

# Outcome of Primary Intraosseous Carcinoma: Cases Review of Single Institution

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## Research

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# Abstract

**Objective:** The purpose of this study was to investigate the prognostic factors and treatment of primary intraosseous carcinoma (PIOC).

**Methods:** Patients who diagnosed with PIOC and received treatment in Sichuan cancer hospital from 1996 to 2020 were followed up and retrospectively reviewed. Univariate and multivariate analyses based on clinical-pathological characteristics and therapeutic modalities were performed using the Log rank test and Cox regression model respectively.

**Result:** A total of 28 patients were included in the study, with a mean age of 60 years (60±10.11). The 2-year and 5-year overall survival (OS) were 60.7% and 38.5% respectively. In the univariate analysis, surgery combined with adjuvant therapy improved the OS compared with surgery or radiotherapy alone (P=0.035), and patients received postoperative adjuvant radiotherapy had a higher OS than those who received radical radiotherapy (P = 0.01). In addition, patients with well differentiated tumors tend to have increased progression free survival (PFS) (P=0.01). Multivariate analyses showed that radiotherapy was independent indicators for OS (HR: 0.212, 95% CI: 0.068–0.660, P = 0.007).

**Conclusion:** surgery combined with adjuvant therapy is the superior treatment strategy for primary intraosseous carcinoma at present. This study is the first to report the important role of radiotherapy in the treatment of primary intraosseous carcinoma.

**Mini Abstract:** surgery plus adjuvant therapy is the preferred treatment for primary intraosseous carcinoma and it is first to illustrate the important role of radiotherapy.

## 1. Introduction

Primary intraosseous carcinoma (PIOC) is a very rare primary malignant tumor of the jaw. According to histological subtypes, PIOC can be classified into salivary gland carcinoma, odontogenic carcinomas, and primary intraosseous squamous cell carcinoma (PIOSCC)<sup>1</sup>. It was first described and named by Loos as intra-alveolar epidermoid carcinoma in 1913<sup>2</sup>. In 1971, the World Health Organization (WHO) renamed this set of disease as primary Intraosseous Carcinoma (PIOC) which includes epithelial and mucoepidermoid carcinoma according to Pindborg's suggestion<sup>3</sup>. In 2005, it was renamed as primary intraosseous squamous cell carcinoma (PIOSCC), including three subcategories: i. solid type tumors, ii. squamous cell carcinoma derived from keratocystic odontogenic tumors, and iii. derived from other benign epithelial odontogenic cysts or tumors<sup>4</sup>. Recently, the fourth edition of WHO classification of head and neck tumors classified this into one type: primary intraosseous carcinoma PIOC<sup>5</sup>. The diagnosis of PIOC needs to be differentiated from alveolar carcinoma from the overlying soft tissue that have invaded the bone, tumors with distant metastases to the jaw, maxillary sinus carcinoma, and other odontogenic tumors<sup>6</sup>. Because of the absence of symptoms in the early stage, PIOC are always diagnosed at the late stage, resulting in poor prognosis, high rate of distant metastasis, and high mortality<sup>7,8</sup>.

Previous studies mainly depict different aspects of the disease, including clinical, histologic, therapeutic and prognostic features, but rarely illustrated the differences among different treatment modalities. In this study, we retrospectively analyzed all of the records of the patients with primary intraosseous carcinoma who were admitted for initial treatment and received full-course radiotherapy between 1996 to 2020 at Sichuan cancer hospital. In this report, we hope to describe new understandings of the treatment and prognosis factors of PIOC.

## 2. Material And Methods

### Ethics Statement

This study was approved by the ethical committees of Sichuan Cancer Hospital, Chengdu, China. There was no need to obtain informed consent from patients, all data was analyzed anonymously.

A total of 37 cases of PIOC treated in Sichuan cancer hospital from 1996 to 2020 were included in this study, of which 3 cases were diagnosed less than 2 years and 6 were lost to follow-up. Finally, a total of 28 cases were included in the retrospective analysis.

The clinical characteristics, pathology, imaging, treatment modalities, and follow-up information of patients were collected. The parameters included sex, age, initial symptoms, surgical procedure, postoperative adjuvant therapy, TNM classification, and histological grade. TNM classification was reclassified by two or more associate chief physicians or above according to the eighth edition of the American Joint Committee on oral cavity classification. All patients received magnetic resonance imaging (MRI)/computed tomography (CT) scanning of the head and neck before treatment.

