Radiotherapy Results for Heterotopic Ossification Prophylaxis: Single Center Experience from Eastern Black Sea Region of Turkey

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ABSTRACT

Heterotopic ossification is the atypical process characterized by de novo bone formation in tissues and can be caused by surgery, trauma and genetic disorders. The most commonly affected sites are the hips, knees, elbows and temporomandibular joints. The aim of the study was to evaluate efficacy of radiotherapy in preventing Heterotopic ossification. Data of 84 eligible patients treated with radiotherapy prophylaxis for Heterotopic ossification between 1997-2017 were retrospectively reviewed. 47 (56%) of the patients were male and 37 (44%) were female. The mean age was 50.4±14.1 (range: 17-82) years. According to the radiotherapy fields; right hip joint 35 (42%), left hip joint 33 (40%), bilateral hip joint 2 (2%), right elbow 10 (11%) and left elbow 4 (5%). After a median follow up of 104 and 95 months, 1 (7%) patient underwent treatment to the elbow site had evidence of Heterotopic ossification after radiotherapy and 8 (11%) patients underwent treatment to the hip sites had evidence of Heterotopic ossification after radiotherapy respectively. When all patients were examined; gender (p= 0.319), age (p= 0.158), etiology (p= 0.167), treatment area (p= 0.532), radiotherapy technique (p= 0.502) and the time between surgery and radiotherapy (p= 0.469) were not statistically significant according to the risk of Heterotopic ossification formation. Radiotherapy with 800 cGy in single fraction is a safe and effective treatment modality in the prophylaxis of patients at high risk for Heterotopic ossification formation. Fractional treatments can also be used for larger treatment areas, but the experience is limited.

Keywords: Heterotopic ossification, Radiotherapy

ÖZET

Heterotopik Ossifikasyon Profilaksisi için Radyoterapi Sonuçları: Türkiye'nin Doğu Karadeniz Bölgesinden Tek Merkez Deneyimi

Heterotopik ossifikasyon dokularda de novo kemik oluşumuyla karakterize atipik bir süreçtir ve cerrahi, travma ve genetik bozukluklardan kaynaklanabilir. En sık etkilenen bölgeler kalça, diz, dirsek ve temporomandibular eklemlerdir. Çalışmanın amacı, radyoterapinin Heterotopik ossifikasyonun önlenmesindeki etkinliğini değerlendirmektir. 1997-2017 yılları arasında Heterotopik ossifikasyon için radyoterapi profilaksisi uygulanan 84 hastanın verileri retrospektif olarak incelendi. Hastaların 47'si (% 56) erkek, 37'si (%44) kadındı. Ortalama yaş 50.4 ± 14.1 (dağılım: 17-82) yıl idi. RT alanlarına göre; sağ kalça eklemi 35 (%42), sol kalça eklemi 33 (%40), bilateral kalça eklemi 2 (%2), sağ dirsek 10 (%11) ve sol dirsek 4 (%5). Ortalama 95 ve 104 aylık takipte dirsek bölgesi hastalarından 1 (%7) hastada ve kalça bölgesi hastalarından 8 (% 11) hastada radyoterapi sonrası Heteretropik ossifikasyon oluşmuştur. Tüm hastalar incelendiğinde; cinsiyet (p= 0.319), yaş (p= 0.158), etiyoloji (p= 0.167), tedavi alanı (p= 0.532), radyoterapi tekniği (p= 0.502) ve cerrahi ile radyoterapi arasındaki süre (p = 0.469) Heterotopik ossifikasyon oluşumu riskine göre istatistiksel olarak anlamlı değildi. Tek fraksiyonda 800 cGy radyoterapi, Heteretropik ossifikasyon oluşumu için yüksek risk altındaki hastaların profilaksisinde güvenli ve etkili bir tedavi modalitesidir. Fraksiyonel tedaviler daha geniş tedavi alanları için kullanılabilir, ancak deneyim sınırlıdır.

Anahtar Kelimeler: Heteretropik ossifikasyon, Radyoterapi

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INTRODUCTION

Heterotopic ossification (HO) is the atypical formation of lamellar bone in soft tissue (nerve, connective tissue or muscle).[1] For the first time in 1918 by Dejerine and Cellier, it is defined as 'paraosteoarthropathy'.[2] HO is a common complication after traumatic brain injuries and spinal cord injuries.

