Title: Treatment outcomes of the patient with sinonasal mucosal melanoma: the role of endoscopic resection and postoperative radiotherapy

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Abstract

Background

The standard of care for sinonasal mucosal melanoma is surgery and postoperative radiotherapy (PORT). Our treatment strategy comprises endoscopic resection and PORT. We performed combined endoscopic and open resection or applied an external approach alone when sufficient resection was difficult to achieve endoscopically. The objective of this study was to evaluate the validity of our treatment strategy.

Methods

We assessed 30 patients with sinonasal mucosal melanoma who underwent definitive therapy between January 2002 and April 2021, and conducted a retrospective analysis. The median follow-up period was 2.2 years. The primary endpoint was overall survival. The Kaplan-Meier method was used for the calculation of survival rates, the cumulative incidence of distant metastasis, and local recurrence.

Results

Twenty-eight patients underwent surgery. The other two patients were treated by definitive proton beam therapy. Twenty-one of 28 (75%) patients underwent resection by

endoscopic approach alone. Postoperative radiotherapy was performed for all 28 patients who underwent surgery. Twenty-one patients (70%) experienced recurrence during the observation period. Overall, distant metastasis was observed in 19 patients. Twelve patients died during the observation period, with 10 of the 12 patients (83%) dying of distant metastasis. The overall survival rate at 2 and 5 years was 70% and 46%, respectively. The cumulative incidence rate of distant metastasis at 2 years was 63%, while the 2-year cumulative incidence rate of local recurrence was 6.7%.

Conclusion

The local disease was controlled by our treatment strategy. To improve treatment outcomes, control of the distant metastasis is needed.

Keywords

Sinonasal mucosal melanoma, endoscopic resection, postoperative radiotherapy, adjuvant therapy, distant metastasis.

Introduction

Mucosal melanoma is a rare malignancy, with an estimated incidence of 0.7 in 100,000 new cases per year [1]. More than 50% of mucosal melanomas arise in the head and neck area, with 66% of these arising in the sinonasal tract [2]. Sinonasal mucosal melanoma (SNMM) is an aggressive malignancy with a poor prognosis due to local recurrence and distant metastasis, with the 5-year overall survival rate (OS) reported to be 24% [3]. Previous studies reported cumulative incidence rates of local and distant recurrences of 43% and 66%, respectively [4, 5].

The standard of care for SNMM is surgery and postoperative radiotherapy (PORT) [6]. Adjuvant treatment with immune checkpoint inhibitors is also a treatment option. However, the respective indications for PORT and adjuvant systemic therapy have not been established. Recent advances in endoscopic resection have enabled endoscopic surgery to be adopted for malignant sinonasal tumors [7, 8]. Some studies reported that endoscopic resection for patients with SNMM had similar outcomes to those for open resection [9–11].

Our treatment strategy is shown in Fig. 1. In general, treatment for the primary lesion comprises endoscopic resection and PORT. We performed combined endoscopic and open resection or applied an external approach alone when sufficient resection was

difficult to achieve endoscopically. We recommended definitive radiotherapy if patients did not want to undergo surgical treatment. We did not perform neoadjuvant or adjuvant systemic therapy. The objective of this study was to evaluate the validity of our treatment strategy.

Patients and methods

Patients

Between January 2002 and April 2021, 32 patients with previously untreated SNMM were treated at Hokkaido University Hospital. We excluded two patients who were not indicated for definitive treatment: one patient had distant metastasis and treatment for the other was regarded as problematic because of poor general condition. These two patients had T4b disease. Thirty patients were eligible for this study. All 30 patients were histologically diagnosed with malignant melanoma. The median follow-up period was 2.2 years (range: 0.5–8.6 years). Patient characteristics are shown in Table 1. No patients with T4b disease were included in our study. This study was approved by the Institutional Review Board at Hokkaido University Hospital (No. C-T2020-0152) and the study was performed in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Pretreatment

The clinical stage was evaluated by endoscopic nasal examination, contrast-enhanced computed tomographic (CT) imaging, magnetic resonance (MR) imaging, and positron emission tomography, where possible. Precontrast CT or MR imaging was acceptable for patients unable to tolerate the contrast agent. Ultrasonography of the neck was used to evaluate lymph node metastasis as required. For all patients, the clinical stage was determined before treatment by the cancer board consisting of head and neck surgeons, radiation oncologists, diagnostic radiologists, and medical oncologists. All staging was completed according to the 7th Union for International Cancer Control (UICC) criteria.

Surgery and radiotherapy

The details of the treatment are shown in Table 2. Twenty-eight patients underwent surgery, with the other two patients treated by definitive proton beam therapy because their tumor involved the nasal wing and they did not want reconstructive surgery. Twenty-one of the 28 (75%) patients underwent resection by endoscopic approach alone. Postoperative radiotherapy was performed for all 28 patients who underwent surgery. The number of patients irradiated with photon or proton beams was 17 and 11, respectively.

Until the year 2017, radiotherapy was predominantly performed with photon beams, and from 2018 with proton beams. Basically, postoperative irradiation was administered via photon beam therapy with a total dose of 60 Gy in 30 fractions or proton beam therapy with 30 Gy relative biological effectiveness (RBE) in 5 fractions. In cases of macroscopic residual tumors after surgery or definitive intent, radiotherapy was performed with proton beams at a total dose of 60 Gy RBE in 15 fractions. One patient was initially scheduled for photon beam therapy with 60 Gy RBE in 15 fractions for macroscopic residual disease. However, because of the subsequent development of interstitial pneumonia and large vessel vasculitis, PORT was performed with photon beams at a total dose of 30 Gy in 5 fractions. Details of radiotherapy are shown in Table 3. No patients underwent preoperative therapy. In patients without neck metastasis, no elective neck treatment was performed.

Follow-up management

Patients were usually monitored monthly for recurrence during the first year, every two months during the second year, and every 3 to 6 months thereafter until death. CT and MR imaging were routinely performed every 3 to 6 months. Positron emission tomography was performed as required. When residual/recurrent disease was suspected,

biopsy or fine needle aspiration cytology was attempted, where possible.

Types of recurrence

Each case of recurrence was categorized when first detected. Categories consisted of local recurrence, nodal recurrence, local and nodal recurrence, or recurrence with distant metastasis. We did not distinguish between residual disease and local recurrence. Patients who had combined local/nodal recurrence and distant metastasis were categorized as recurrence with distant metastasis. Patient prognosis was assessed by type of recurrence.

Statistics

All statistical analyses were performed using JMP Pro 16.0.0 statistical software (SAS Institute, Cary, NC). The primary outcome was OS. The Kaplan-Meier method was used for the calculation of OS, recurrence-free survival rate, cumulative incidence of distant metastasis, and local recurrence. The time of interest was the period from the first day of the initial treatment to death or failure. Follow-up data were obtained until June 31, 2022. Survival or cumulative incidence rates were calculated for each T classification. Differences in probabilities between curves were evaluated by log-rank test. The level of statistical significance was set at $p < 0.05$.

Univariate hazard ratios and corresponding 95% confidence intervals were calculated according to the Cox proportional hazards model for OS and cumulative incidence of distant metastasis, including age, gender, anatomical site, and T and N classification. Multivariate Cox regression analysis was not conducted because of the limited number of patients.

Results

Clinical outcomes

Twenty-one patients (70%) experienced recurrence during the observation period. Figure 2a shows the distribution of first recurrence sites. Recurrence was first observed locally in three patients, while three other patients had isolated nodal recurrence. Thirteen patients who experienced distant metastasis alone and two with combined nodal and distant recurrence were categorized as recurrence with distant metastasis. Figure 2b shows the distribution of recurrence sites over the whole observation period. Overall, distant metastasis was observed in 19 patients (63%). The sites of distant metastasis are shown in Table 4. The most frequent site of metastasis was the lung (n = 11), followed by the liver (n = 10) and the adrenal gland (n = 6).

The treatment course of the patients is shown in Fig. 3. All three patients with local

recurrence had subsequent distant metastasis (Fig. 3b). Two of the three patients with nodal recurrence underwent neck dissection and the other was treated with an immune checkpoint inhibitor (Fig. 3c). Twelve of the 15 patients with distant metastasis were treated with systemic therapy (Fig. 3d) and two patients underwent systemic therapy followed by salvage surgery for isolated residual metastatic disease, with one of those patients undergoing distal pancreatectomy and the other undergoing left hepatectomy. These two patients discontinued systemic therapy and were alive with no evidence of disease at the latest follow-up. Twelve patients died during the observation period. Ten of the 12 patients (83%) died of distant metastasis, while the other two patients died of other cancer. Two patients undergoing definitive proton beam therapy were alive without recurrence at the latest follow-up (Fig. 3a).

Nine patients had positive surgical margins due to multiple skip lesions or advanced mucosal extension. Among these nine patients, seven had microscopic residual disease while the other two had macroscopic residual disease. These two patients with macroscopic residual disease underwent endoscopic resection or combined approach. One patient had a skull base extension and the other had a lachrymal sac extension. Therefore, the tumor could not be resected completely. The number of unknown or negative margins was 7 and 12, respectively. Postoperative surgical complications were

found in three patients. Wound infection was experienced in two patients who underwent total maxillectomy. Every complication was equal to or lower than grade 2 (Clavien-Dingo classification) and no patients died during the perioperative period.

The OS for the entire cohort at 2 years was 70%, while that at 5 years was 46% (Fig. 4a). Figure 4b shows the OS of the patients stratified by T classification. T classification was significantly associated with OS (P = 0.049). The recurrence-free survival rate at 2 and 5 years was 29% and 17%, respectively (Fig. 4c). Patients with higher T classification were associated with an inferior recurrence-free survival rate (Fig. 4d, P = 0.022). The cumulative incidence rate of distant metastasis at 2 years was 63% (Fig. 4e) and patients with T4 disease had a higher rate of distant metastasis (Fig. 4f, P = 0.023). On the other hand, the 2-year cumulative incidence rate of local recurrence was 6.7% and no patients with T4 disease experienced local recurrence (Fig. 4g, h).

Table 5 shows the univariate analyses of the predictive factors for OS. No factor was significantly associated with OS. Higher T classification (HR = 3.8; 95%CI, 1.3–11) and sinus disease (HR = 19; 95%CI, 2.6–139) were associated with a cumulative incidence rate of distant metastasis (Table 6).

