



Title	Salvage operations for patients with persistent or recurrent cancer of the maxillary sinus after superselective intra-arterial infusion of cisplatin with concurrent radiotherapy
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**Title:** Salvage surgery for patients with persistent or recurrent maxillary sinus cancer after superselective intra-arterial cisplatin infusion with concomitant radiotherapy.

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**Running title:** Salvage surgery for patients with recurrent maxillary sinus cancer

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## **ABSTRACT**

The purpose of our study was to evaluate the feasibility of salvage surgery for patients with persistent or recurrent maxillary sinus cancer after superselective intra-arterial cisplatin infusion with concomitant radiotherapy (RADPLAT). We retrospectively analyzed 61 patients with maxillary sinus cancer who underwent RADPLAT. Chemotherapy comprised 100–120 mg/m<sup>2</sup> superselective intra-arterial cisplatin administered at a median rate of four times weekly. Concurrent radiation therapy was administered at a median dose of 65Gy. Persistent/recurrent maxillary sinus cancer was observed in 17 patients. Salvage surgery was performed in 11 patients. Persistent/recurrent primary disease was controlled in 8 of 11 patients undergoing salvage surgery (72.7%). Seven of 11 patients undergoing salvage surgery (63.6%) have survived without any evidence of disease. The 5-year overall survival rate of patients undergoing salvage surgery was calculated to be 60.6%. The incidence rate of significant perioperative complications was 18.2% (2/11). Salvage surgery for patients with persistent/recurrent maxillary sinus cancer after RADPLAT is considered to be both safe and successful. We also consider that salvage surgery is good option when persistent/recurrent maxillary sinus cancer is observed after RADPLAT.

## **Introduction**

Maxillary sinus cancer is not common, comprising only about 3% of all head and neck cancer and about 0.5% of all malignant disease. The annual incidence rate is 0.5-1.0 per 100,000 population, and squamous cell carcinoma is the most frequent histologic type and was found in 57% of patients with maxillary sinus cancer [1-3].

Many authors have recommended combined therapies consisting of en bloc radical resection together with irradiation [4-6]. However, the cosmetic problems for patients undergoing en bloc resection are significant. Therefore, multi-modality treatments have been introduced to avoid cosmetic problems as well as to preserve ocular function and to improve patient outcomes. In Japan, superselective intra-arterial cisplatin infusion with concomitant radiotherapy (RADPLAT) has been introduced to preserve the orbital contents and ocular function in patients with advanced maxillary sinus cancer [7,8]. This non-surgical treatment has been reported to be both safe and highly effective.

Salvage surgery is generally attempted, when localized persistent or recurrent primary tumors are observed after initial chemoradiotherapy [9-12]. However, there have been no reports of salvage surgery for patients with persistent/recurrent maxillary sinus cancer after intensive chemoradiotherapy to date. The purpose of our study was to evaluate the feasibility of salvage surgery as well as prove its efficacy for patients with persistent/recurrent maxillary sinus cancer after RADPLAT.

## **Method**

**Patients.** We retrospectively analyzed 61 patients with maxillary sinus squamous cell carcinomas who underwent RADPLAT in Hokkaido University Hospital, Japan between September 1999 and July 2012. T and N stages were classified according to the American Joint Committee on Cancer (AJCC) staging system 2010. Table 1 presents patient demographics.

**Radiotherapy.** The irradiation plan during the period 2006–2012 was 40 Gy in 20

fractions of 2 Gy over four weeks for the primary site and involved nodal areas, immediately followed by a boost of 30 Gy in 15 fractions to the primary cancer over an additional three weeks (total dose, 70 Gy). Between 1999 and 2005, involved nodal areas and the primary site were irradiated with 40 Gy in 16 fractions of 2.5 Gy over four weeks, with a boost irradiation of 25 Gy in 10 fractions to the primary tumor over an additional 2.5 weeks (total dose, 65 Gy).