Multivariate hazard ratios (HRs) were analyzed with Cox regression model to identify independent prognostic factors using descriptive statistical analysis. Overall survival (OS) and curves describing survival were generated with the Kaplan–Meier method. Statistical significance was tested with the log-rank test. Univariate analysis was performed by log-rank test to identify potential prognostic factors.  $P < 0.05$  was considered to be statistically significant. Statistical analysis was performed with IBM SPSS statistics 22 (SPSS Inc, Chicago, Illinois, USA).

## 3. Result

### 3.1. Clinical characteristics

Three out of 37 cases were diagnosed shorter than 2 years, 6 were lost during the follow-up, and the final number of cases included in the statistical study was 28. Clinical data of the 28 patients are shown in table1. Primary intraosseous carcinoma patients were predominantly male (19:9), with a mean age of 60 years [60±10.11]; 12 cases occurred in the maxilla and 16 in the mandible; all patients were T4 stage; 19 patients had cervical lymph node metastasis; The initial symptoms of PIOC were mostly facial masses (50%) and pain (42.9%). One patient presented with distant metastasis at the time of initial consult.

## 3.2. Treatment modalities and Histopathological Features

Twenty-five (89.3%) patients received surgical treatment, 17 out of these 25 patients underwent simultaneous cervical lymph node dissection; Among 20 patients who underwent radiotherapy, 17 patients had postoperative adjuvant radiotherapy (3 patients with imaging-approved tumor residue were treated with radical radiotherapy) and the rest 3 patients were treated with radical radiotherapy without surgery. Eighteen patients were treated with chemotherapy (including 16 chemoradiotherapy). In addition, 3 patients received targeted therapy, including nimotuzumab and cetuximab administration. For patients who received postoperative adjuvant radiotherapy, the total dose of postoperative tumor bed and cervical lymph nodes lesions were 50-66 Gray (Gy), while those who underwent radical radiotherapy had a total dose of tumor volume 70-78.8 Gy. All radiotherapy was performed using intensity-modulated radiotherapy (IMRT) technique. Cisplatin was most frequently used and was mostly combined with paclitaxel or gemcitabine. The histological grade was classified into three types as good, moderate, and poor differentiation. Thirteen patients had tumors with high differentiation, 9 cases with moderate differentiation, and 6 cases with poor differentiation. Data of Treatment modalities and Histopathological Features are summarized in table2.

## 3.3. Survival analysis

The median follow-up was 27.5 months (1-146 months). By the end of follow-up, 16 of 28 patients died. Two out of 16 patients died with local recurrence and 8 out of 16 patients died with distant metastasis. The 2-year and 5-year overall survival (OS) rate was 60.7% and 38.5% respectively. The 2-year and the 5-year progression-free survival (PFS) rate was 42.9% and 30.8% respectively. Univariate survival analysis showed that poor histological grade was significantly correlated with poor prognostic factor for PFS ( $P=0.01$ ) but not OS (Fig 1). Sex, age, tumor size, lymph node metastasis (n grade), histopathological classification, or cervical lymph node dissection did not show significant association with OS (Table 3). Interestingly, surgery combined with adjuvant therapy resulted in a higher overall survival rate compared with surgery (52.6% vs 16.7%) or radiotherapy (52.6% vs 33.3%) alone ( $P = 0.035$ ). However, among patients treated with radiotherapy, those who received postoperative adjuvant radiotherapy dose had a significantly ( $P = 0.01$ ) higher survival rate than those who received radical dose radiotherapy (64.3% vs 33.3%), the result had statistical significance (Fig 2). On multivariate statistical analysis, only radiotherapy remained a significant independent risk factor for OS (HR: 0.212, 95% CI: 0.068–0.660,  $P = 0.007$ ). The results of multivariate analysis for overall survival and progression-free survival are shown in Table 4.