Discussion

In the current study, the 2-year and 5-year OS for the entire cohort were 70% and 46%, respectively. These rates were comparable with those in previous reports [4, 5, 12–14] (Table 6). Therefore, we consider our treatment strategy appropriate for patients with SNMM. However, 19 patients (63%) experienced distant metastasis during the observation period. The incidence rate of distant metastasis was especially high in patients with T4 disease (Fig. 4f). Ten patients died of the disease and with the cause of death being distant metastasis for all (Fig. 3). In general, distant metastatic disease was treated by systemic therapy. While the treatment outcomes of the two patients who underwent salvage surgery were promising, we consider the indication for salvage surgery for distant metastasis to be a single, relatively slow-glowing lesion evaluated as resectable. We think salvage surgery for distant metastasis would improve treatment outcomes, at least in part.

Adjuvant systemic therapy is one of the standard treatments for cutaneous malignant melanoma. Previous studies reported that adjuvant systemic therapy with immune checkpoint inhibitor improved distant metastasis-free survival, recurrence-free survival, or OS in patients with completely resected cutaneous malignant melanoma [15, 16]. Checkmate 238 compared nivolumab with ipilimumab as an adjuvant treatment for patients with high-risk resected cutaneous and mucosal melanoma [17, 18]. Nivolumab was found to provide longer recurrence-free survival than did ipilimumab. However, this

result has limitation as the number of mucosal melanoma patients was as small as 29, compared to 877 cutaneous melanoma patients. Checkmate 067 was conducted on 945 patients with unresectable or metastatic malignant melanoma, which included 79 patients with mucosal melanoma [19]. OS and recurrence-free survival were longer in patients who received nivolumab and ipilimumab or nivolumab alone than in those who received ipilimumab alone. However, Checkmate 067 was not conducted as adjuvant therapy. Although a large-scale prospective study has not been conducted, adjuvant systemic therapy with nivolumab may improve the treatment outcomes for patients with SNMM.

The cumulative incidence rate of local recurrence at 2 and 5 years was 6.7% and 28%, respectively (Fig. 4g). Local recurrence was detected in four patients with T3 disease, but was not seen in those with T4 disease. These four patients had positive surgical margins. In the current study, nine patients had positive surgical margins. Therefore, five of the nine patients undergoing incomplete resection did not experience local recurrence. Residual diseases may, therefore, be considered to be controlled by PORT. Wide resection sometimes results in severe postoperative impairment. In some cases, decision-making regarding the extent of resection is challenging. We think that local recurrence was not detected in T4 disease patients due to the small population size and poor survival outcomes. The number of enrolled patients with T4 disease was eight

and their 2-year recurrence-free survival rate was 0%. All cases of recurrence with T4 disease had distant metastasis. Our treatment strategy for SNMM consisted of endoscopic resection and PORT. Previous studies reported that endoscopic resection is associated with similar outcomes, in terms of OS or local control, as open resection [8–11, 20, 21]. We resected the tumor with reference to "attachment-oriented surgery" with some modifications [7]. The surgery begins with debulking of the tumor to identify the area in which the tumor originated. After identifying the entire attachment area of the tumor, a 6–8 point biopsy is performed at 1.0 cm from the tumor margin for rapid intraoperative diagnosis. A mucosal incision is then performed at a pathologically confirmed tumor-negative area. If the underlying tumor bone is eroded, the bone is resected with a diamond bar. In the current study, one patient underwent bone resection with this method. This patient had pancreatic metastasis 1 year 8 months after surgery. However, the patient is alive with no evidence of disease after treatment by systemic therapy followed by salvage surgery. The tumor in this patient originated in the nasal septum. On the other hand, the subsite in the majority of patients in our study was the nasal lateral wall (20/30). In many such cases, the underlying bone was widely resected with the primary lesions. Therefore, most patients did not undergo bone resection with a diamond bar. We have not performed extended resection, such as craniofacial resection or orbital exenteration, as such surgery

is not considered to afford survival benefits. Previous studies reported postoperative mortality and complication rates of 6% and 26%, respectively [22]. These rates were comparable to those for other malignant tumors of the skull base. However, the survival rates for SNMM were much poorer.

The validity of PORT for SNMM is controversial [23]. Several studies reported that although local control was improved, OS was not improved by PORT [14, 24]. The tumor burden of local recurrence strongly decreased the quality of life because of pain, bleeding, and deformation. In the current study, the external approach was applied only in cases in which the tumor was difficult to resect endoscopically. Extended resection, such as craniofacial resection or orbital exenteration, was not performed. Therefore, in our study, the resection margins were narrower than those in previous studies. Nevertheless, we observed a relatively low local recurrence rate due, to a large degree, on the effectiveness of PORT. The precise judgment of the surgical margin for SNMM was difficult because the tumor was sometimes resected piece by piece and often presented as skip lesions [25]. It has been unclear as to what patients PORT can be omitted; thus, we recommend that every patient undergo PORT.

Nodal recurrence was observed in 6 patients (20%, Fig. 2b). However, nodal recurrence did not directly result in any deaths. The management of patients with

clinically N0 SNMM has not been established [26] and omitting elective neck dissection or irradiation can allow various adverse effects to be avoided. In consideration of the pros and cons, we have not performed elective neck treatment for patients with clinically N0 disease.

We acknowledge several limitations to our study. First, this retrospective study was based on a small number of eligible patients. This may be acceptable as SNMM is a rare disease and our treatment strategy, consisting of endoscopic resection and PORT, was not changed over the observation period. Second, the long-term survival rate was difficult to estimate because of the short median follow-up period (2.2 years), which was shortened due to the generally poor prognosis. Ten patients died of distant metastasis and the 2-year cumulative incidence rate was 63%. The established standard of care for SNMM is local therapy, consisting of surgical resection and PORT. Distant metastasis was not controlled by the current treatment strategy.

In terms of local control, our treatment strategy is regarded as appropriate. However, to improve treatment outcomes, control of distant metastasis is needed. The role of adjuvant systemic therapy also needs to be clarified by prospective studies.

Conclusion

Treatment outcomes based on our treatment strategy were favorable enough for it to be recommended as a local therapy. The local disease was controlled by our treatment strategy; however, to improve treatment outcomes, control of the distant metastasis is needed. Appropriate adjuvant systemic therapy should also be examined in prospective studies.

Disclosure statement: The authors declare no conflicts of interest associated with this manuscript.

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Figure Legends

Table 1. Characteristic of the eligible patients (n = 30).

Table 2. Details of the treatment.

Table 3. Irradiation doses of postoperative radiotherapy.

Table 4. Details of the distant metastasis sites.

Table 5. Univariate Cox regression analyses for overall survival rate.

Table 6. Univariate Cox regression analyses for distant metastasis.

Table 7. Overall survival rates for the current and previous studies.

Fig. 1. Treatment strategy. Patients undergo an external approach when sufficient resection is difficult to achieve endoscopically. Abbreviations: SNMM, sinonasal mucosal melanoma

Fig. 2. Patterns of first recurrence (a). Fifteen patients were categorized as recurrence with distant metastasis. Patterns of recurrence over the whole observation period (b). Nineteen patients experienced distant metastasis.

Fig. 3. Treatment course (a). Patients were categorized by first recurrence pattern; local

recurrence (b), nodal recurrence (c), and distant metastasis (d). Abbreviations: SNMM, sinonasal mucosal melanoma; PORT, postoperative radiotherapy; NED, no evidence of disease; DOOD, dead of other disease; ICI, immune checkpoint inhibitor therapy; BSC, best supportive care; DOD, dead of disease; AWD, alive with disease; ND, neck dissection; RT, radiotherapy.

Fig. 4. Overall survival rates for all patients (a), and patients stratified by T classification (b). Recurrence-free survival rates for all patients (c), and patients stratified by T classification (d). Cumulative incidence rates of distant metastasis (e, f) and local recurrence (g, h). No patients with T4b disease were included.

Table 1. Characteristics of the eligible patients (n = 30).

Characteristic	
Overall	30
Gender	
Male	18
Female	12
Age, years	
Median (range)	72 (45–83)
Follow-up period, years	
Median (range)	2.2 (0.5–8.6)
Site and subsite	
Nasal cavity	28
Lateral wall	20
Nasal septum	6
Nasal floor	2
Paranasal sinus	2
Maxillary sinus	2
T	
3	22
4a	8
4b	0
N	
0	28
1	2
Stage	
III	22
IV	8

Table 2. Details of the treatment.

Treatment	
Surgery	28
Endoscopic resection	21
Combined approach	1
External approach	6
Postoperative radiotherapy	28
X-ray/Proton beam	17/11
Definitive radiotherapy	2
X-ray/Proton beam	0/2

Table 3. Irradiation doses of postoperative radiotherapy.

Details of Radiotherapy (RT)	n
Postoperative RT for negative margin or microscopic residual tumor	26
Photon	17
60 Gy/30 fr	13
60 Gy/24 fr	1
65 Gy/26 fr	1
70 Gy/35 fr	1
30 Gy/5 fr*	1
Proton	9
30 GyE/5 fr	9
Definitive RT or RT for macroscopic residual tumor after surgery	4
Proton	4
60 GyE/15 fr	3
65 GyE/26 fr	1

* One patient was initially scheduled for proton beam therapy with 60 Gy relative biological effectiveness for macroscopic residual disease. However, because of the subsequent development of interstitial pneumonia and large vessel vasculitis, radiation therapy was performed with photon beams at a total dose of 30 Gy in 5 fractions.

Table 4. Details of the distant metastasis sites.

Site of distant metastasis	n
Lung	11
Liver	10
Adrenal gland	6
Bone	5
Subcutaneous	4
Peritoneum	4
Muscle	3
Pancreas	3
Brain	2
Skin	1
Mediastinum	1

Table 5. Univariate Cox regression analyses for overall survival rate.

		Univariate analysis	
	n	HR (95% CI)	P-value
Gender			0.59
Male	18	1	
Female	12	1.29 (0.52–3.2)	
Age			0.70
<70	15	1	
71≤	15	0.83 (0.33–2.1)	
Subsite			0.004
Nasal cavity	28	1	
Sinus	2	19 (2.6–139)	
T			0.011
3	22	1	
4	8	3.8 (1.3–11)	
N			0.99
0	28	1	
1	2	n. s	

Abbreviation: n. s, not significant

Table 6. Univariate Cox regression analyses for distant metastasis.

