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Preoperative chemoradiotherapy but not chemotherapy is associated with reduced risk of postoperative pancreatic fistula after pancreatoduodenectomy for pancreatic ductal adenocarcinoma: a nationwide analysis

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ABSTRACT

Background: Postoperative pancreatic fistula remains the leading cause of significant morbidity after pancreatoduodenectomy for pancreatic ductal adenocarcinoma. Preoperative chemoradiotherapy has been described to reduce the risk of postoperative pancreatic fistula, but randomized trials on neo-adjuvant treatment in pancreatic ductal adenocarcinoma focus increasingly on preoperative chemotherapy rather than preoperative chemoradiotherapy. This study aimed to investigate the impact of preoperative chemotherapy and preoperative chemoradiotherapy on postoperative pancreatic fistula and other pancreatic-specific surgery related complications on a nationwide level.

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Methods: All patients after pancreatoduodenectomy for pancreatic ductal adenocarcinoma were included in the mandatory nationwide prospective Dutch Pancreatic Cancer Audit (2014–2020). Baseline and treatment characteristics were compared between immediate surgery, preoperative chemotherapy, and preoperative chemoradiotherapy. The relationship between preoperative chemotherapy, chemoradiotherapy, and clinically relevant postoperative pancreatic fistula (International Study Group of Pancreatic Surgery grade B/C) was investigated using multivariable logistic regression analyses.

Results: Overall, 2,019 patients after pancreatoduodenectomy for pancreatic ductal adenocarcinoma were included, of whom 1,678 underwent immediate surgery (83.1%), 192 (9.5%) received preoperative chemotherapy, and 149 (7.4%) received preoperative chemoradiotherapy. Postoperative pancreatic fistula occurred in 8.3% of patients after immediate surgery, 4.2% after preoperative chemotherapy, and 2.0% after preoperative chemoradiotherapy ($P = .004$). In multivariable analysis, the use of preoperative chemoradiotherapy was associated with reduced risk of postoperative pancreatic fistula (odds ratio, 0.21; 95% confidence interval, 0.03–0.69; $P = .033$) compared with immediate surgery, whereas preoperative chemotherapy was not (odds ratio, 0.59; 95% confidence interval, 0.25–1.25; $P = .199$). Intraoperatively hard, or fibrotic pancreatic texture was most frequently observed after preoperative chemoradiotherapy (53% immediate surgery, 62% preoperative chemotherapy, 77% preoperative chemoradiotherapy, $P < .001$).

Conclusion: This nationwide analysis demonstrated that in patients undergoing pancreatoduodenectomy for pancreatic ductal adenocarcinoma, only preoperative chemoradiotherapy, but not preoperative chemotherapy, was associated with a reduced risk of postoperative pancreatic fistula.

Introduction

Pancreatic cancer is projected to become the second leading cause of cancer-related deaths by 2030, with a poor overall 5-year survival of <5%.[1,2] The majority of pancreatic tumors arise from the pancreatic head, and among these patients, only 16% are eligible for surgery.[3] Surgery combined with systemic therapy is the best option to improve survival. However, pancreatic surgery, especially pancreatoduodenectomy, is associated with a 19%–26% risk of major postoperative complications.[4,5] Postoperative pancreatic fistula (POPF) is the most common and feared major complication in patients after pancreatoduodenectomy. POPF (ie, leakage of pancreatic fluid) can cause secondary complications, such as sepsis, postpancreatectomy hemorrhage, and subsequent organ failure.[6,7]

In the past decade, the administration of preoperative chemotherapy (PCT) or chemoradiotherapy (PCRT) has increasingly been studied to improve survival in PDAC patients.[8-14] Initially, concerns were raised about the potential negative impact of preoperative therapy on POPF and other postoperative complications. However, some studies suggest that preoperative therapy even lowers the incidence of POPF compared with immediate surgery.[10,15-24] Due to the scarcity of studies directly comparing the different types of preoperative therapy, it remains unclear whether this is due to the chemotherapy or only observed after chemoradiotherapy. Therefore, this study aimed to investigate the effect of PCT and PCRT on POPF and other pancreas-specific complications in a nationwide cohort of patients after pancreatoduodenectomy.

