylaxis

Although slightly artificial, a risk of death can be considered to exist for patients who develop severe HO, since a proportion may require further surgery to reduce morbidity, carrying a risk of peri-operative death. In the meta-analysis, the overall risk of severe HO following surgery using the Kocher-Langenbeck approach was 11.6% [17]. The mean delay before reoperation was 2 years [17]. In another large series, 22.5% patients who developed severe HO required further surgery, with a mean interval of 24 months [14]. Combining these suggests that 2.6% of patients without prophylaxis (or with failed prophylaxis) would need re-operation. If the risk of peri-operative death is 1%, this gives an upper limit of risk of around 1 in 4000 (Table 1). A systematic review of peri-operative mortality [50] suggested an overall risk of peri-operative death of 0.12%. Using this figure suggests a risk of around 1 in 30,000. This does not include the risk of malignancy from RT given as prophylaxis after second surgery, but since only 2.6% of patients are estimated to require second operation, this does not materially change the overall estimates.

Comparing risk estimates

These methods can achieve a population estimate of risk, within broad limits. The use of a range of risk acknowledges the uncertainty but at the same time provides at least approximate limits on the upper and lower values of risk. For RT prophylaxis the risk estimates are in the range 1 in 1000 to 1 in 10,000, and the treatment is effective (Table 1). The risk of developing severe HO after a posterior Kocher-Langenbeck surgical approach without prophylaxis is reported to be about 1 in 8. The risks associated with re-operation for severe HO are in the range 1 in 4000 to 1 in 30,000, the exact figure depending on the mortality rate for elective surgery. These ranges overlap considerably, emphasizing their similarity, and also indicating the difficulties in providing precise estimates of risk. The absolute risks are small, lower by several orders of magnitude than the lifetime

risk from spontaneous cancer, which is about 1 in 3, and, assuming a global 50% cure rate, a risk of death of 1 in 6.

The risk associated with indometacin prophylaxis is rather high, at least in older patients. Some authors have reported stopping this form of treatment because of observed complications [18]. Our current work to estimate the risks of different approaches has influenced our practice such that we avoid indometacin wherever possible, and certainly in older patients.

This work was driven by the clinical need for us to evaluate our practice and also to provide information to patients considering RT prophylaxis. This was relevant for younger patients in whom RT risks might be larger and older patients in whom indometacin risks might be higher. These results, together with the review of published work from large series, have allowed us to provide more balanced recommendations to patients, and underpin our clinical protocol for multidisciplinary management.

Conclusions

Our clinical results of multidisciplinary management of patients with traumatic pelvic fractures are encouraging and compare well with published studies, with a minority of patients developing only Grade I HO, and none suffering severe grades. We attribute this to early intervention with meticulous surgical technique and reconstruction, followed by timely post-operative radiotherapy. Estimates of risk of death from fatal radiation-induced malignancy are in the range of 1 in 1000 to 1 in 10,000, with 1 in 3000 being a credible mid-range figure. For younger patients this might rise to 1 in 2000, while for older patients it may fall to 1 in 6000. This is substantially lower, by several orders of magnitude, than the lifetime risk of spontaneous cancer. Prophylaxis with indometacin is less effective with a higher risk of death from complications, of 1 in 900 or more. Omitting prophylaxis obviously carries the lowest estimated risk, in the range 1 in 4000 to 1 in 30,000, but with a 1 in 8 risk of developing severe (grades III-IV) HO. Overall, the risk from RT prophylaxis is small, and the estimated range substantially overlaps with the range for no prophylaxis, suggesting it is safe as well as effective.

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Conflict of Interest Statement

There are no conflicts of interest to declare.

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Figure legends

Figure 1. Frequency distribution of age of the 34 treated patients. Mean age was 44.4 years, median 41.5, range 21 – 72. Note that 15 (44%) were aged under 40.

Figure 2.

Pelvic X-rays of a 37 year old patient who suffered a fracture dislocation of the left hip requiring reconstruction. Multiple other injuries, including pneumothorax and compound fractures at the knee, precluded early post-operative RT, which would otherwise have been recommended. No alternative prophylaxis was given.
(a) Postoperative film. Skin sutures and a catheter can be seen.
(b) Follow up film at 14 months, with Brooker grade IV HO. This was evident within weeks of the reconstruction. Note the spur of HO extending from the acetabulum to ankylose the joint (arrowed). HO had also formed posteriorly and can be seen in projection just above the lesser trochanter.
(c) 8 months following revision total hip replacement, performed at 19 months, with prophylactic RT delivered the following day. No HO has reformed.

Figure 3.
(a) Digitally reconstructed radiograph (DRR) showing the RT anterior field projection, in a young woman with a complex posterior acetabular fracture dislocation requiring reconstruction, following an RTA. The ovary, fully shielded, is shown in light blue.
(b) Coronal CT reconstruction with the projection at depth of the anterior treatment field with corner MLC shielding, and ovary contour.