## 4. Discussion

PIOC is a rare malignancy that may develop from the remnants of odontogenic epithelium and is located within bone without demonstrable evidence of a primary carcinoma in oral or sinusal mucosa<sup>9</sup>. Due to the rarity of primary intraosseous carcinoma, few studies and related clinical data are available for this

disease, which prompt us to sought to investigate the prognostic factors and treatment of primary intraosseous carcinoma. In previous studies, swelling, pain, and pyorrhea after tooth extraction and cyst enucleation were the main complaints at the initial diagnosis of PIOC. The most common clinical manifestation of PIOC is swelling, pain, facial asymmetry, and diffuse distension of the jaws<sup>10</sup>. Half of the patients in our cohort presented with facial masses and pain, which is consistent with previous reports.

In the 1960s, the 5-year OS of primary intraosseous carcinoma, known as intra-alveolar epidermoid carcinoma at that time, was reported to be 30-40% by Shear et. al.<sup>11</sup>. Huang et. al. reported a 2-years OS of 69.8% and a 5-year OS of 36.3% for 39 patients with PIOC<sup>12</sup>. Similar findings have been reported by Xu and others<sup>8,13,14</sup>. In our cohort, the 2-year OS and 5-year OS of PIOC are 60.7% and 38.5% respectively, which are close to previous reports. A definite diagnosis of PIOC at early stage is often challenging resulting in poor prognosis, based on unobvious symptoms and difficulty to distinguish squamous cell carcinoma of surface mucosal origin and other odontogenic carcinomas which warrants early diagnosis and treatment.

Histologically, these tumors are squamous cell carcinomas which range from well differentiated to poorly differentiated lesions. In present study, patients with well differentiated tumors had better OS (46.2% vs. 16.7%) and PFS (46.2% vs. 0%,  $P = 0.01$ ) than those with poorly differentiated tumors, which was consistent with previous studies<sup>8,13</sup>.

PICO is considered to have infiltrated into the mandible, surgical procedures included resection of the lesion mass, partial or total removal of the upper / lower jaws, and radical or select cervical lymph node dissection to ensure that the tumor is thoroughly excised<sup>8,15</sup>. Surgical intervention is currently the first choice for this disease, and 89.3% of patients received surgical. It has been reported that patients with positive lymph nodes had a lower 2-year OS compared to those with negative lymph nodes<sup>13</sup>. Whereas in the present study, patients with negative lymph nodes (N0) had an OS of 55.6% and those with positive lymph nodes (n1-3) had an OS of 36.8%.

PIOC is an aggressive disease that tends to locally recurrent and metastases distantly. Nowadays the staging system and treatment guideline for PIOC still remain uncertain although we used American Joint Committee on Cancer (AJCC) classification for oral cancer in this study which was not perfect enough. Meanwhile the specific treatment guidelines for PIOC are not available yet, Naruse et al. believe that the treatment of PIOSCC should be similar with that of at least stage T3N0 oral cancer<sup>14</sup>. In addition to surgical treatment, other recommended treatments according to National Comprehensive Cancer Network (NCCN) guidelines include radiotherapy, chemotherapy, targeted treatment etc. Recent studies have shown that appropriate adjuvant treatment can achieve the lowest local recurrence and ensure a better survival<sup>16</sup>. Chen et al. concluded that postoperative radiotherapy should be given to patients with i. positive operative margins, ii. tumor involvement of adjacent soft tissues, iii. metastatic neck nodes, and iv. partial excision of the primary tumor<sup>17</sup>. Alotaibi O et al. reported that patients with PIOC who received

adjuvant radiotherapy after surgery had better survival, demonstrating the effectiveness of adjuvant therapy after surgery<sup>18</sup>. However Xu et al. believed that patients treated by surgery alone had a better survival rate than those who were treated with combined chemoradiotherapy, because the latter cohort of patients had more aggressive tumor and higher clinical and pathological stage of the tumor<sup>8</sup>, Some studies also believe that whether adjuvant radiotherapy or chemotherapy after surgery has no significant statistical difference in the OS<sup>19</sup>

In the present study, 6 patients who received surgical treatment alone, had an OS of 16.7%. The other 19 patients who were treated with radiotherapy and/or chemotherapy after surgery had an OS of 52.6%, which is significantly higher than that in patients who underwent surgery alone. The result showed that radiotherapy could significantly improve the survival rate of patients. Patients with tumor-free surgical margins and received adjuvant radiation had a higher survival rate (64.3% vs 33.3%) compared with those who received a radical radiotherapy. This may be associated with a lighter adverse effect of radiotherapy. It's the first time to report that radiotherapy can improve the survival for the patient with PIOC of the jaw with data to back it up. The reason for the differences among these studies may be that the number of patients included in some studies using radiotherapy or chemotherapy was too small, which failed to yield positive results. Moreover, patients in some of the studies received chemoradiotherapy in an insufficient dose, which made patients being unable to benefit from chemoradiotherapy and suffering increased toxic side effects. This study confirmed the indispensable role of surgical treatment in the management of PIOC patients and also emphasized that radiotherapy plays an irreplaceable role in the treatment of PIOC.