Methods

Study Design and Patient Cohort

This is a retrospective cohort study using data from the nationwide, prospective Dutch Pancreatic Cancer Audit (DPCA). All adult patients after pancreatoduodenectomy for postoperative pathologically confirmed PDAC between 2014 and 2020 were included. The DPCA is a mandatory, prospectively maintained nationwide audit that includes all 16 Dutch centers performing pancreatic surgery. The DPCA questionnaires are completed by healthcare professionals and do not only contain pre- and postoperative findings but also detailed information about surgical technique, pancreatic duct size, and texture of the pancreatic remnant available. As patient and hospital data are anonymously registered, informed consent or ethical review was not required. The present study was approved by the scientific committee of the Dutch Pancreatic Cancer Group.[25] In this study, patients after pancreatoduodenectomy for (borderline) resectable or locally advanced PDAC were included. During the study period, neoadjuvant therapy in the Netherlands was not routinely used and was mostly administered in clinical trials for (borderline) resectable disease.[9,11] The neoadjuvant chemotherapy regimen consisted of FOLFIRINOX followed by surgery. The neoadjuvant chemoradiotherapy regimen was gemcitabine-based in combination with 15 fractions of radiotherapy. In the case of locally advanced disease, induction chemotherapy was given before surgery.

Variables and Outcomes

The primary outcome was the incidence of grade B/C POPF according to the International Study Group of Pancreatic Surgery (ISGPS) 2016 classification.[26,27] Secondary outcomes were clinically relevant complications: postpancreatectomy hemorrhage (grade B/C), delayed gastric emptying (grade B/C), bile leak (grade B/C), major morbidity (Clavien-Dindo classification $\geq$3), readmissions, and in-hospital/30-day mortality. Complications were defined following the ISGPS and the International Study Group of Liver Surgery criteria.[26,28-30] In the Netherlands, the majority of the patients initially undergo endoscopic retrograde cholangiopancreatography with the placement of a stent in cases of obstructive jaundice before surgery if bilirubin values are higher than 250 mcmol/L (14.6 mg/dL). Percutaneous transhepatic bile duct drainage is performed in case endoscopic retrograde cholangiopancreatography is not feasible. During the study period, intraoperative intraperitoneal drain placement was routinely performed after pancreatectomy. The diameter of the pancreatic duct was measured on the preoperative computed tomography (CT) scan from 2014 to 2017. Hereafter, intraoperative measurement was performed. Resectability status (resectable, borderline resectable, or locally advanced) and tumor diameter were based on the preoperative CT scan. Resectability was defined according to the criteria established by the Dutch Pancreatic Cancer Group.[31] Tumors without arterial involvement and with venous involvement <90° were considered resectable; tumors with arterial

involvement <90° and/or venous involvement between 90 and 270 degrees without occlusion were considered borderline resectable.[31] Operation time and blood loss were collected in patients from 2018–2020. The externally validated updated alternative fistula risk score (ua-FRS; see www.pancreascalculator.com) and auditing FRS (auditing-FRS), which includes sex, body mass index (BMI), diabetes mellitus, diagnosis, and pancreatic duct diameter, were calculated.[32,33]

Statistical Analysis

Continuous data were expressed as median with IQR. Categorical data were presented as absolute numbers and percentages. Patients were stratified based on preoperative treatment. Differences in baseline and treatment characteristics were assessed via Pearson's χ^2 statistic, Mann–Whitney *U* test, Kruskal–Wallis rank-sum test, and Fisher exact test, as appropriate. The association between preoperative therapy and POPF was assessed using multivariable logistic regression analyses, adjusted for age, BMI, biliary drainage, resectability status, pancreatic duct diameter, octreotide, and preoperative therapy type. *P* values were based on complete case analysis unless unknown is displayed. Results were presented as odds ratios (OR) with a 95% CI. Multicollinearity was determined by a variance inflation factor >2.5. All tests were two-tailed. Statistical analysis was performed with R statistical software (version 4.1.1).