Several risk factors have been identified for HO as direct trauma to muscle tissue, extensive burns, femoral and acetabular fractures and arthroplasty operations.[3] Usually, HO is asymptomatic and is coincidentally defined on imaging. In symptomatic conditions, the earliest findings are pain, swelling, fluid accumulation in the joint, erythema and increased temperature. These may result in decreased range of motion and, rarely, joint ankylosis. With the complete placement of heterotopic ossification, pain is reduced.[4]

Patients with a high risk of developing HO are often given prophylactic treatment. Prophylaxis options include radiotherapy (RT) and non-steroidal anti-inflammatory drugs (NSAIDs) while the standard treatment of HO is complete surgical excision of the ectopic bone, However, because of its high local recurrence rate, a need has been recognized for adjuvant therapies after surgical treatment.[5-7] RT is the only prophylaxis agent that can be administered locally when compared to other methods.[8]

The reason for RT use for prevention of HO is based on the hypothesized that radiation works as a method of prophylaxis by inactivating pluripotent mesenchymal cells before they begin differentiating into osteoblasts are especially radiosensitive.[9] RT can be either given preoperatively or postoperatively, although more often preferred postoperatively.[10]

Complications of heterotopic ossification include ankylosis, scarring, lymphedema, vein and nerve compression.[11]

Recently, a number of studies have been undertaken to identify new aspects of the etiology of HO formation and to seek more efficacy and new prophylactic modalities with more side effects. The objective of this study was to determine the effect of postoperative RT on the prevention of HO.

PATIENTS and METHODS

This retrospective clinical study was conducted with due to permission from the Ethics Committee at the Karadeniz Technical University Faculty of Medicine (2018-11). Between 1997 and 2016, a total of 84 patients who underwent treatment for HO prophylaxis after the surgery were included in this study. The medical records of all patients were retrospectively reviewed to obtain demographic data about their age, gender, affected the joint, surgical type, timing RT and RT dose.

Treatment

Seventy patients received a total hip replacement and 14 patients underwent elbow surgery. All operations were performed by arthroplasty surgeons at our university hospital using a posterior or direct lateral approach. Patients at high risk for HO were guided in the first 24-96 hours postoperatively after orthopedic surgery. All patients were given a first-generation cephalosporin 1 hour preoperatively and for 48 hours postoperatively. Coumadin or low-molecular-weight heparin was used for deep venous thrombosis prophylaxis. Patients discontinued nonsteroidal anti-inflammatory medication preoperatively and postoperatively.

Our patients were treated with 62 patients, 2D conformal RT until 2010, and then 22 patients, three-dimensional conformal RT. Prior to RT, all patients underwent simulation. Four patients were treated with 20 Gy in 10 fractions and 80 patients were treated with 8 Gy in a single fraction. RT was delivered with 6-18 MV linac photons' to anterior-posterior/posterior-anterior isocentrically arranged portals.

Follow-up

After 1 month of RT, the patients' were clinically examined and their complete blood test and direct radiography were performed. Patients had routine follow-up appointments at 3 months, 6 months, 9 months, and 1 year from after the first check. Radiological assessments were performed according to ossification degree (0-4 points) by using Brooker's Grading Scale. Computerized tomography of

the joint was applied when considered clinically requirement.

Statistical Analysis

The obtained data were subjected to the statistical analysis by using the SPSS 16.0 software. Chi-square test was used to compare the results of HO treatment in the different groups (age, gender). Correlation of Brooker classification based on radiation dosage, as well as immediate postoperative Brooker score with risk of progression, and for the prevention of HO, we also compared the efficacy of duration between surgery and radiotherapy, was performed with Fisher's exact test. All tests were considered statistically significant at $p< 0.05$.

RESULTS

Eighty-four patients have participated in the study. 47 (56%) of the patients were male and 37 (44%) were female. The mean age was 50.4 ± 14.1 (range: 17-82) years. According to the RT fields; right hip joint 35 (42%), left hip joint 33 (40%), bilateral hip joint 2 (2%), right elbow 10 (11%) and left elbow 4 (5%).Ten patients were treated with 1 x 800 cGy and 4 patients were treated with 10 x 200cGy RT. The mean follow-up period was 104.6±68.4 months (range: 3-204). HO developed in one patient (7% (1/14)) who underwent radiotherapy in elbow area 180 months later and treated with surgery.

