OPEN ACCESS

Clinics Oncology

Case Report

Article Information

Received date: Jan 02, 2020
Accepted date: Jan 06, 2020
Published date: Jan 07, 2020

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Adjuvant Radiation for R1-Resected Parathyroid Cancer after Surgery in High-Risk Patients

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Abstract

Parathyroid cancer is a rare endocrine malignancy. However, it is an aggressive cancer and has a high risk of recurrence. The main treatment modality for this tumor is surgery with adequate resection. Adjuvant radiation in parathyroid cancer is still debated. We present a case of 63 year-old male who had parathyroid cancers. He underwent Right lobectomy and Right inferior parathyroidectomy with central neck dissection and his pathologic results showed very close margin. So he received adjuvant radiation 6600 centigray. After completing radiation seven years ago, he remains without evidence of local recurrence and distant metastasis.

Keywords: Parathyroid cancer; Adjuvant radiation; R1-resection

Introduction

Parathyroid cancer is the rarest endocrine tumor [1,2]. It was first described by De Quervain in 1904 [3,4]. It is an aggressive tumor and has a high risk of recurrence [5]. To distinguish between being benign and malignant of parathyroid gland, the imaging or intraoperative findings is quite difficult to be applied [3,4,6]. Therefore, the diagnosis may depend on histopathologic and immunohistochemical features. Most cases showed board fibrous bands, necrosis and solid growth pattern [3,4]. Immunohistochemical findings of this cancer included loss of expression parafibromin, retinoblastoma protein, p-27, BcL-2a, mdm 2, APC and positivity of galectin-3, overexpression of p-53 and increasing MIB1, Ki67 proliferation index more than 5% [4]. The most appropriate treatment is curative resection with R0 margins [5]. Previous studies demonstrated that adjuvant radiation following surgery had ineffective outcomes [3,7]. So, we reported a rare case of parathyroid cancer who cannot achieve clear margins, received adjuvant radiation, and had a good result from adjuvant radiation.

Case Presentation

A 63-year-old Thai male had primary hyperparathyroidism. His investigation showed hypercalcemia (Calcium 13.4) and hyperparathyroid (PTH 1480) in February 2012. He underwent fine needle aspiration of the neck and the results showed atypical cell; malignancy cannot be excluded. The MIBI scan was performed and the results were increased uptake at inferior of right thyroid gland. He was subsequently treated with right lobectomy and right inferior parathyroidectomy with central neck dissection in July 2012. The pathologic results demonstrated parathyroid carcinoma, size 3.7x3.5x3 cm with vascular invasion, no evidence of soft tissue invasion. The tumor was very close to the line of resection and lymph nodes were negative. This case was presented in the multidisplinary team conference and they decided to give him

adjuvant radiation. So he was treated with anterior and posterior neck irradiation and changed to lateral opposing filed after 4000cGy. The target volume included tumor bed, lymph node level II to VI. The radiation dose was 6600 cGy. He completed his radiation in December 2012. After completing radiation for 3 months, his PTH was 204. After that, he underwent parathyroid scan and the results was no residual or recurrent tumor. At 7-year follow up, he remained without evidence of local recurrence and distant metastasis.

Discussion

Parathyroid cancer was first described by De Quervain in 1904. It was defined as functioning metastatic carcinoma [3,4]. Additionally, it was the rarest endocrine tumor. For prevalence of parathyroid cancer was 0.005% of all cancers [1,2]. It is also an aggressive cancer and has a high risk of recurrence [5]. It can occur with all age of patients. The peak incidence was the fifth decade [6]. Most patients (90%) presented with hyperparathyroidism. Whereas, less than 1-5% of hyperparathyroidism was diagnosed as parathyroid cancer [3,4]. Some patients may present with overt hyperparathyroidism such as nephrolithiasis, nephrocalcinosis, bone pain, osteopenia, anxiety and depression. The overt hyperparathyroidism that had renal and skeletal involvement is uncommon in benign parathyroid disease. Non-functioning parathyroid cancer may occur in less than 10% and the patients may present with compression or invasion of adjacent structures and neck mass or dysphagia. The family history of hypercalcemia genetic syndrome like hyperparathyroidism jaw tumor syndrome, multiple endocrine neoplasm syndrome and familial parathyroid disease should lead us to think of parathyroid cancer. Even etiology of parathyroid cancer is unknown; it is likely to be caused by environmental factors and hereditary factor. The main pathway that involved carcinogenesis of this cancer included aberrant CaSR, cyclin D1 and Wnt /B catenin signaling. Most genetic abnormality is related with inactivating somatic mutation of parafibromin gene (CDC73/HRPT2), altered expression of p53 and retinoblastoma protein and oncosuppressor gene on chromosome 13 [3,4].