Results

Baseline and Operative Characteristics

Out of 2,019 patients undergoing pancreatoduodenectomy for PDAC, 1,678 patients (83%) underwent immediate surgery, 192 (9.5%) received PCT, and 149 patients (7.4%) received PCRT. At the last preoperative CT scan, 1,367 (71%) patients had resectable disease, 435 (22%) patients borderline resectable, and 19 (7%) patients locally advanced disease. Almost 90% of the patients with resectable disease underwent immediate surgery. Patient and treatment characteristics are shown in Table I. Biliary drainage was performed in 60% before immediate surgery, 74% before PCT, and 76% before PCRT ($P < .001$). Patients undergoing immediate surgery had a wider pancreatic duct (immediate surgery, 5.0 mm; PCT, 4.0 mm; PCRT, 4.0 mm; $P < .001$). During surgery, surgeons categorized the texture of the pancreas as "hard or fibrotic" most frequently after PCRT (immediate surgery 53%, PCT 62%, PCRT 77%, $P < .001$). The median ua-FRS was 17.8 for immediate surgery, 17.8 for PCT, and 14.8 for PRCT ($P = .062$). The median auditing-FRS differed (immediate surgery 5.7, PCT 6.8, PCRT 6.1, $P = .028$). Venous resections were more often performed after preoperative therapy (immediate surgery 17%, PCT 31%, PCRT 28%, $P < .001$).

Surgical Outcomes

Table II shows the surgical outcome per treatment group. The incidence of grade B/C POPF was 8.3% for the patients who underwent immediate surgery, 4.2% after PCT, and 2.0% after PCRT ($P = .004$). Overall, 1,651 (80%) patients were included in the complete-case multivariable analysis. PCRT remained independently associated with a decreased rate of POPF (OR, 0.21; $P = .033$), whereas PCT was not significantly associated with a decreased rate of POPF compared with immediate surgery (OR, 0.59; $P = .199$). Other factors associated with POPF were high BMI (OR, 2.02; $P = .048$), borderline resectable disease (OR, 0.47; $P = .016$), and preoperative biliary drainage (OR, 0.56; $P = .004$; Table III). Grade B/C post-pancreatectomy hemorrhage, delayed gastric emptying, bile leak, in-hospital/30-day mortality and operation time did not differ between the groups. Intraoperative blood loss volume was higher in preoperative therapy groups than in immediate surgery (immediate surgery, 500 mL; PCT, 600 mL; and PCRT, 558 mL; $P < .001$).

Discussion

This nationwide audit-based cohort study in 2,019 patients undergoing pancreatoduodenectomy for PDAC found that PCRT, but not PCT, was associated with a reduced rate of POPF compared with immediate surgery. Rates of delayed gastric emptying, post-pancreatectomy hemorrhage and bile leakage did not differ between these 3 treatment groups.

The gap in knowledge regarding the effect of different types of preoperative therapy on POPF after pancreatoduodenectomy arises from the lack of studies directly comparing the types of preoperative therapy (PCT and PCRT). To our knowledge, only one previous study performed a direct comparison between PCT and PCRT concerning the rate of POPF.[18] This National Surgical Quality Improvement Program–based study (2014–2016) reported a lower rate of POPF after PCRT compared with PCT (3.5% vs 11.2%, $P < .001$).[18] The reported protective effect of PCRT on POPF aligns with the results of this present more recent study, which found a POPF rate of only 2.0% after PCRT. Because the National Surgical Quality Improvement Program database only covers a select group of mostly high-volume hospitals in the United States and Canada, the results of this nationwide study provide a valuable addition, as data from outside North America have not yet been published.

Several other studies have investigated the effect of preoperative therapy on POPF. A recent study within a randomized controlled trial reported a significantly lower incidence of POPF in 66 patients after PCRT, compared with 98 patients after immediate surgery (0% vs 9.2%, $P = .011$).[21] However, this trial (PREOPANC) did not include a PCT arm.[9] A recent meta-analysis, including 41 comparative studies, concluded that preoperative therapy significantly decreased the incidence of POPF compared with immediate surgery (OR, 0.47; 95% CI, 0.38–0.58). In accordance with the present study, the reduction was the strongest for PCRT. Again, most of the studies included in this meta-analysis assessed the effect of any preoperative treatment on the rate of complications. Because substantial heterogeneity among the preoperative treatment regimens existed, determining what caused the decrease in POPF rates was only possible in a minority of cases.