The mean age of the upper extremity patients was 36.3 ± 12.6 years (range: 17-56) and 10 patients were male and 4 were female. HO 13 (15%) was caused by trauma in the patient and 1 (1%) was due to osteoarthritis in the patient. The mean time from trauma to surgery was 11.4 ± 20.6 months (range: 1-75) and the mean time between surgery and RT application was 46 ± 26 hours (range: 24-96). 10 patients were treated with 1x800cGy and 4 patients were treated with 10x200cGy RT. The mean follow-up period was 104.6±68.4 months (range: 3-204). Of these 14 patients, 1(7%) patient developed new HO after RT in elbow area 180 months later and treated with surgery.

All of the lower extremity patients were received total hip arthroplasty. Immediate postoperative radiograph Brooker score was evaluated to assess association with risk of progression and high-risk patients of developing HO were identified. RT was given postoperatively. The indications for RT were; 1 (1%) ankylosing spondylitis, 6 (7%) congenital hip dislocation, 1 (1%) diabetes mellitus, 1

Table 1. Patient characteristics and results of log-rank univariate analysis of risk of HO

	Elbow	Hip Joint	p value
Patient number (n, %)	14 (16)	70 (84)	-
Age (mean)	36 (17-56)	53 (27-82)	0.158
Sex (n, %)			
Male	10 (12)	37 (44)	0.319
Female	4 (4)	33 (40)	
Risk factors (n, %)			
Trauma	13 (15)	3 (4)	
Idiopatic skeletal hyperostosis	–	48 (57)	0.167
Contralateral total hip arthroplasty	–	6 (7%)	
Congenital hip dislocation	–	6 (7%)	
Others	1 (1)	7 (9)	
Time between surgery and RT (hour)	46 (3-204)	33.7 (24-96)	0.469
RT Dose (n, %)			
1x800 cGy	10 (12)	70 (84)	0.502
10x200 cGy	4 (4)	–	
HO incidence (n, %)	1 (1)	8 (10)	

(1%) osteoarthritis, 1 (1%) rheumatoid arthritis, 1 (1%) osteomyelitis, 6 (7%) contralateral total hip arthroplasty, 3 (4%) trauma story, 2 (3%) extremity shortening and 48 (57%) previous surgery on ipsilateral side. 35 (42%) were affected by right hip joint, 33 (40%) by left hip joint and 2 (2%) patients by bilateral hip joint. Except for 3 patients, the mean time between surgery and RT was 33.7 ± 21.5 hours (range: 24-96), while the other patients were approximately 7 days. All patients received 1 x 800 cGy RT. Mean follow-up time was 95.1 ± 39.4 months (range: 3-162). Of these 70 hip patients, 8 (11%) patients developed new HO after RT and required re-excision after a mean of 35.3±34.5 months (range: 4-96).

One patient was diagnosed with non-small cell lung cancer 13 months later and 1 patient was diagnosed with bladder cancer 37 months later. After a median follows up of 104 and 95 months for elbow and hip, respectively, the incidence of HO in all patients was 7% (1/14) and 11% (8/70), despite the use of RT. When all patients are examined; there were no association between HO incidence and gender (p= 0.319), age (p= 0.158), etiology (p= 0.167), disease area (p= 0.532), RT technique (p= 0.502) and the time between surgery and radiotherapy (p= 0.469) (Table 1). No early or later side effects were observed in both elbow and hip patients.

DISCUSSION

This study presents our Department's experience of postoperative RT for the prevention of HO after surgery. Although the pathophysiology of HO has not yet been fully elucidated, it has been reported that a metaplastic response of mesenchymal cells may result.[3] Development of heterotopic ossification is a typical complication after total hip replacement.

Several contributory factors for HO formation have been reported. Male gender, hypertrophic osteoarthritis, previous surgery on the ipsilateral side, ankylosing spondylitis, tissue hypoxia, a history of post-traumatic arthritis with prominent osteophyte formation, hypercalcemia, prostaglandin activity specifically PGE2, and imbalances between parathyroid hormone and calcitonin activities, alterations in sympathetic nerve activity and past HO have all been shown to contribute.[12] In our study, the ratio of male to female was 1/1.3 and the most common causes were previous surgery on the ipsilateral side, trauma, congenital hip dislocation and contralateral total hip arthroplasty. Eggli et al. showed a correlation between the incidence of HO and age and gender.[13] However gender was no relevant variable in our study.