		Univariate analysis	
	n	HR (95% CI)	P-value
Gender			0.52
Male	18	1	
Female	12	1.4 (0.48–4.3)	
Age			0.09
< 71	15	1	
≥ 71	15	2.6 (0.86–8.3)	
Subsite			0.08
Nasal cavity	28	1	
Sinus	2	4.0 (0.86–18)	
T			0.06
3	22	1	
4	8	2.9 (0.96–8.9)	
N			0.99
0	28	1	
1	2	n. s	

Abbreviation: n. s, not significant

Table 7. Overall survival rates for the current and previous studies.

	n	Observation period	2y-OS (%)	5y-OS (%)
Present study	30	2002–2021	70	46
Stephanie F et al.	100	1997–2018	68	38
Moran A et al.	198	1991–2016	-	38
Davide L et al.	58	2002–2013	-	29
Samstein RM et al.	78	1998–2013	-	31
Sun CZ et al.	68	1976–2005	-	30

Abbreviation: OS, overall survival rate

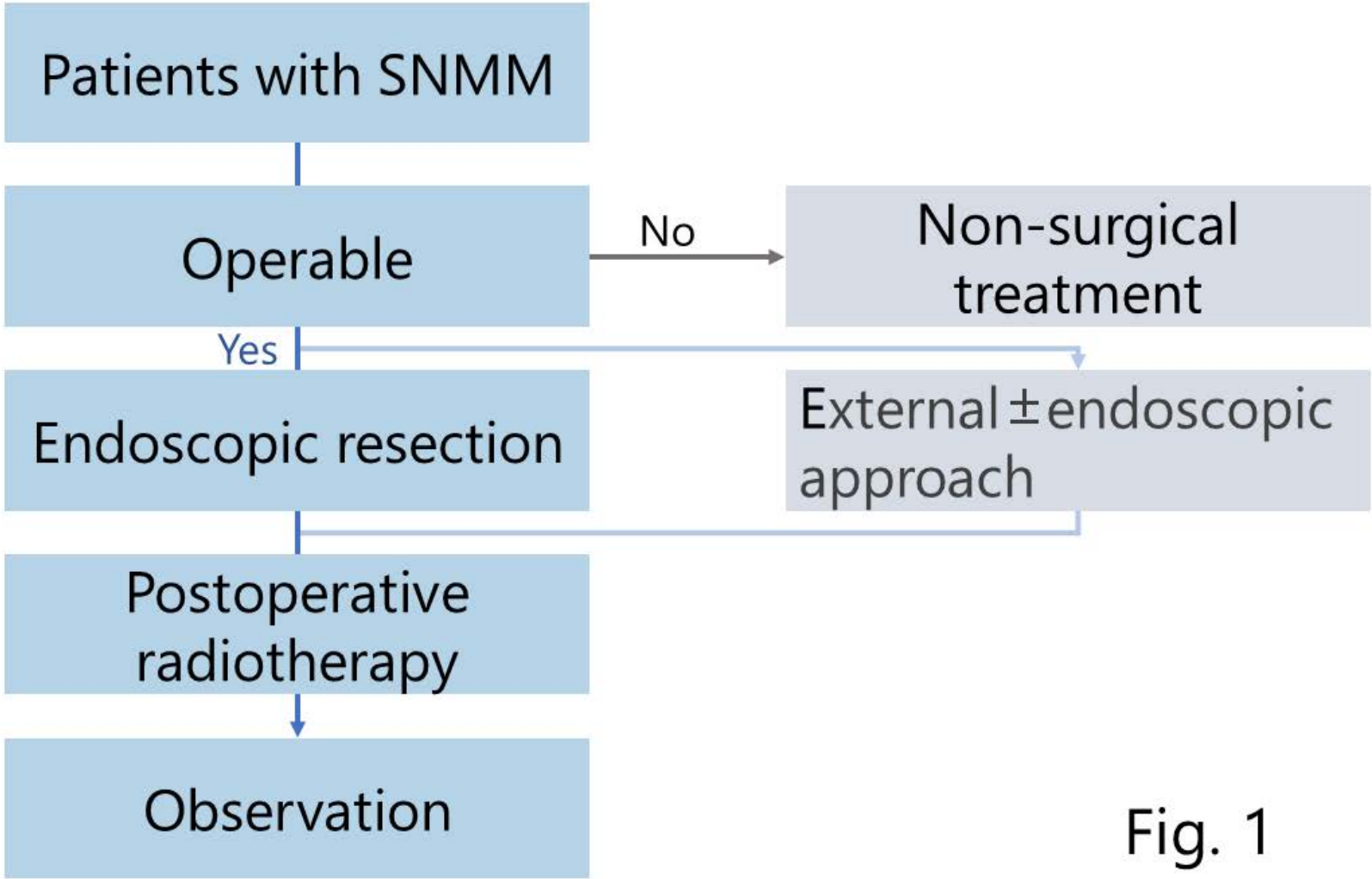

Patients with SNMM
Operable
No
Non-surgical treatment
Yes
Endoscopic resection
External ± endoscopic approach
Postoperative radiotherapy
Observation