The investigation for parathyroid cancer will show that serum calcium is more than 3.5 mmol/L and serum parathyroid hormone is 3-5 times of upper normal limit. The serum alkaline phosphatase is also much more than parathyroid adenoma [3]. To distinguish between being benign and malignant of parathyroid, the imaging usually cannot be used. Neck ultrasonography and 99mTc sestamibi scintigraphy can be operated to localize abnormal parathyroid glands. Findings of neck ultrasonography of parathyroid cancer are infiltration and/ or calcification. For intraoperative consultation, it is quite difficult to distinguish between benign and malignant parathyroid disease. Most studies found that median maximal diameter of parathyroid cancer are about 3-3.5 cm, firm or stony hard consistency, lobulated, usually surrounded with dense fibrous capsule and the cancer invades or adheres to adjacent structure. Whereas parathyroid adenoma are smaller (size 1.5 cm), soft, reddish brown color, round or oval shape. Most common histologic findings of parathyroid cancer are board fibrous bands, necrosis and solid growth pattern [3,4]. In 1973 Schantz and Castleman reported the histologic findings that discriminated between parathyroid cancer and parathyroid adenoma were fibrous bands arranged in trabecular design, capsular invasion, vascular invasion and mitotic activity [3]. Recent studies concluded that the histologic features that indicated parathyroid cancer are vascular invasion, perineural invasion, invasion to adjacent anatomical structures and metastasis.

For biomarkers, more than 70% of sporadic parathyroid cancer is related with sporadic mutation in CDC73/HRPT2 gene [4]. Moreover, immunohistochemical findings included loss of expression parafibromin, retinoblastoma protein, p-27, BcL -2a, mdm 2, APC and positivity for galectin-3, overexpression of p53 and increasing MIB1, Ki67 proliferation index more than 5%. When the findings detected suspected histologic feature, they also confirmed the diagnosis of parathyroid cancer. TNM classification of Saha 1999 and High risk/ Low risk classification of Schulte 2010 has been utilized for staging system of parathyroid cancer. It can be applied to predict recurrence and survival for this cancer. Nonetheless, it has not been extensively used [3,6].

Nowadays, the treatment of choice for parathyroid cancer is en bloc resection combined with ipsilateral hemithyroidectomy [2,4]. Central neck dissection is recommended if not any harm does for the patient. There is a 15-30 % risk of lymph node level VI metastasis [4,5]. The most appropriate treatment is curative resection with R0 margins, WHO criteria defined R0 resection margins as no tumor cell at margin and R1 margins as presence of cancer cell at edge of specimen or within less than 1mm from resection margin. It is also

Table 1: Staging and risk classification of parathyroid cancer

Proposed TNM classification	Disease stage	Histological criteria	Risk classification
T1 (capsular invasion) or T2 (invasion of surrounding soft tissues excluding vital organs trachea, larynx and esophagus) N0 M0	I	Capsular invasion and/or invasion of surrounding soft tissue	Low risk
T3 (vascular invasion) N0 M0	II	Vascular invasion	High risk
Any T, N1 (regional lymph node metastases) or T4 (invasion of vital organs: hypopharynx, trachea, esophagus, larynx, recurrent laryngeal nerve, carotid artery)	III	Vascular invasion and/or lymph node metastases and/or invasion of vital organs	High risk
Any T or N, M1 (distant metastases)	IV	Distant metastases	High risk

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implied that local excision results less complete resection. Schulte and colleagues analyzed the results to identify which type of surgery had the best outcomes for parathyroid cancer. The studies showed that local excision is related with a high rate of local recurrence and lower disease free survival. They also found that R1 resection is associated with lower disease-free survival. Locoregional recurrence free survival (LRFS) in oncologic surgery was 93% and LRFS in non-oncologic surgery was 50%. No recurrence was also found in R0 resection and 71% recurrence was found in R1 resection. This study confirmed that oncologic resection can prevent locoregional recurrence by total removal of tumor and lymph node metastasis [5].