The importance of postoperative irradiation for prevention of HO was shown initially by Coventry in 1981 and was investigated by many studies.[14] Several studies showed the same effectiveness for single and multifractionated irradiation.[15,16] Single fraction irradiation is less demanding due to the possibility of causing late radiation fibrosis theoretically. Furthermore, there has been no description of late fibrosis to date in studies applying RT for prevention of HO and it is more economical.[17,18]

Prophylaxis includes RT and NSAIDs is more important than treatment in HO. It is estimated that surgery process stimulates mesenchymal cells present in the soft tissue to transform into osteoblasts, peaking around 32- 48 hours postoperatively,[19] which prevents this conversion of RT and it is the only prophylaxis method that can be administered locally. Although acute side effects are minimal with RT, the possible carcinogenic risks of RT are always an important concern in the treatment of benign disorders.[20]

RT is used both prophylactically pre- and postoperatively. Many studies have shown that in both high-risk patients the HO risk is reduced by 80-90% to 10%. However, the greatest advantage of preop care is increased patient comfort, ease of treatment and prevention of possible postoperative complications due to the patient's posture and postoperative period. In a study performed, preop and postop could not compare because pre-operative treatment was not applied. In conclusion, preoperative RT should be applied within 4 h prior to surgery or postoperatively within 96 h after surgery.[10] In our study, 96% of our patients underwent post-op RT within the first 96 hours after surgery.

In a study from Cleveland Clinic, 36 patients who underwent surgical and postoperative single fraction RT to the elbow were reported.[21] After treatment, only 3 (8%) of the patients found that they

had developed a new HO. In our study, the HO risk after elbow joint RT was found to be 7%. On the other hand postoperative single fraction RT was found to increase fracture union rate to reduce the risk of HO formation after trauma to the elbow joint.[22]

A study which evaluated 44 patients who underwent RT after surgery to the elbow, was conducted by Rush University in 2011. In a 136-day follow-up, 21 (48%) of the patients found HO to develop.[23]

Comparing single or multiple fractions, Pellegrini et al.[24] the patients divided them into 1 x 8Gy and 2 x 5 Gy arms. There was no difference between them. Knelles et al.[25] compared 1200/4 cGy with 700/1 cGy and 500/1 cGy. As a result, they found a statistically significant difference in the prevalence of HO in 1 x 5 Gy arm. In our study, we could not compare fraction schedules because there were not enough and an equal number of patients in treatment arms

Coventry et al. noted that prophylactic treatment for HO by irradiating the hips of 42 patients who underwent hip surgery. Patients who were identified as high risk for HO formation. were treated with a total dose of 20 Gy. HO incidence after the total hip replacement was reported as 19%.[26] In another study, the incidence of HO was found to be 21.6% in general, and 6.6% in NSAID users, regardless of NSAID use.[27] Evan et al. also reported that heterotopic bone was formed in only 27% with RT, 37% with indomethacin and 12% with RT plus indomethacin.[28] In our study, we detected only 11% of hip patients with RT.

Radiation-induced second malignancies are one of the critical components of RT and have an impact on optimal treatment decision-making. The evidence for the magnitude of this risk is limited by the small number of long-term studies in relevant clinical cohorts. Furthermore, there have been no documented cases of cancers resulting from RT after prophylaxis against HO. Kim et al. documented the records of patients who developed a radiation-induced sarcoma over a 50-year period and found no cases of soft tissue or bone sarcomas in patients who received less than 30 Gy.[29] During our past 20-year clinical experience no second malignancies related to RT were observed.

The capacity of our study includes its relatively large pattern size comprising known high-risk patients. Our study has some limitations. First, it was a retrospective study conducted at a single center, thereby requiring caution while interpreting the results. Second, this retrospective report includes patients treated in the 20-year period. During this period, the imaging modalities and RT techniques improved, which may have resulted in selection bias and advances in surgical technique may affect the rate of HO formation.

CONCLUSION

RT prophylaxis after surgery used as a safe and effective treatment for hip and non-hip sites. Although postoperative single-dose RT is an acceptable treatment for the HO prophylaxis, there is a need for further clinical trials with a larger sample size that assess the effectiveness and adverse effects of prophylactic RT in HO. The long term relationship with secondary malignancies should be considered.

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