Fig. 1

Fig. 2a

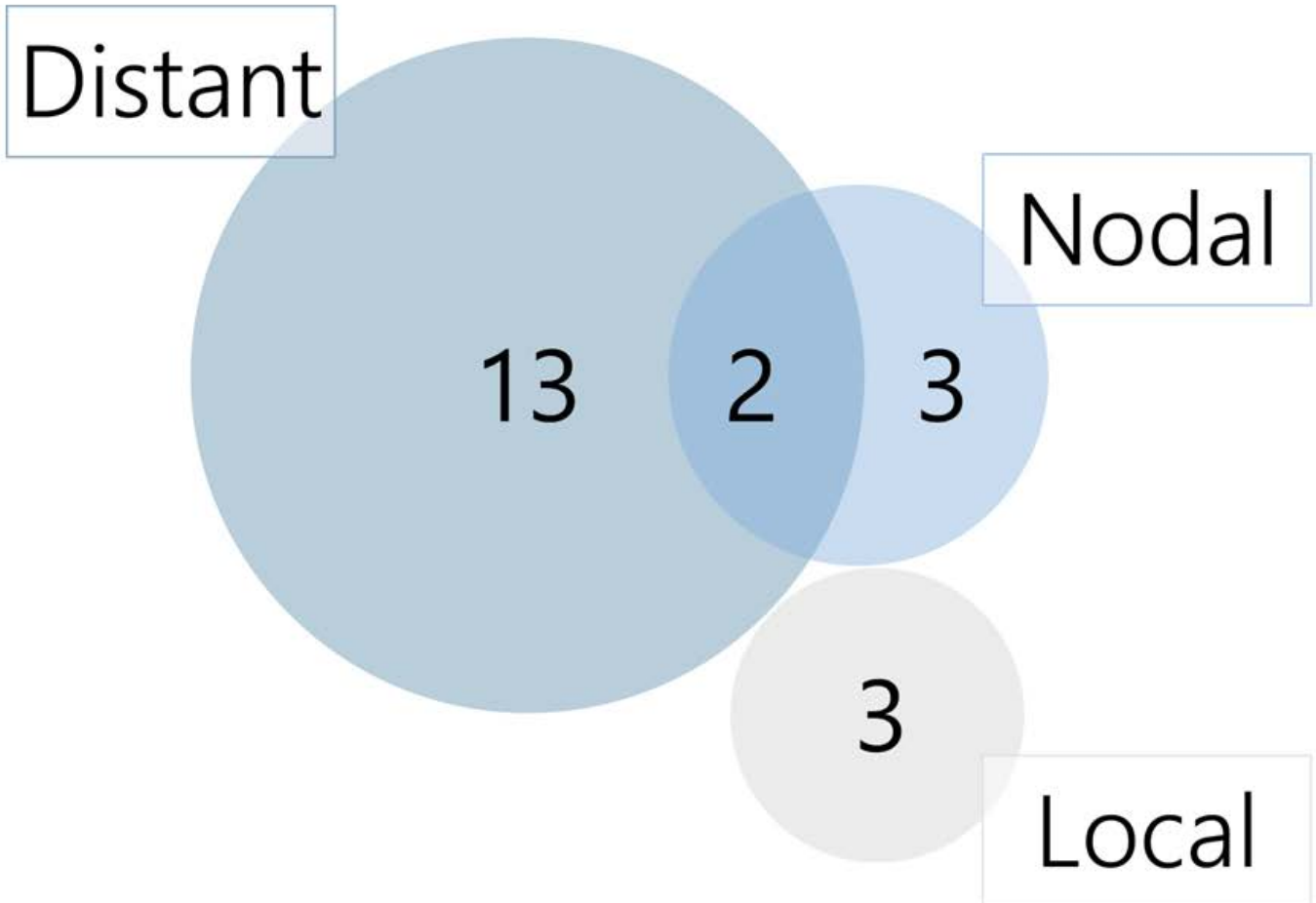


Fig. 2b

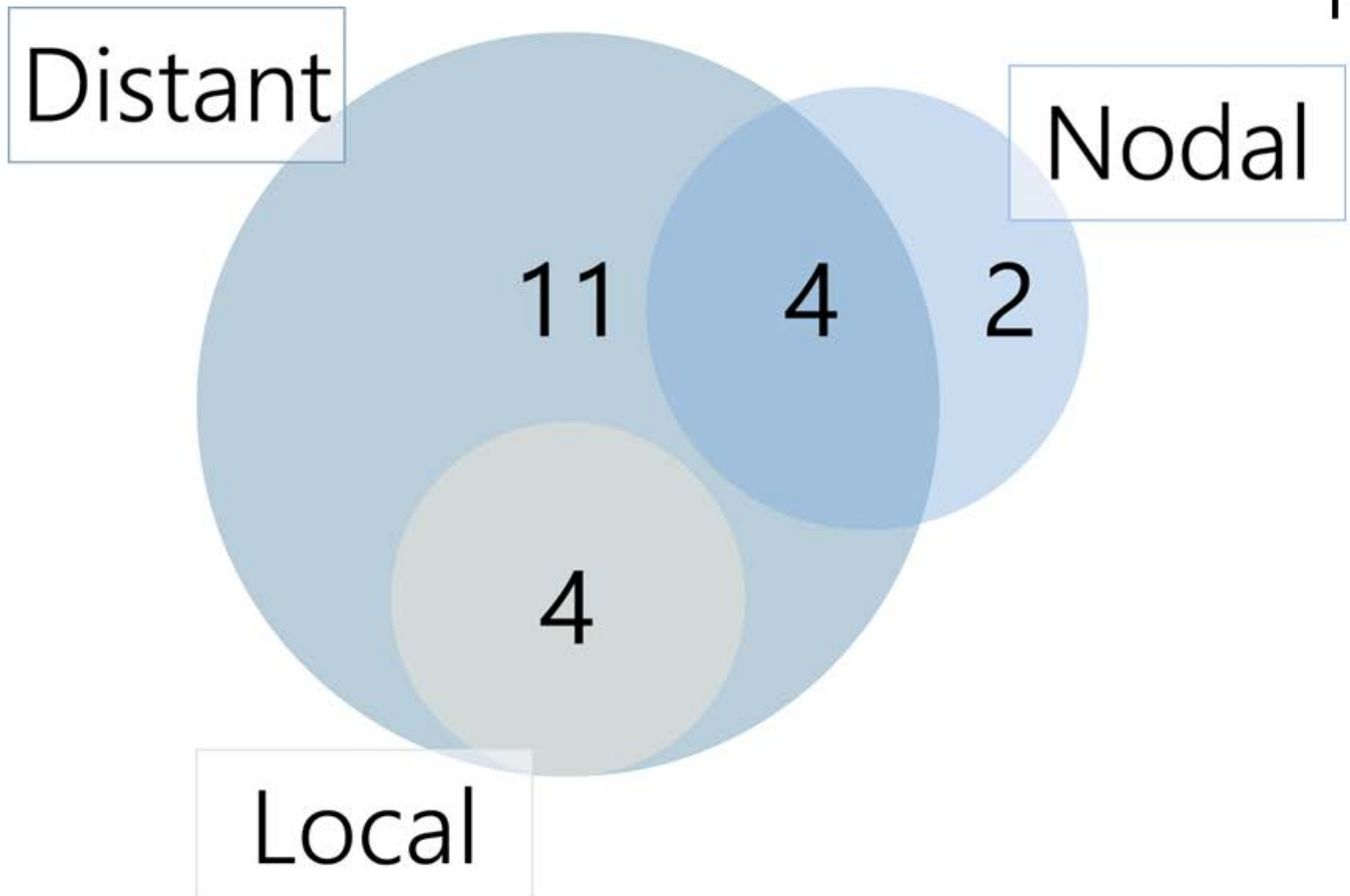


Fig. 3a

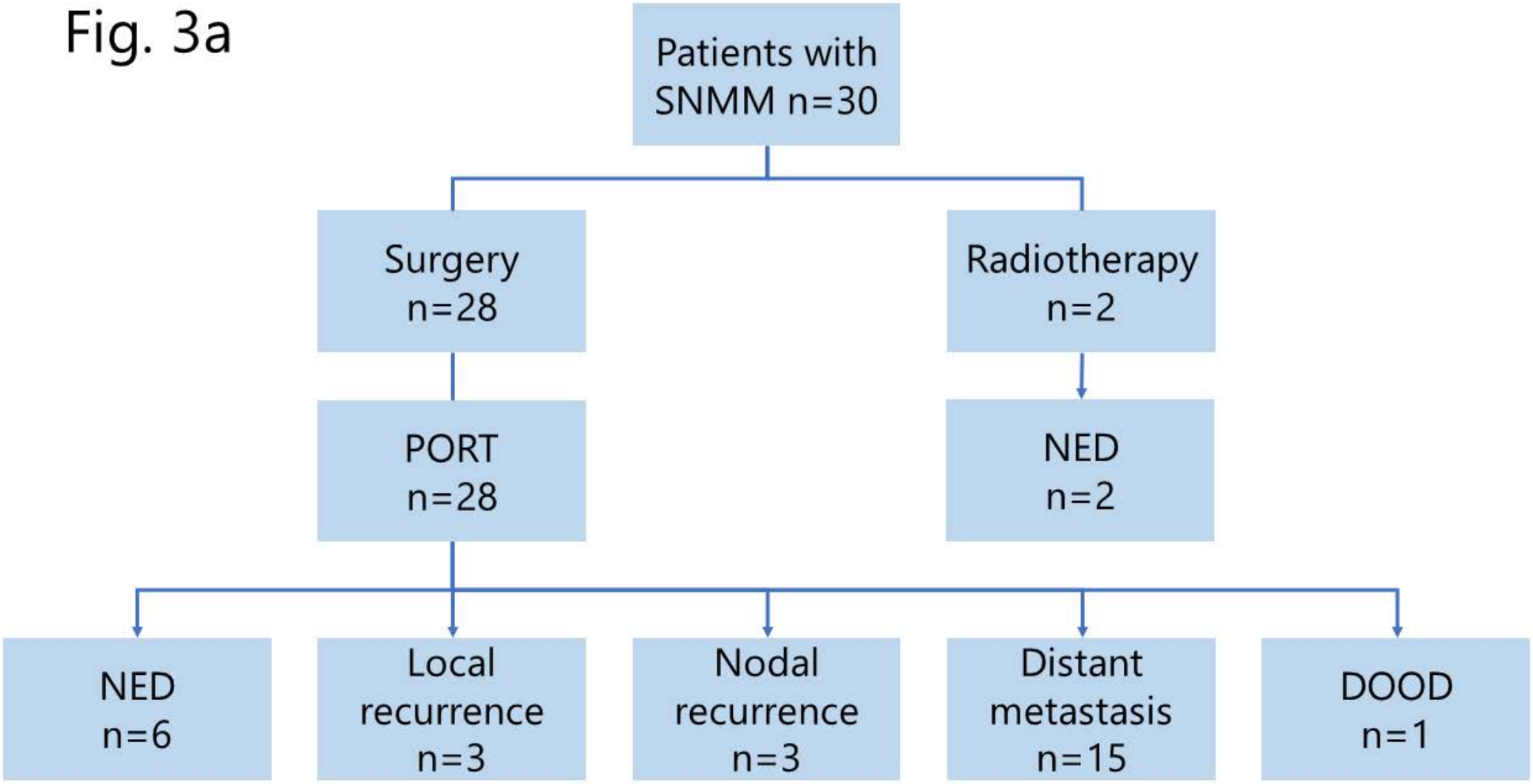

Patients with SNMM n=30
Surgery n=28
Radiotherapy n=2
PORT n=28
NED n=2
NED n=6
Local recurrence n=3
Nodal recurrence n=3
Distant metastasis n=15
DOOD n=1

Fig. 3b

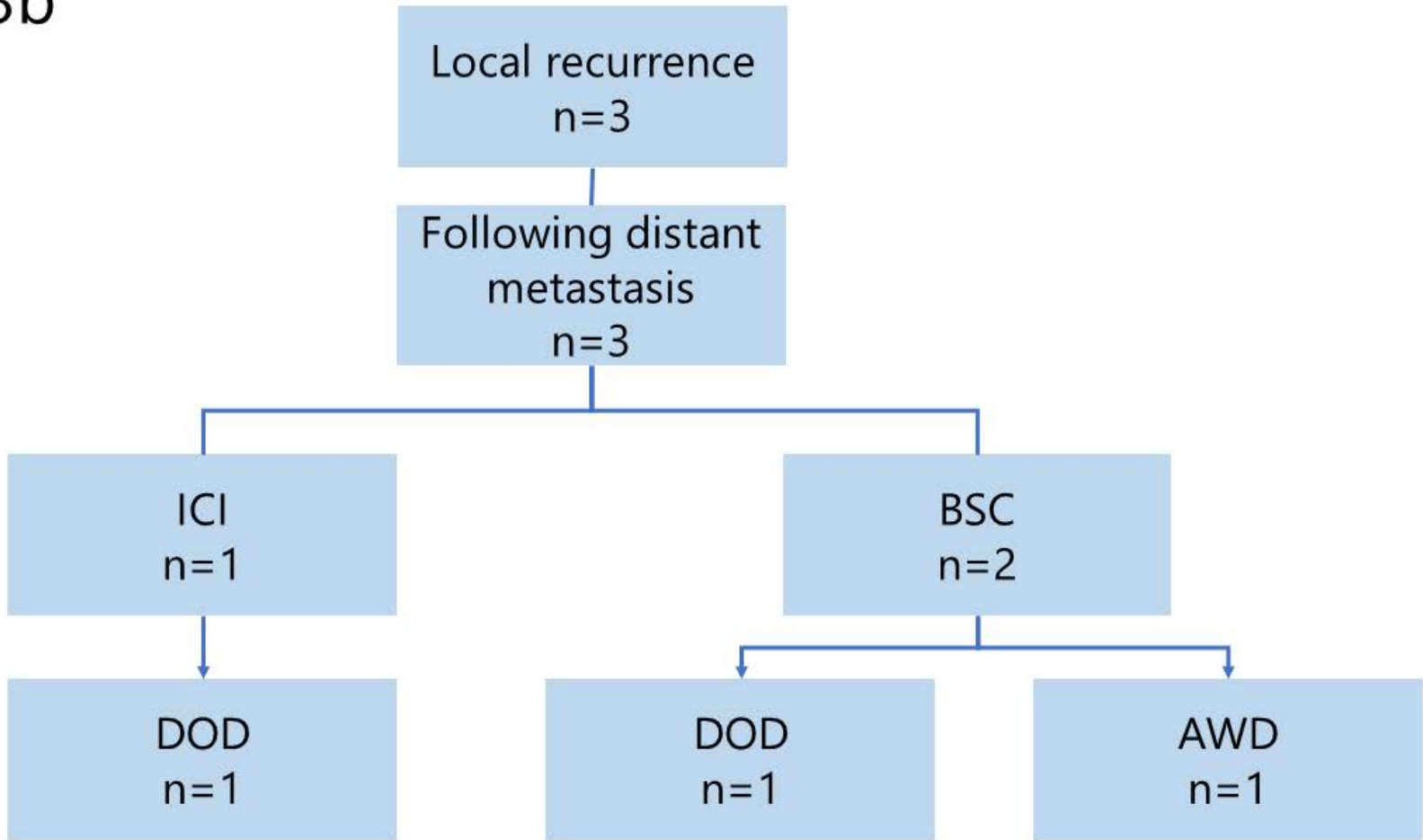

Local recurrence
n=3
Following distant metastasis
n=3
ICI
n=1
BSC
n=2
DOD
n=1
DOD
n=1
AWD
n=1