Adjuvant radiation for parathyroid cancer has been reported to have an unsatisfactory effect [3,7]. Nevertheless, Busaidy et al., considered postoperative radiation in positive margins, local excision and multiple recurrence. The study demonstrated that there was 1 of 6 patients who received adjuvant radiation, who developed local relapse and 10 of 20 patients who did not received adjuvant radiation, who developed local relapse [2]. Furthermore, Chow et al. reported their experience of parathyroid cancer, especially the role of adjuvant radiation in high risk of microscopic residual disease following surgery. There are a total of 10 parathyroid cancer patients who underwent surgery in their study and six of them were treated with adjuvant radiation. When follow up patients after about 62.3 months, all six patients who received adjuvant radiation had no recurrence. It is likely to be that adjuvant radiation can reduce the risk of locoregional recurrence and does not depend on the type of surgery and staging [7]. Likewise study of Munson et al, they added radiation in 4 patients who concerned regarding residual subclinical or microscopic disease and all of 4 patients alive without disease within 5 years (median follow up 60 months). They concluded that adjuvant radiation may lower locoregional disease progression for parathyroid cancer after treated with surgery. They also found that surgical margin status indicated of locoregional disease progression from univariate analysis (p= 0.03) [8]. Erovic et al., evaluated about histological parameters and outcomes in term of recurrence and survival rate of parathyroid cancer patients. They found that 11 patients had vascular invasion, 4 of 11 patients developed locoregional recurrence and 1 of 11 patients developed metastases. There are also 2 patients had no vascular invasion and none of them developed locoregional recurrence. They implied that presence of vascular invasion associated with clinical outcomes in parathyroid cancer. Whereas there are 5 patients who had positive margins received adjuvant radiation and 3 of them developed recurrence. Therefore adjuvant radiation may not be sufficient for parathyroid cancer in case of inadequate resection [9].

Mostly, locoregional recurrence of parathyroid cancer occurred within three years. It may be multiple locoregional recurrence or can occur with or without metastasis to lung, bone and liver. Previous studies identified that tumor size, nodal status, vascular and soft tissue invasion and mitotic index are associated with high risk of recurrence and mortality [1]. However, it remains unknown regarding the particular importance of these combined measure on prognosis [1,10,11,12]. Schulte et al. examined about the validated prognostic classification of parathyroid cancer. They classified parathyroid cancer into low risk and high risk based on histopathology as demonstrated in Table 1. It was used to consider the need of close follow up and adjuvant therapy. They also found that high-risk patients has 5-year mortality rate around 50% [10,13].

In addition, Xue et al., examined prognostic factors that predict parathyroid cancer patients. They found that local invasion, stage III in Schulte staging system and high risk in Schulte classification are significantly related with local recurrence of cancers (p=0.008, p= 0.039 and p=0.012 respectively). Lymph node status associated with prognosis in parathyroid cancer is still debated. Xue et al., also found that the presence of central lymph node dissection in the first operation did not have an effect on tumor recurrence or death. On the contrary, Schulte and Spanish parathyroid carcinoma study group (SPCSG) detected that lymph node status is significantly involved with prognosis of parathyroid cancers [3]. They also suggested that curative treatment of parathyroid cancers should be en bloc resection with ipsilateral thyroid lobectomy and central lymph node dissection [6,11,14]. As we know, parathyroid cancer patients who developed metastasis had decreased overall survival and poor quality of life. These patients with high risk of metastasis are good candidates for systemic therapy.

There is a recent study of Asare et al., revealing that cumulative incidence of distant metastasis at 5 years is 20 %, 10 years is 30% and 20 years is 38%. The patients with tumor size more than 3.2 cm and age less than 47.5 years had higher cumulative incidence of distant metastasis (p=0.0005). Moreover, patients who developed distant metastasis had significantly decreased overall survival when compared with those who did not develop distant metastasis. Parathyroid cancer patients with bone metastasis also had lower survival when compared with metastasis to other sites [15]. For this case, there was vascular invasion from pathological findings which are high risk in Schulte classification. His pathological reports also had very close margin that indicated high risk of microscopic residual disease following surgery as reported in the study of Chow et al., Therefore we considered postoperative radiation to tumor bed for him.

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