Figure 1

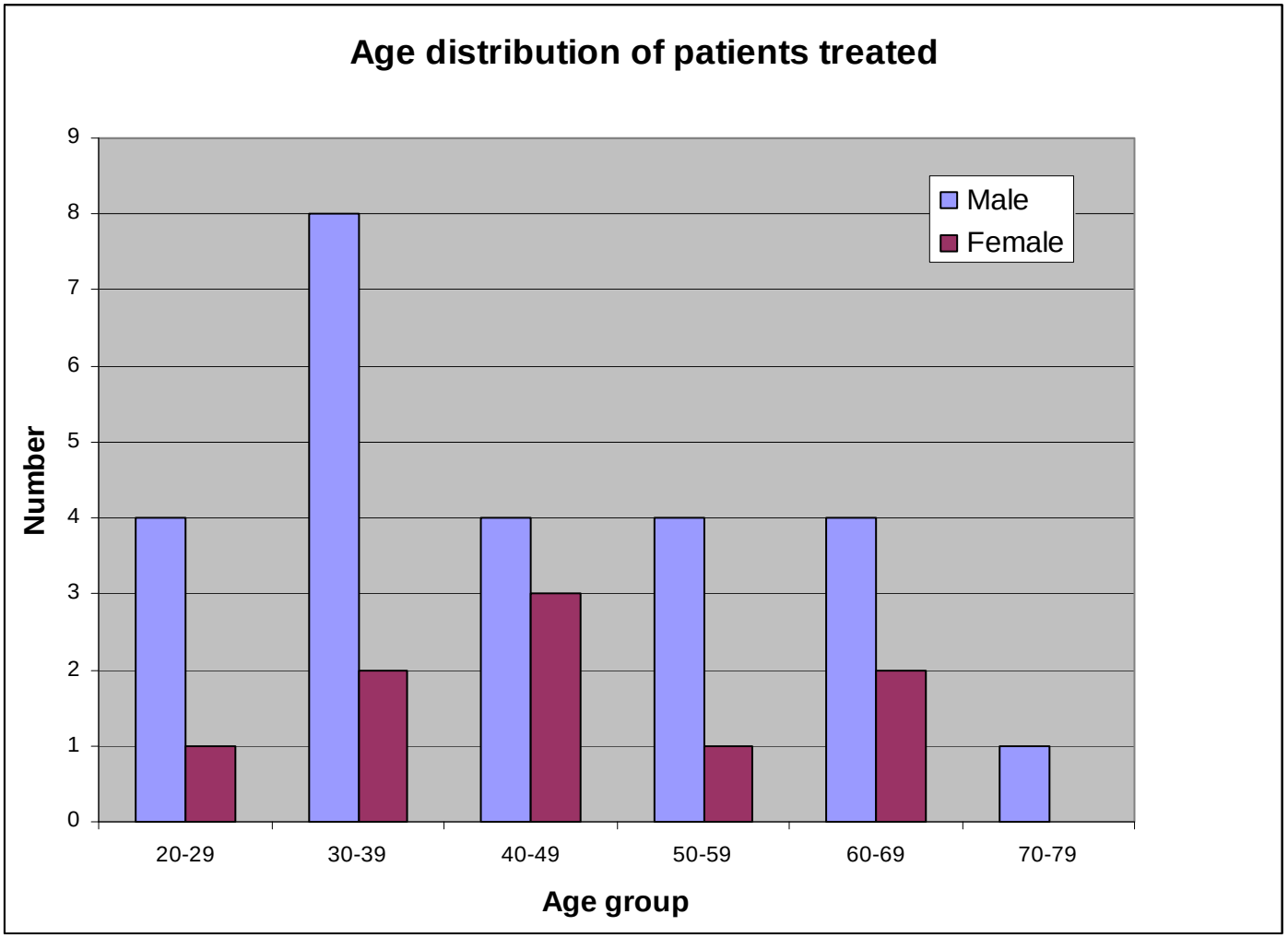
Age distribution of patients treated
Number
0
1
2
3
4
5
6
7
8
9
20-29
30-39
40-49
50-59
60-69
70-79
Age group
Male
Female

Figure 2

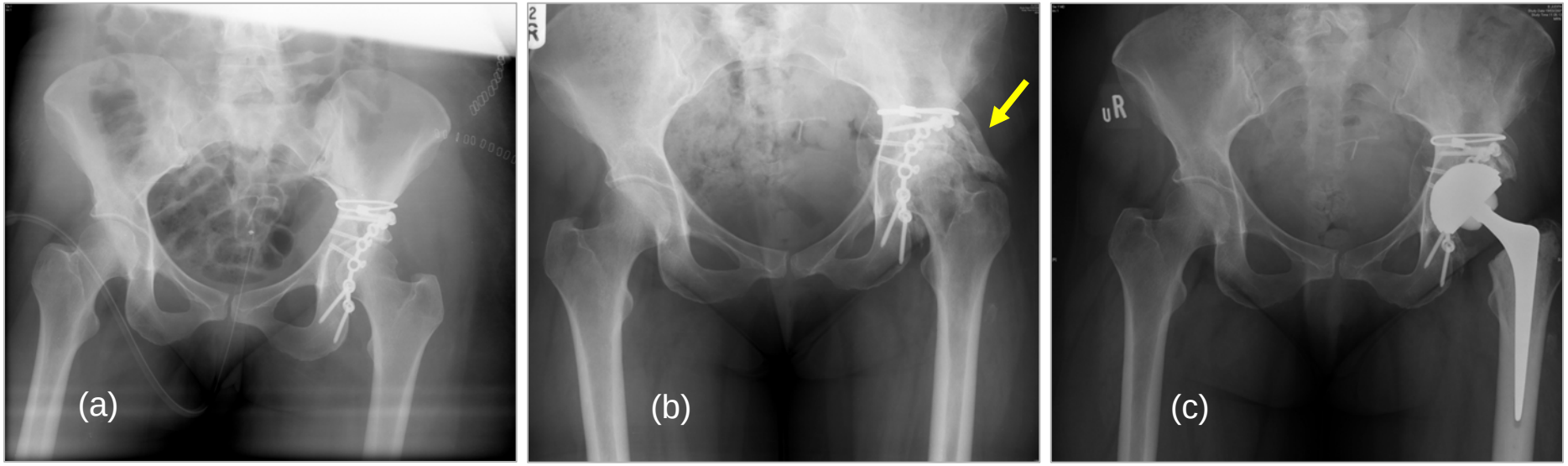

Figure 3