**Chemotherapy.** Chemotherapy comprised the administration of 100–120 mg/m<sup>2</sup> superselective intra-arterial cisplatin at a median rate of four times weekly (range, 2–5 times, mean 3.7 times). At the same time, sodium thiosulfate was administered intravenously (24 g/body) to provide effective cisplatin neutralization.

**Salvage surgery:** Patients not receiving a full course of irradiation (<65 Gy) were referred for salvage surgery at the end of radiotherapy. For patients receiving a full course of irradiation dose (>65 Gy), computed tomography (CT) and/or magnetic resonance (MR) imaging were performed within three months after the completion of treatment. If persistent primary disease was observed, biopsy was attempted and salvage surgery was indicated by the presence of viable tumor cells.

Patients were usually monitored monthly for recurrence in the first year, every couple of months in the second year, and every 6 or 12 months thereafter until death or data censoring. CT scans or MR imaging were routinely performed once every three months in the first year, and every 6 or 12 months thereafter. If recurrent primary disease was suspected, biopsy was attempted and, again, salvage surgery was indicated by the presence of tumor cells. Surgical complications were graded using the Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0.

**Statistics.** The Kaplan-Meier method was applied for survival and local control rates. The time of interest for survival and local control rates was the duration from the start of treatment to death or failure. A p-value of less than 0.05 was considered statistically significant. JMP Pro 10.0.2 statistical software (SAS Institute, Cary, NC) was used for the statistical analysis.

## Results

**Chemoradiotherapy.** Intra-arterial chemotherapy was performed a median 4 times. The median irradiation dose was 65 Gy. Fifty-eight patients (95%) underwent a full course of irradiation (>65 Gy). In one patient, RADPLAT was cancelled due to severe neutropenia and sepsis after the second intra-arterial cisplatin infusion, and palliative treatment was administered. In another patient, ischemic colitis developed after the first intra-arterial chemotherapy. Intra-arterial chemotherapy was, therefore, suspended, and he underwent 50 Gy of radiotherapy followed by salvage surgery. In the final patient, intra-arterial chemotherapy was performed four times. However, he chose to suspend the subsequent radiation therapy after receiving 48 Gy of irradiation out of concern for severe late complications of radiotherapy.

**Clinical outcomes.** Persistent/recurrent maxillary sinus cancer was observed in 17 patients (27.9%), with salvage surgery performed in 11 of the 17 patients with persistent/recurrent primary disease (64.7%). Local recurrence developed in 3 patients at a median five months (range, 2-22 months) after salvage surgery, and all three patients died of primary disease. In another patient, distant metastasis developed 15 months after salvage surgery and he died of distant disease at 20 months after salvage surgery. The remaining seven patients survived without any evidence of diseases (Figure 1). Persistent/recurrent primary disease was controlled in eight of 11 patients undergoing salvage surgery (72.7%), and seven patients of all 17 patients with persistent/recurrent maxillary sinus cancer (41.2%) have survived without any evidence of disease after undergoing salvage surgery.

Of the 17 patients with persistent/recurrent primary disease, salvage surgery was not performed in 6 patients (35.3%). Details of these patients are shown in Table 2. Various chemotherapies were used for three patients according to their general conditions. Only one patient, who received adjunctive chemotherapy, remains alive with primary disease.

The 5-year overall survival rate of all 61 patients was 68.1%. The 5-year local control rate by RADPLAT and salvage surgery was 81.3% (Figure 2). Figure 3 shows

the overall survival curves for the 17 patients with persistent/recurrent primary disease, the 11 patients undergoing salvage surgery, and the 6 patients not receiving salvage surgery. The 5-year overall survival rate of the 11 patients undergoing salvage surgery was calculated to be 60.6% by the Kaplan-Meier method.