Fig. 3c

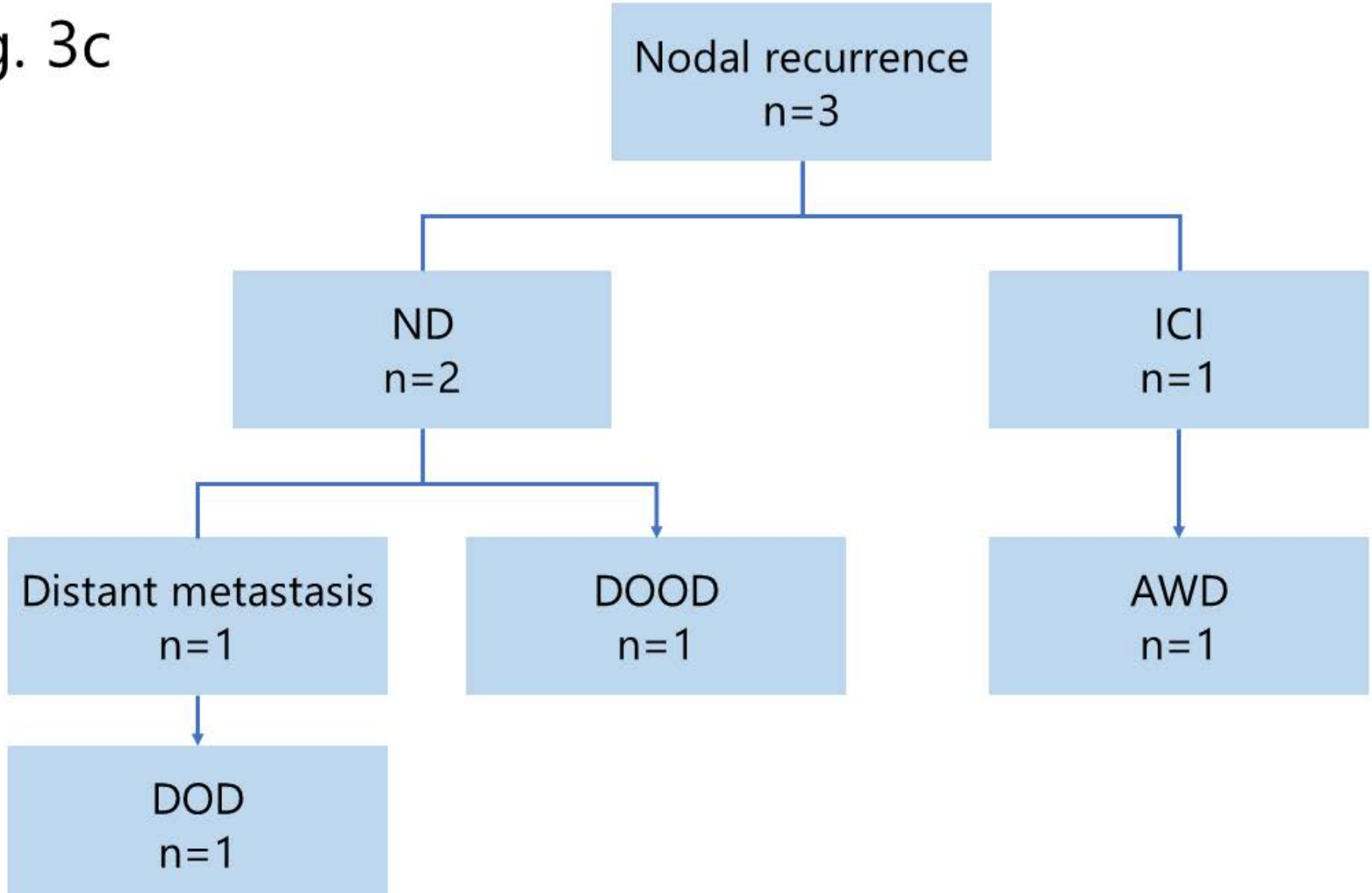

Nodal recurrence
n=3
ND
n=2
ICI
n=1
Distant metastasis
n=1
DOOD
n=1
AWD
n=1
DOD
n=1

Fig. 3d

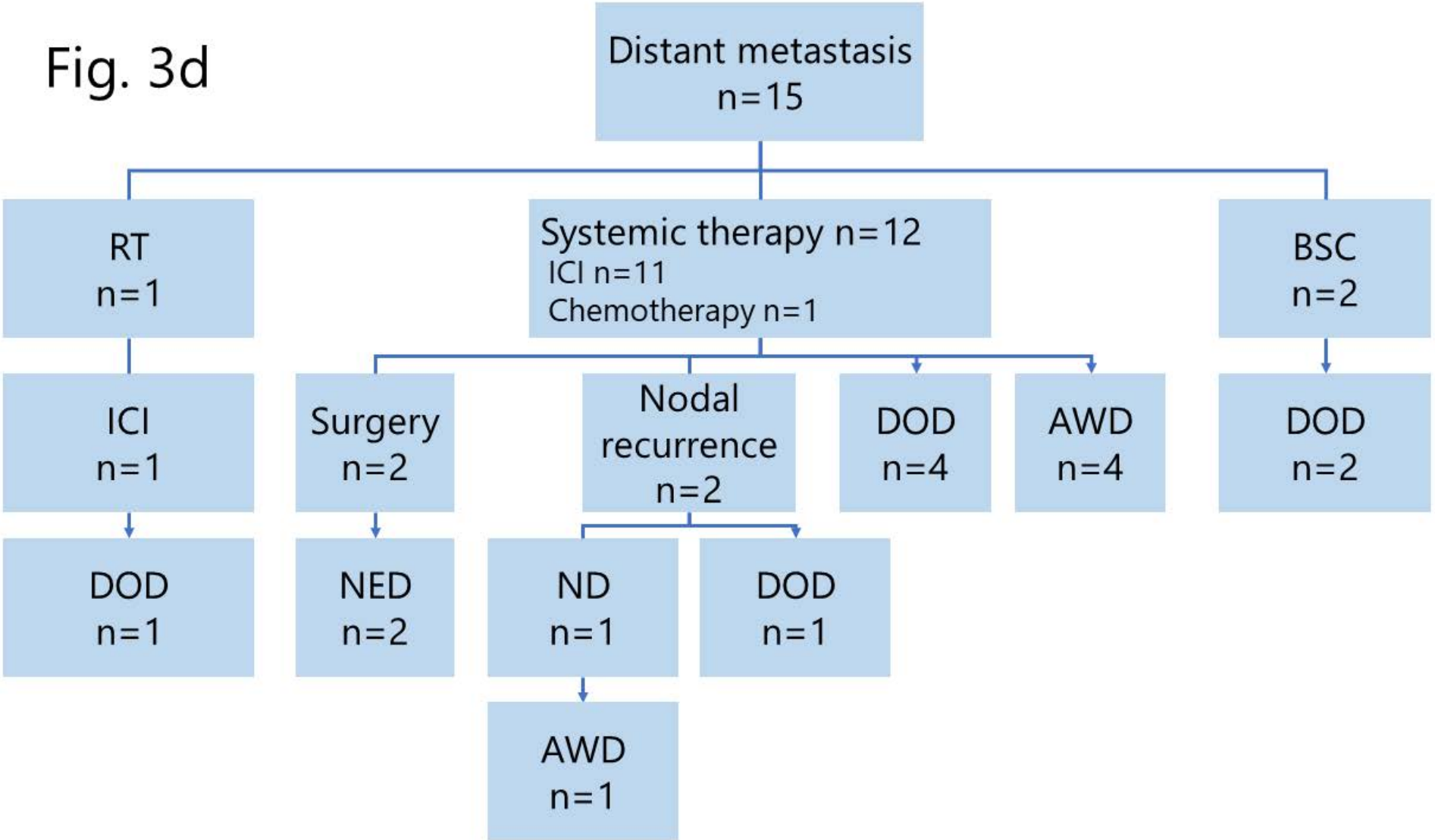

Distant metastasis
n=15
RT
n=1
Systemic therapy n=12
ICI n=11
Chemotherapy n=1
BSC
n=2
ICI
n=1
Surgery
n=2
Nodal
recurrence
n=2
DOD
n=4
AWD
n=4
DOD
n=2
DOD
n=1
NED
n=2
ND
n=1
DOD
n=1
AWD
n=1