In the treatment of advanced squamous cell carcinoma of the head and neck, targeted therapy has become a routine treatment, which can shrink the tumor mass and kill micro tumor metastases, at the same time, it can reduce the dose of chemotherapy drugs to achieve better efficacy with fewer side effects<sup>20</sup>. Studies on PIOC targeted therapy are rarely reported. In our cohort, two patients were administrated nimotuzumab and one patient took cetuximab. The role of targeted therapy in PIOC needs further investigation because of the small size of sample.

## 5. Conclusions

Surgery remains an important treatment for primary intraosseous carcinoma; radio-therapy plays an increasingly important role in it; and the role of targeted and immuno-therapy in the treatment of primary intraosseous carcinoma needs further exploration. Further investigate should be carried out on classification, staging, radiotherapy technique, and standard treatment strategy for PIOC.

## 6. Abbreviations

PIOC primary intraosseous carcinoma

OS overall survival

PFS: progression free survival

PIOSCC: primary intraosseous squamous cell carcinoma

WHO: World Health Organization

MRI: magnetic resonance imaging

CT: computed tomography

HRs: hazard ratios

IMRT: intensity-modulated radiotherapy

AJCC: American Joint Committee on Cancer

NCCN: National Comprehensive Cancer Network

## Declarations

**Ethical Approval and Consent to participate:** The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the ethical committees of Sichuan Cancer Hospital, Chengdu, China. Patient consent was waived due to all data was analyzed anonymously.

**Consent for publication:** All authors agreed to be published.

**Availability of supporting data:** Not applicable

**Competing interests:** The authors declare no conflict of interest.

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## Tables

**Table 1.** Clinical characteristics of primary intraosseous carcinoma.

Characteristics		No. (%)
sex	male	19 (67.9%)
	female	9 (32.1%)
age	<60	12 (42.9%)
	≥60	16 (57.1%)
Location of tumor	Maxilla	12 (42.9%)
	Mandible	16 (57.1%)
Signs and Symptoms	mass	14 (50%)
	Pain	12 (42.9%)
	other	2 (7.1%)
sizes	<4cm	12 (42.9%)
	≥4cm	16 (57.1%)
T stage	T4	28 (100%)
N stage	N0	9 (32.1%)
	N+	19 (67.9%)
M stage	M0	27 (96.4%)
	M1	1 (3.6%)

**Table 2.** Pathologic and treatment characteristics of primary intraosseous carcinoma.

Characteristics		No. (%)
Histologic grade	Well differentiated	13 (46.4%)
	Moderately differentiated	9 (32.1%)
	poorly differentiated	6 (21.5%)
treatment	Surgery	6 (21.5%)
	Surgery+ adjuvant therapy	19 (67.8%)
	radiotherapy	3 (10.7%)
cervical lymph node dissection	no	11 (39.3%)
	yes	17 (60.7%)
radiotherapy	Radical radiotherapy	6 (21.4%)
	Postoperative adjuvant radiotherapy	14 (50%)
	without radiotherapy	8 (28.6%)