**Salvage surgery.** Salvage surgery was performed for 11 patients at a median 4.2 months (range, 1 to 46 months) after the completion of RADPLAT. Details of the salvage surgery are given in Table 3. Seven of the 11 patients underwent total maxillectomy with a Weber-Ferguson skin incision. Skull base resection and endoscopic partial maxillectomy was performed in one patient, and the remaining three patients underwent partial maxillectomy. Post-operative complications (Grade 2-4) were observed in two patients (18.2%), comprising deep vein thrombosis (Grade 2) in one patient and local infection and sepsis (Grade 3) in the other.

## **Discussion**

For most maxillary sinus squamous cell carcinomas, a combination of radical surgery and preoperative or postoperative radiation therapy constitute the standard treatment. Total maxillectomy, with or without orbital exenteration, is the most commonly performed surgical operation for maxillary sinus cancers. However, functional and cosmetic outcomes after surgical treatment for patients with advanced tumors are also far from satisfactory from the patient standpoint. In our institution, RADPLAT was attempted to preserve ocular function and avoid cosmetic problems for patients with advanced maxillary sinus cancer who hoped to undergo non-surgical treatment. In particular, we think that the unresectable tumors or the tumors with orbital invasion may be a good indication for RADPLAT. In Japan, RADPLAT has been reported to be both safe and effective for patients with maxillary sinus cancer [7,8]. However, additional treatment is often problematic when persistent/recurrent maxillary sinus cancer is observed. We, therefore, focused on salvage surgery for patients with persistent/recurrent maxillary sinus cancer after RADPLAT, and evaluated the feasibility of salvage surgery after RADPLAT in terms of the complication rate and

salvage rate.

The complication rate of salvage surgery after intensive chemoradiation therapy for patients with head and neck cancer was reported to be 11%–63.2% [7-10]. In 1998, Curran *et al.* reported salvage surgery after radiotherapy for patients with paranasal malignancies [13]. In this article, the complication rate of salvage surgery was indicated to be 24%. In our current study, the post-operative complication rate was 18.2%, which is comparable to those published in recent reports. Therefore, salvage surgery after RADPLAT is considered to be both safe and feasible.

Intensive chemoradiation therapy, such as RADPLAT is available for the purpose of avoiding surgical stress. However, salvage surgery may be almost the only alternative for the treatment against persistent/recurrent primary disease after intensive chemoradiation therapy. It was reported that salvage surgery for persistent/recurrent cancer of head and neck can be difficult in terms of surgical technique, and has not only high complication rates but also low salvage rates [14,15]. In addition, salvage surgery for patients with recurrent upper-aerodigestive-tract cancer may frequently lead to fistula formation and/or severe infectious complications, which may cause carotid artery bleeding or prolong hospitalization. In cases of persistent/recurrent maxillary sinus cancer, we believe that salvage surgery is safer as there is no potential for fistula formation associated with maxillectomy.

Persistent/recurrent primary disease was controlled in 8 of 11 patients undergoing salvage surgery (72.7%). Seven of the 17 patients with persistent/recurrent maxillary sinus cancer (41.2%) have survived without any evidence of disease after undergoing salvage surgery. The cause of this favorable salvage rate might be that persistent/recurrent primary disease is frequently localized and oncologically resectable after RADPLAT in patients with maxillary sinus cancer.

In conclusion, salvage surgery for patients with persistent/recurrent maxillary cancer after RADPLAT is considered to be safe and successful. We further considered that the overall survival rate of patients undergoing salvage surgery is favorable (60.6%), and that salvage surgery is a good option in cases where persistent/recurrent maxillary



sinus cancer is observed after RADPLAT. It is also important to recognize persistent/recurrent primary disease as soon as possible so as not to miss the opportunity to perform salvage surgery.

### **Conflict of interest statement**

None declared.

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laryngopharyngectomy and salvage laryngopharyngectomy for advanced hypopharyngeal cancer. *Head Neck*. 2010;32:1494-1500.