Fig. 4a

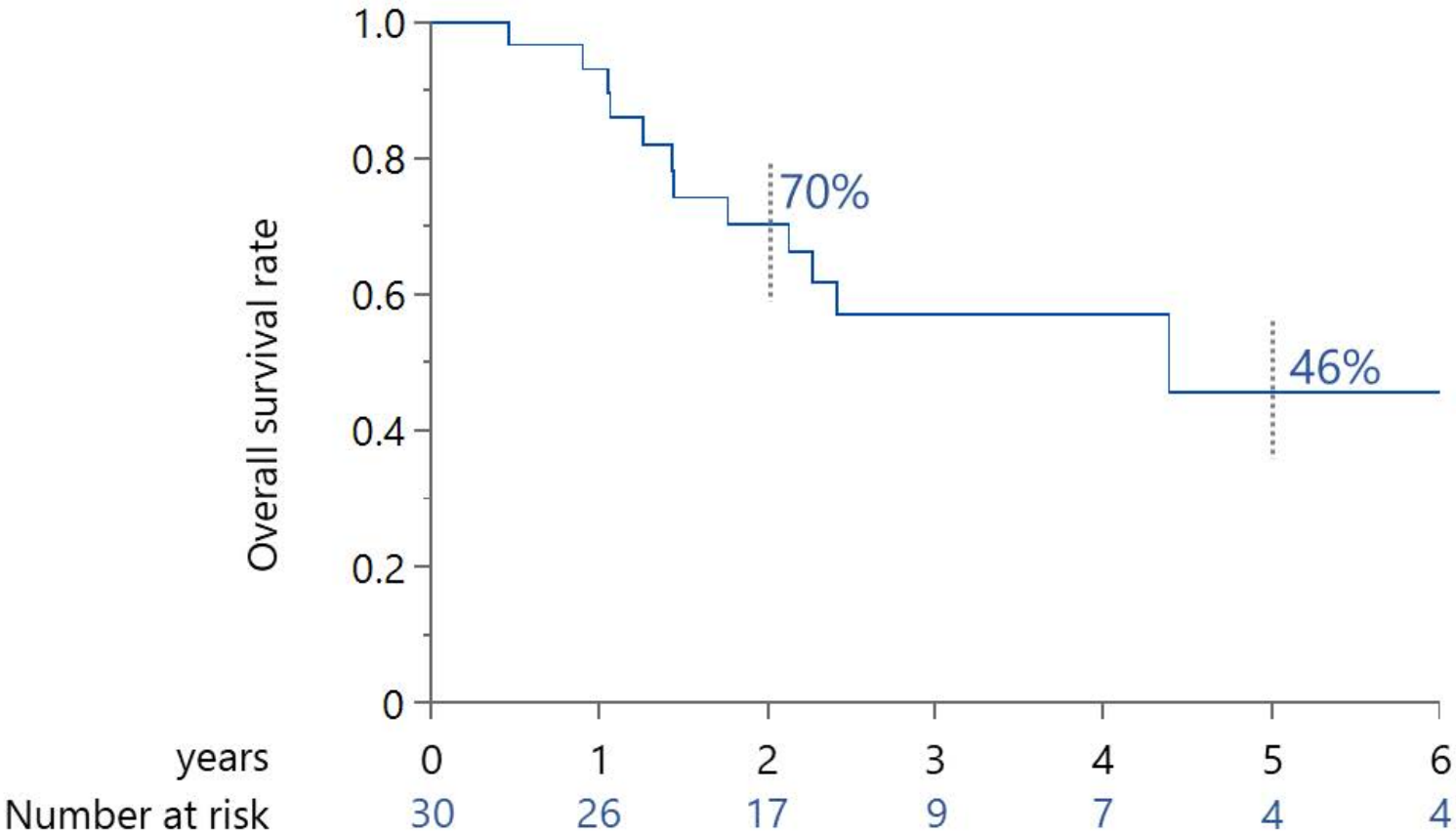

1.0
0.8
0.6
0.4
0.2
0
Overall survival rate
70%
46%
years
0
1
2
3
4
5
6
Number at risk
30
26
17
9
7
4
4

Fig. 4b

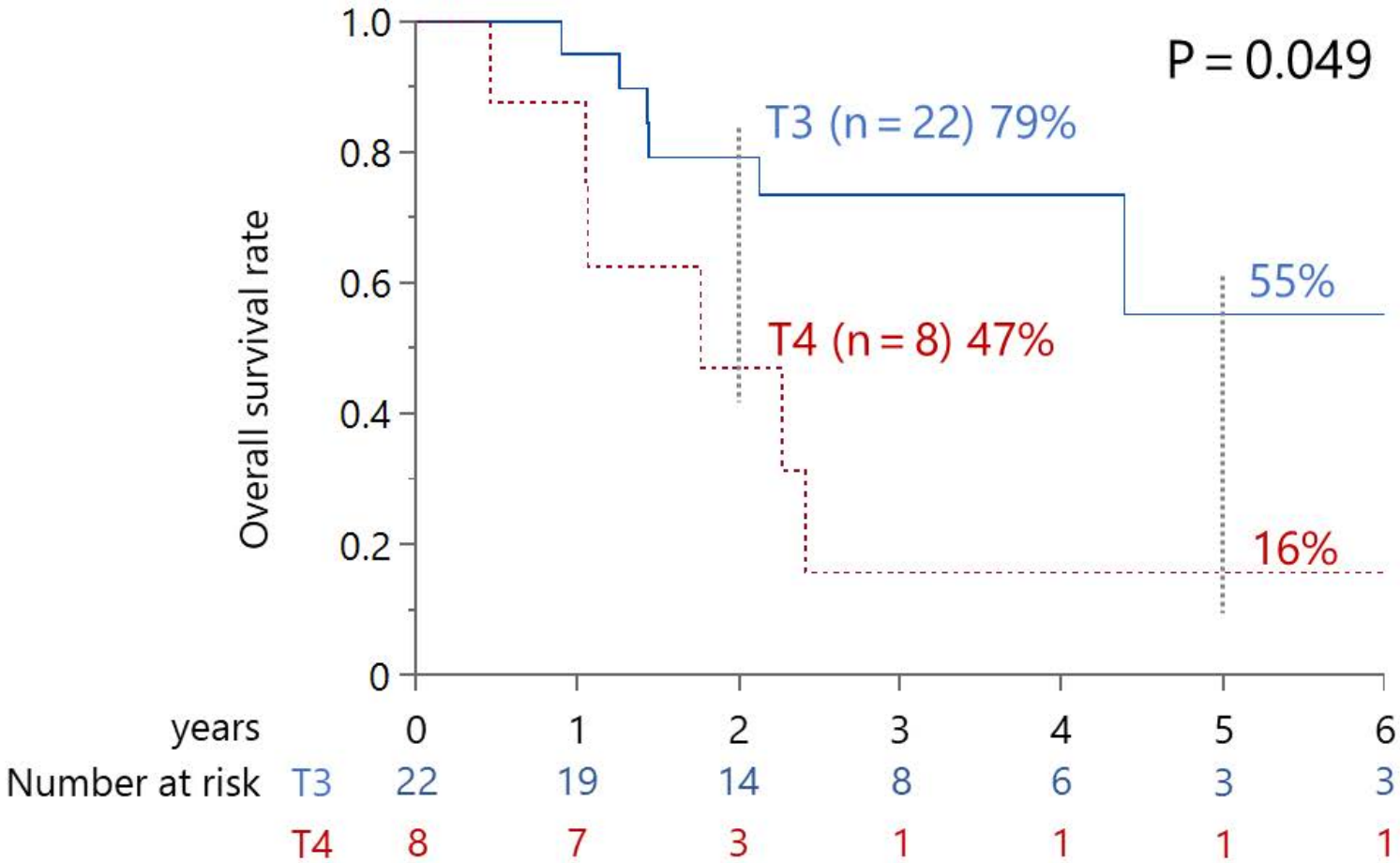

P = 0.049
T3 (n = 22) 79%
55%
T4 (n = 8) 47%
16%
Overall survival rate
1.0
0.8
0.6
0.4
0.2
0
years
0
1
2
3
4
5
6
Number at risk
T3
22
19
14
8
6
3
3
T4
8
7
3
1
1
1
1

Fig. 4c

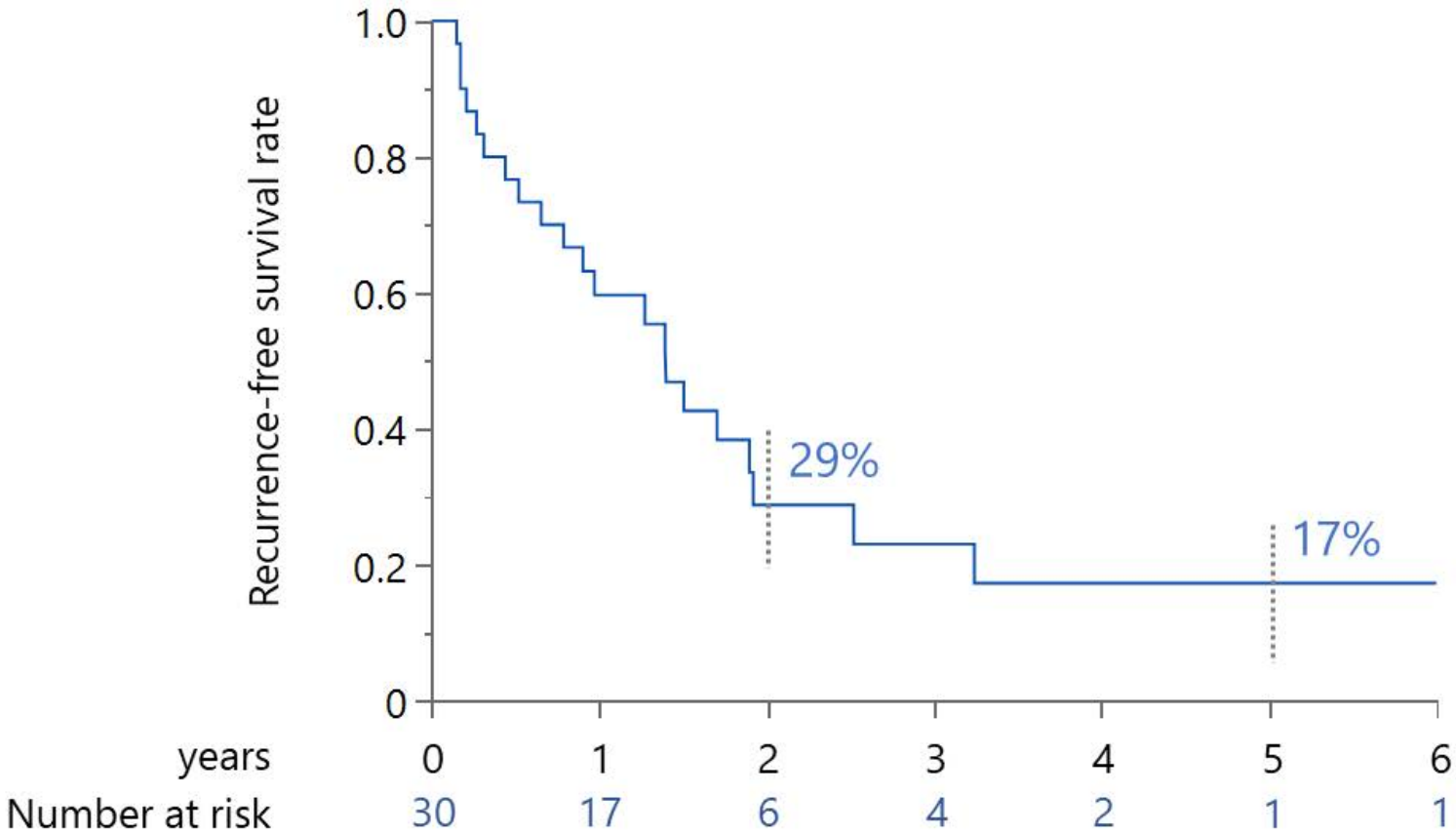

Recurrence-free survival rate
1.0
0.8
0.6
0.4
0.2
0
29%
17%
years
0
1
2
3
4
5
6
Number at risk
30
17
6
4
2
1
1