**Table 3.** univariate analysis for overall survival and progression-free survival

Variants		OS(%)	P	PFS(%)	P
Sex	Male	8(42.1%)	0.785	8(42.1%)	0.659
	Female	4(44.4%)		3(33.3%)	
Age	<60	5(41.7%)	0.791	5(41.7%)	0.817
	≥60	7(43.8%)		6(37.5%)	
Location of tumor	Maxilla	5(41.7%)	0.953	4(33.3%)	0.574
	Mandible	7(43.7%)		7(43.8%)	
Size	<4cm	6(50%)	0.282	5(41.7%)	0.689
	≥4cm	6(37.5%)		6(37.5%)	
N stage	N0	5(55.6%)	0.498	5(55.6%)	0.22
	N+	7(36.8%)		6(31.6%)	
Histologic grade	Well differentiated	6(46.2%)	0.313	6(46.2%)	<b>0.01*</b>
	moderately differentiated	5(55.6%)		5(55.6%)	
	poorly differentiated	1(16.7%)		0(0%)	
treatment	Surgery	1(16.7%)	<b>0.035*</b>	1(16.7%)	0.347
	Surgery+ adjuvant radiotherapy	10(52.6%)		9(47.4%)	
	radiotherapy	1(33.3%)		1(33.3%)	
neck dissection	no	5(45.5%)	0.375	4(36.4%)	0.828
	yes	7(41.2%)		7(41.2%)	
radiotherapy	Radical radiotherapy	2(33.3%)	<b>0.01*</b>	2(33.3%)	0.168
	Postoperative adjuvant radiotherapy	9(64.3%)		8(57.1%)	

without radiotherapy

1 (12.5%)

1 (12.5%)

**Table 4** Cox's regression analysis involved in overall survival and progression-free survival—multivariate analysis

Variable	OS		PFS	
	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)
Histologic grade	0.745	1.187 (0.422-3.335)	0.351	1.602 (0.594-4.319)
radiotherapy	<b>0.007*</b>	0.212 (0.068-0.660)	0.069	0.397 (0.147-1.074)