### **Figure legends**

Figure 1. Clinical outcomes of 61 patients with maxillary sinus cancer after intra-arterial cisplatin infusion with concomitant radiotherapy.

RADPLAT: intra-arterial cisplatin infusion with concomitant radiotherapy, NED: no evidence of disease, AWD: alive with disease, DOD: dead of disease

Figure 2. The overall survival curve and the local control curve of all 61 patients with maxillary sinus cancer after intra-arterial cisplatin infusion with concomitant radiotherapy.

Figure 3. The overall survival curves of the 17 patients with persistent/recurrent maxillary cancer, 11 patients undergoing salvage surgery, and 6 patients not receiving salvage surgery.

Table 1. Patient Demographics

Characteristic	No. of patients (%)
Total	61
Gender	
Male	50 (82%)
Female	11 (18%)
Age, years	
Median	61
Range	35-74 (Ave. 59.3)
Follow-up period, months	
Median	64.4
Range	8.9-142.5 (Ave. 60.7)
T classification	
T2	1 (1%)
T3	17 (28%)
T4a	30 (49%)
T4b	13 (21%)
N classification	
N0	49 (80%)
N1	7 (11%)
N2b	5 (9%)

Table 2. Details of the seven patients not undergoing salvage surgery

Case	Age	Sex	Classification		Radiation dose	Times of chemotherapy	Reason for not undergoing salvage surgery	Additional treatment	Outcome (Observation period after recurrence)
			T	N					
1	72	M	4b	0	65	3	Poor general condition	Chemotherapy	DOD (11 months)
2	68	M	3	0	65	3	Poor general condition	Palliative treatment	DOD (12 months)
3	57	M	4b	2b	65	4	Unresectable	Chemotherapy	DOD (7 months)
4	70	M	4b	0	70	4	Poor general condition	Palliative treatment	DOD (1 months)
5	72	M	3	0	70	2	Refusal of surgery	Chemotherapy	AWD (3 months)
6	73	M	4a	0	24	2	Poor general condition	Palliative treatment	DOD (3 months)

DOD: dead of disease, AWD: alive with disease

Table 3. Details of the eleven patients undergoing salvage surgery

Case	Age	Sex	Classification		Radiation dose	Times of chemotherapy	Type of surgery	Reconstruction for palate defects	Orbital exenteration	Complications	Outcome (Observation period after surgery)
			T	N							
1	60	M	4a	0	65	1	Total maxillectomy	STSG + Prothesis	+	-	Dead of primary disease (13 months)
2	69	F	3	0	65	3	Frontal craniotomy + ESS	none	+	-	NED (4 years)
3	67	M	4a	0	50	2	Total maxillectomy	STSG + Prothesis	-	-	NED (6 years)
4	48	M	4b	0	48	4	Partial maxillectomy	none	-	-	NED (5 years)
5	37	M	4a	0	70	4	Partial maxillectomy	STSG + Prothesis	+	-	NED (4 years)
6	73	M	4a	1	64	4	Total maxillectomy	RAMCF	+	Sepsis (Gr3)	NED (4 years)
7	64	M	3	1	70	4	Total maxillectomy	STSG + Prothesis	-	DVT (Gr2)	Dead of distant disease (20 months)
8	62	M	4a	1	70	5	Total maxillectomy	STSG + Prothesis	+	-	Dead of primary disease (43 months)
9	63	M	4a	0	70	5	Partial maxillectomy	none	-	-	NED (2 years)
10	60	M	4a	0	50	1	Total maxillectomy	STSG + Prothesis	-	-	NED (2 years)
11	60	M	4a	2b	70	4	Total maxillectomy	Prothesis	+	-	Dead of primary disease (7 months)

ESS: Endoscopic sinus surgery, STSG: Split thickness skin graft, RAMCF: Rectus abdominis myocutaneous flap, DVT: Deep vein thrombosis, NED: No evidence of disease