Fig. 4d

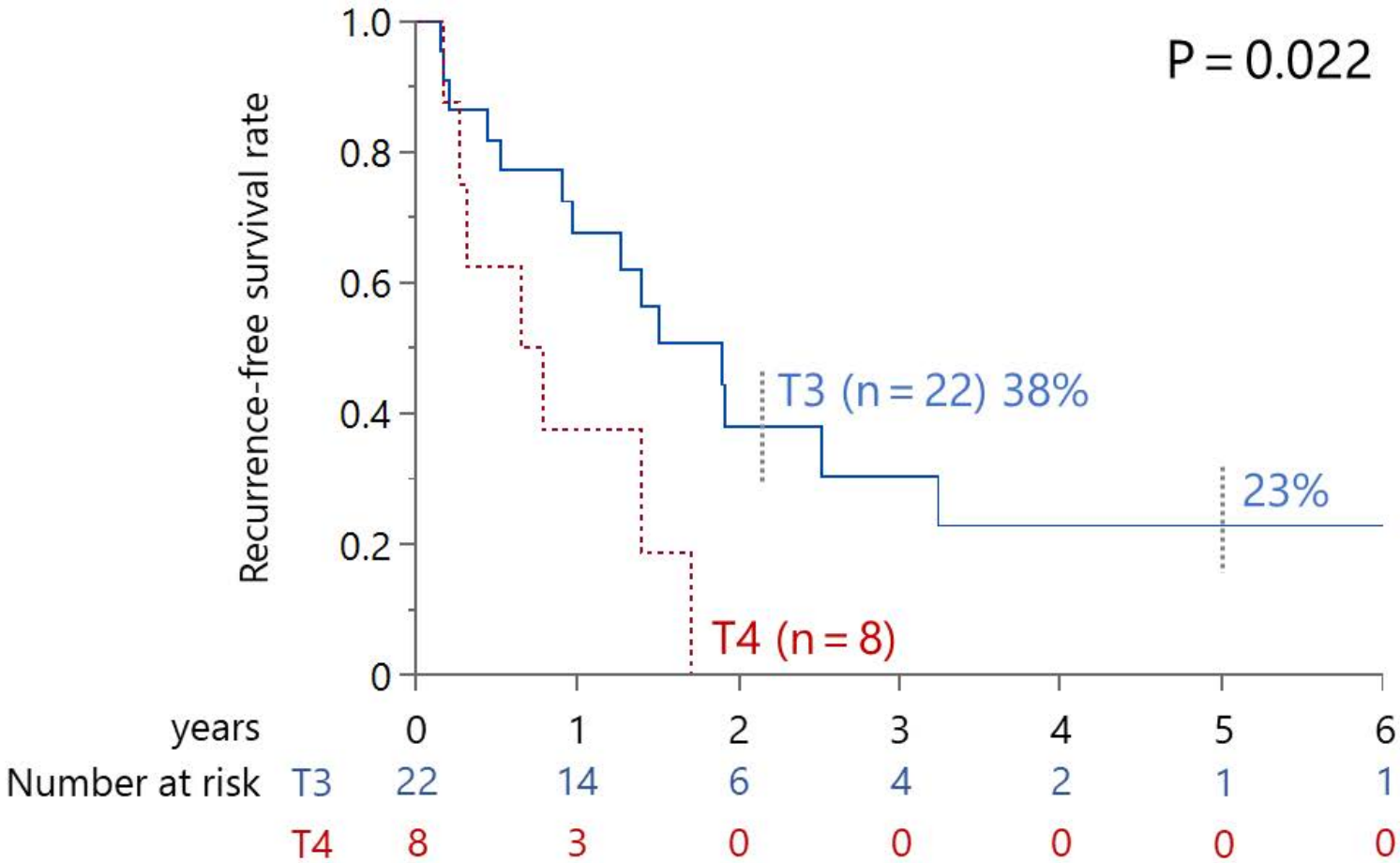

P = 0.022
Recurrence-free survival rate
1.0
0.8
0.6
0.4
0.2
0
T3 (n = 22) 38%
23%
T4 (n = 8)
years
0
1
2
3
4
5
6
Number at risk
T3
22
14
6
4
2
1
1
T4
8
3
0
0
0
0
0

Fig. 4e

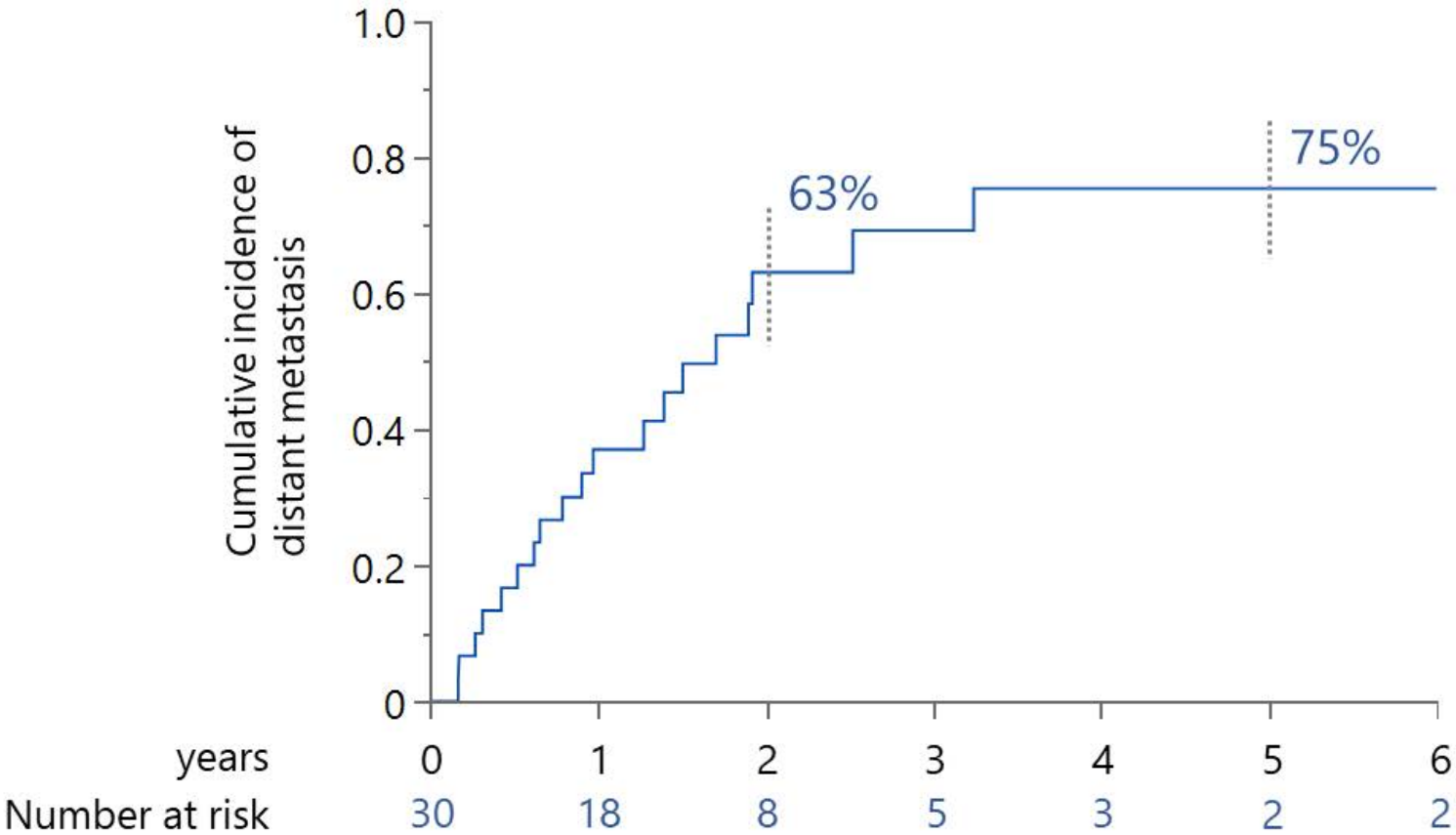

1.0
0.8
0.6
0.4
0.2
0
Cumulative incidence of distant metastasis
63%
75%
years
0
1
2
3
4
5
6
Number at risk
30
18
8
5
3
2
2