## Figures

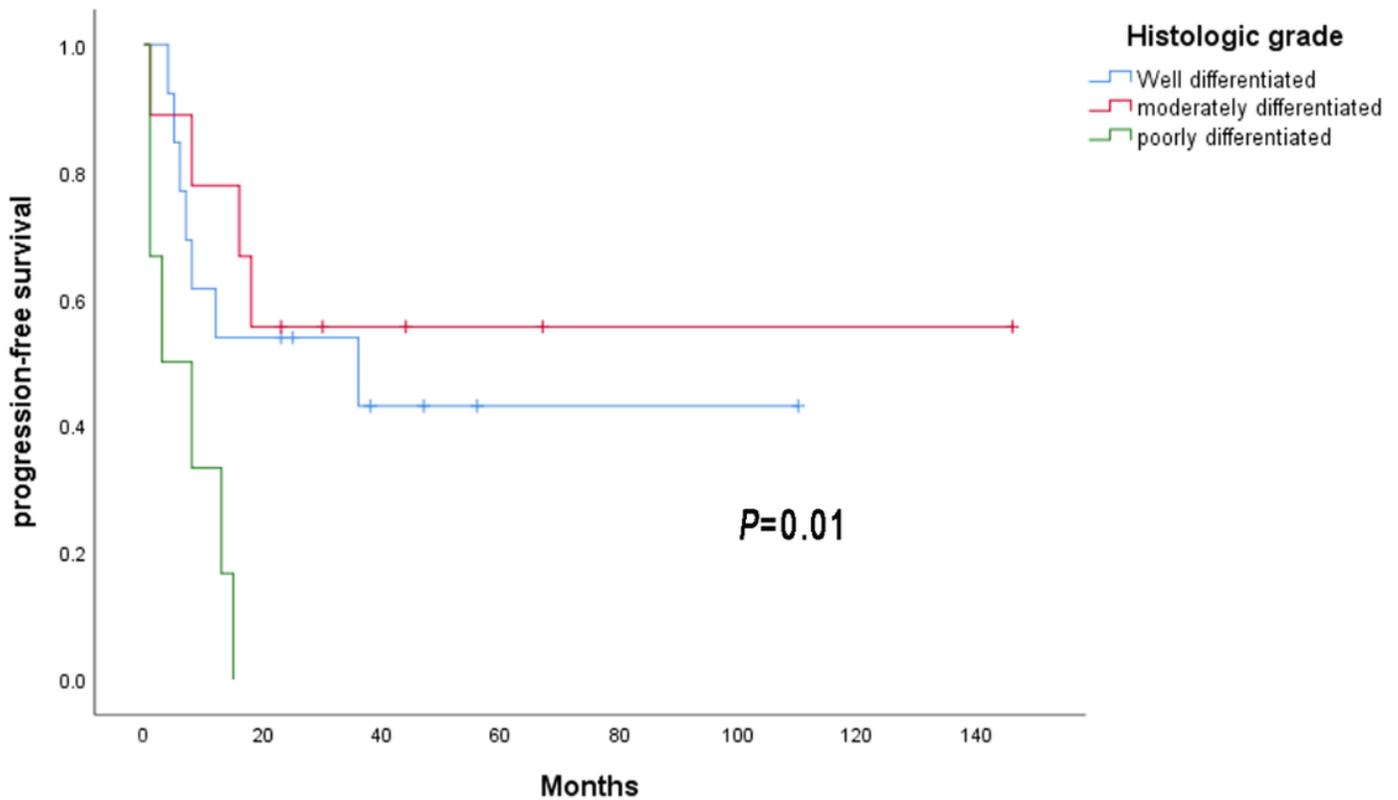


Figure 1

## Progression-free survival by different histologic grade

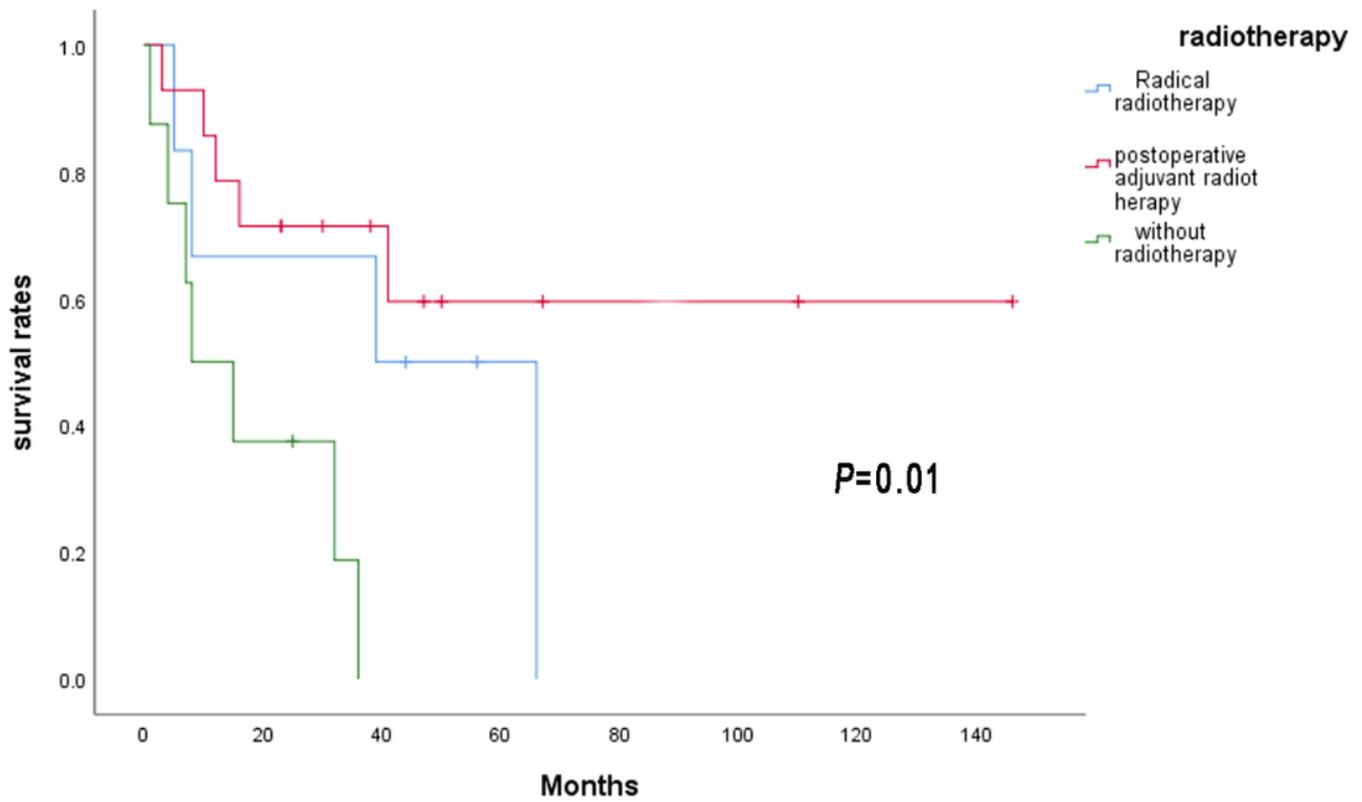


Figure 2

Overall survival by different radiotherapy modalities