Figure 1

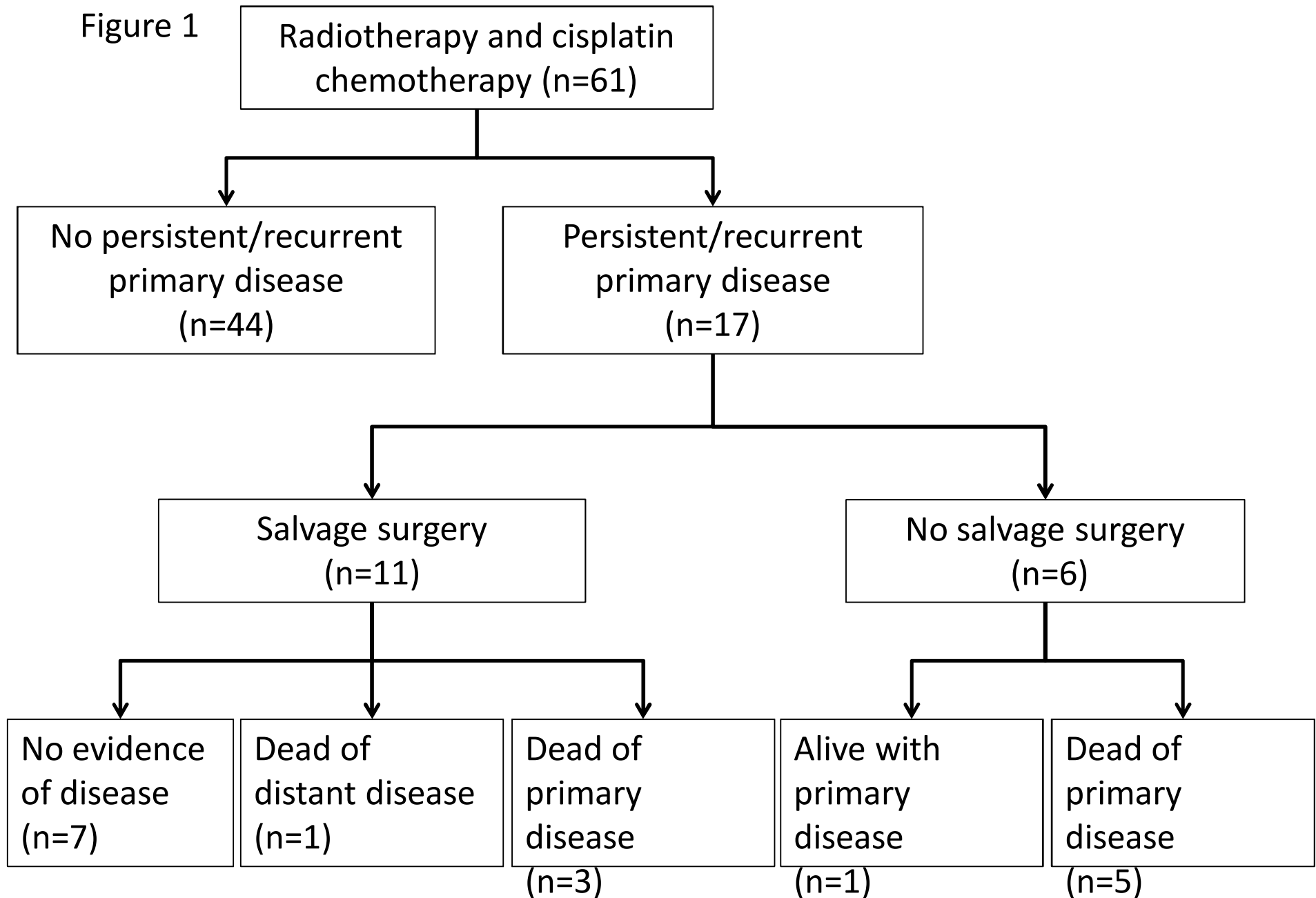