Fig. 4f

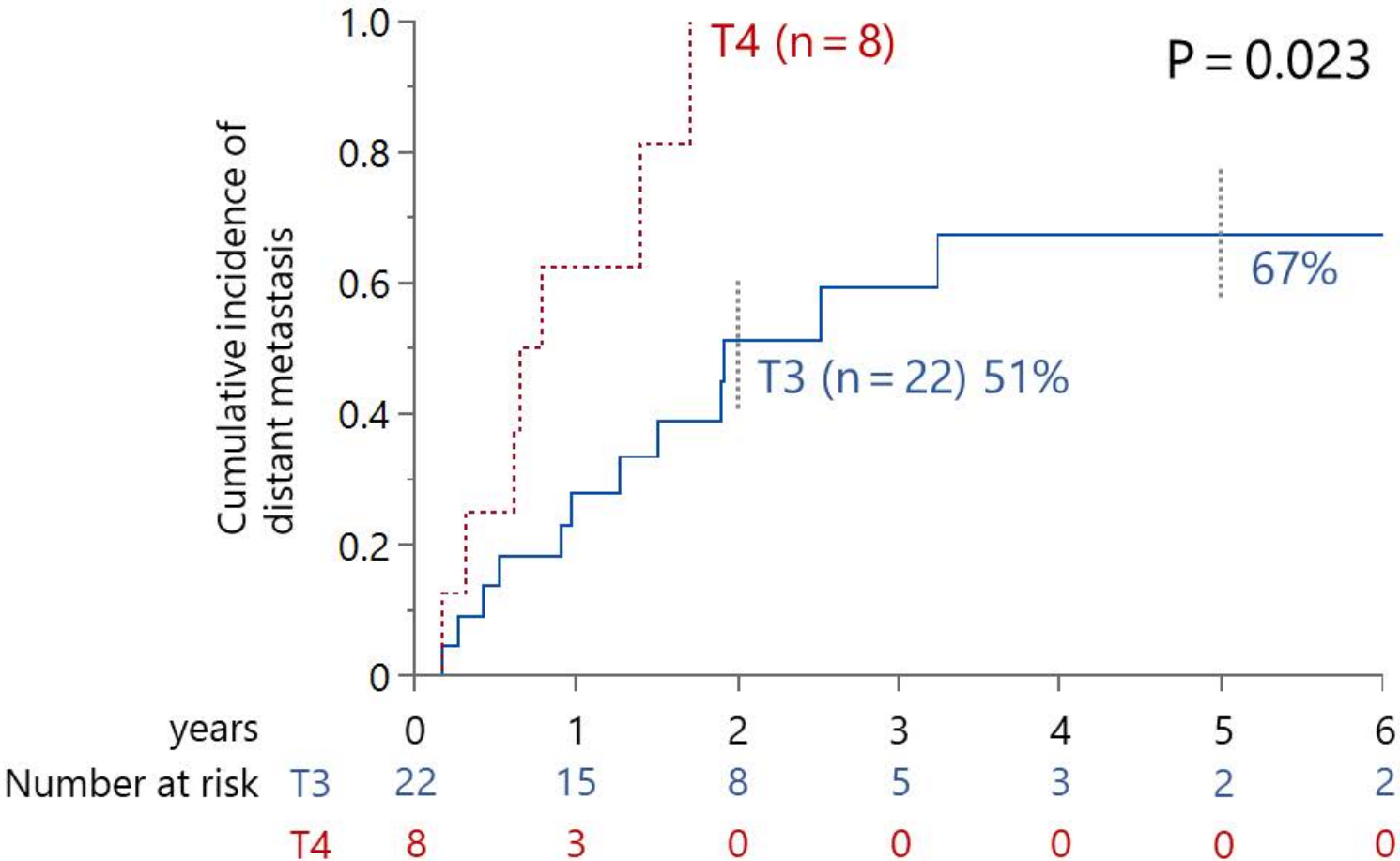

T4 (n = 8)
P = 0.023
67%
T3 (n = 22) 51%
Cumulative incidence of distant metastasis
1.0
0.8
0.6
0.4
0.2
0
years
0
1
2
3
4
5
6
Number at risk
T3
22
15
8
5
3
2
2
T4
8
3
0
0
0
0
0

Fig. 4g

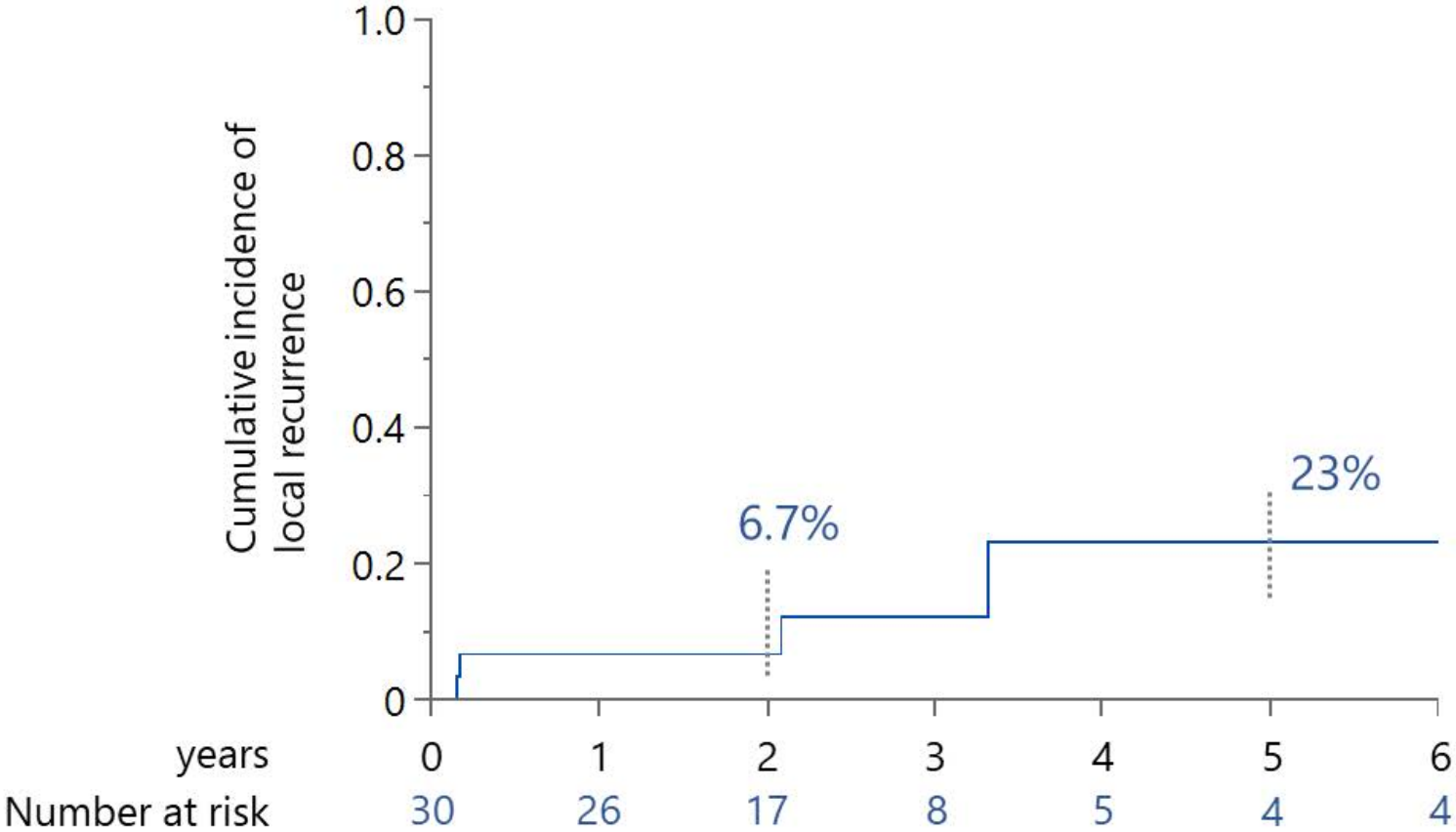
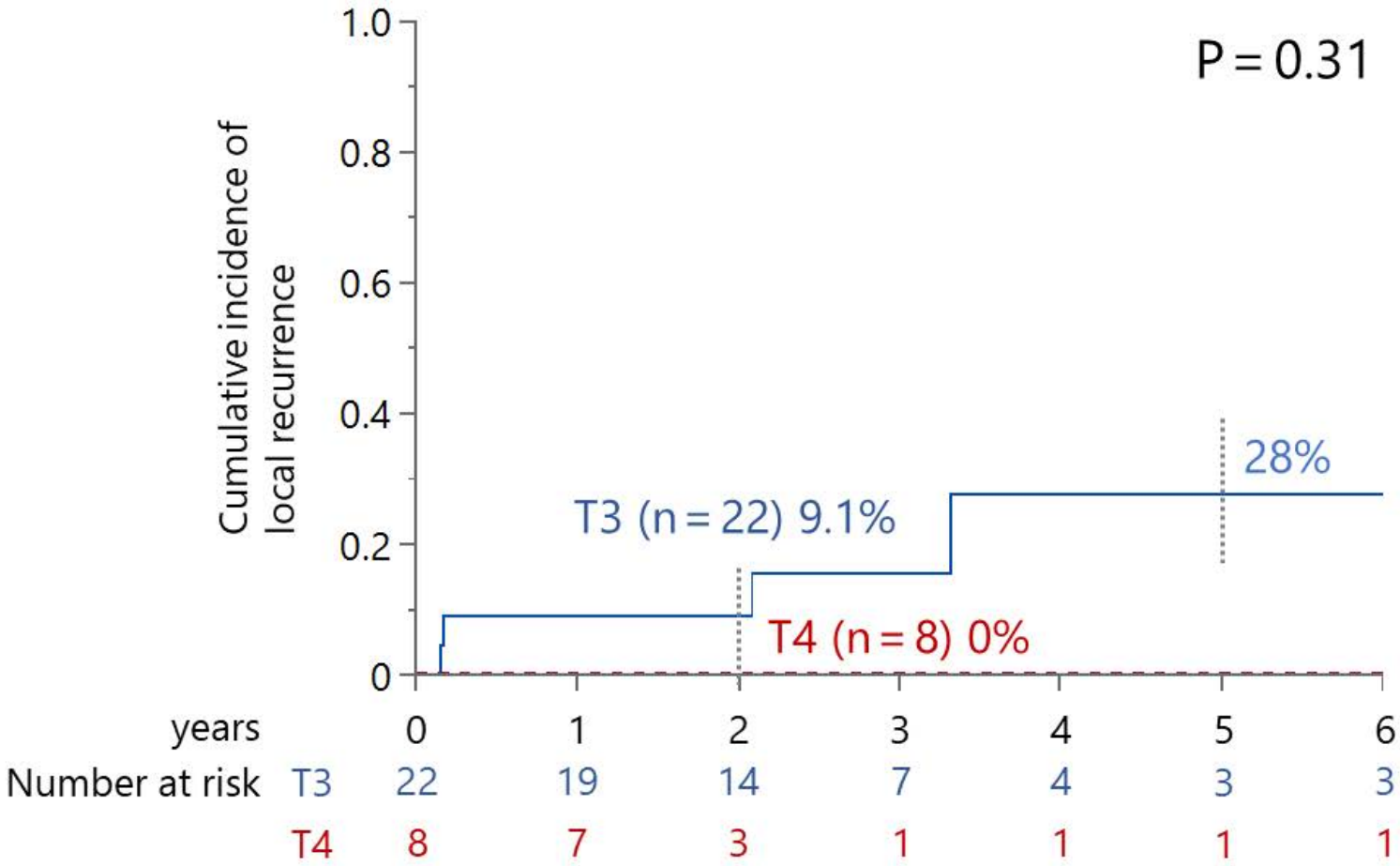

Cumulative incidence of local recurrence
1.0
0.8
0.6
0.4
0.2
0
6.7%
23%
years
0
1
2
3
4
5
6
Number at risk
30
26
17
8
5
4
4

Fig. 4h


P = 0.31
Cumulative incidence of local recurrence
1.0
0.8
0.6
0.4
0.2
0
28%
T3 (n = 22) 9.1%
T4 (n = 8) 0%
years
0
1
2
3
4
5
6
Number at risk
T3
22
19
14
7
4
3
3
T4
8
7
3
1
1
1
1