Figure 2

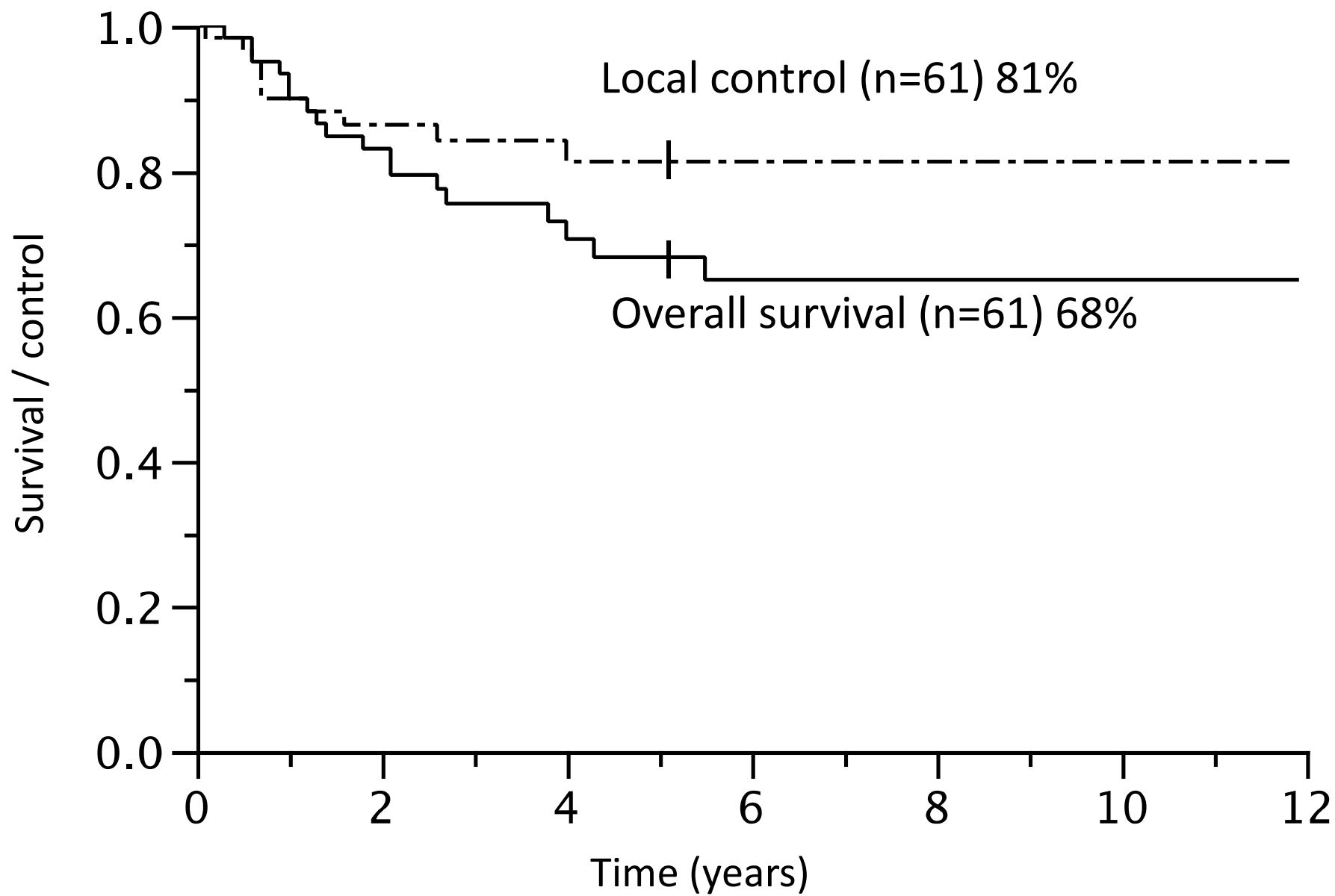


Figure 3