Several patient-related and pancreas-related risk factors for the occurrence of POPF after pancreatoduodenectomy have been identified and widely validated in the literature.[34,35] The ua-FRS did not show significant differences between patients undergoing immediate surgery, PCT, and PCRT. The auditing-FRS, was the lowest in patients undergoing immediate surgery, suggesting a lower risk compared with preoperative therapy groups if pancreatic texture is not considered as a risk factor. Yet, the highest rate of POPF in this study was observed in patients after immediate surgery. The results of this study suggest that risk models for predicting POPF should include preoperative therapy.

The soft pancreatic texture is one of the most critical risk factors for POPF.[35] The suggested effect of PCRT on POPF may be explained by loss of acinar cell function and changes in pancreatic texture. Histologic evaluation of irradiated pancreatic tissue shows atrophy and distortion of the lobular structure with a decreased volume of acinar cells.[36] It is presumed that radiotherapy causes oxidative tissue damage, followed by an inflammatory process leading to fibrosis.[37] The fibrosis may prevent local pancreatitis at the anastomosis, which is often the cause of POPF. Additionally, radiotherapy-induced fibrosis could lead to firm pancreatic texture, preventing parenchymal tearing at the pancreatic-enteric

Table I
Baseline characteristics of patients with pancreatic cancer undergoing pancreatoduodenectomy

	Immediate surgery $N = 1,678$	Preoperative chemotherapy $N = 192$	Preoperative chemoradiotherapy $N = 149$	P value
Sex				.349
Male	910 (54%)	113 (59%)	76 (51%)	
Female	768 (46%)	79 (41%)	72 (49%)	
Missing	0	0	1	
Age, y	69.0 (62.0–75.0)	66.0 (56.8–72.0)	65.0 (59.0–71.0)	< .001
Missing	3	0	0	
Charlson comorbidity index				.298
0	765 (46%)	96 (50%)	79 (53%)	
1	418 (25%)	46 (24%)	36 (24%)	
≥2	495 (29%)	50 (26%)	34 (23%)	
Missing	0	0	0	
ASA classification				.925
1	154 (9.3%)	14 (7.4%)	13 (8.8%)	
2	1,028 (62%)	122 (65%)	92 (62%)	
≥3	479 (29%)	53 (28%)	43 (29%)	
Missing	17	3	1	
Body mass index, kg/m^2	24.0 (22.0–26.0)	23.0 (21.0–25.0)	24.0 (22.0–27.0)	.079
Missing	59	4	1	
Biliary drainage	989 (60%)	140 (74%)	112 (76%)	<.001
Missing	43	3	2	
CT scan resectability status				< .001
Resectable	1,220 (75%)	74 (41%)	73 (52%)	
Borderline resectable	335 (21%)	52 (29%)	48 (34%)	
Locally advanced	61 (3.8%)	56 (31%)	19 (14%)	
Missing	62	10	3	
Tumor diameter, mm	30 (23–40)	25 (18–32)	25 (20–30)	< .001
Diameter ductus pancreaticus	5.0 (3.0–7.0)	4.0 (3.0–5.0)	4.0 (3.0–6.0)	< .001
Missing	467	27	35	
Minimal invasive surgery	218 (13%)	27 (14%)	23 (15%)	.720
Missing	37	4	0	
Arterial resection	23 (1.4%)	6 (3.1%)	4 (2.7%)	.086
Missing	9	0	1	
Venous resection	252 (17%)	50 (31%)	34 (28%)	< .001
Missing	157	30	27	
Pancreatic texture				< .001
Soft or normal	715 (47%)	64 (38%)	33 (23%)	
Hard or fibrotic	792 (53%)	106 (62%)	108 (77%)	
Missing	171	22	8	
Ua-FRS[33]	17.8 (11.3–31.1)	17.8 (11.8–31.9)	14.8 (1.6–26.1)	.062
Missing	588	40	40	
auditing-FRS[32]	5.7 (4.1–9.1)	6.8 (4.9–1.6)	6.1 (4.1–9.0)	.028
Missing	508	29	36	

N (%); Median (IQR). Pearson's χ^2 test; Kruskal–Wallis rank-sum test; Fisher exact test, based on complete case analysis.
ASA, American Society of Anesthesiologists; *CT*, computed tomography; *ua-FRS*, (updated alternative) fistula risk score.

anastomosis and providing better suture hold capacity.[38,39] Indeed, in this study, we most frequently observed hard or fibrotic pancreatic texture after PCRT. However, pancreatic texture remains a subjective measure as it is based on the surgeon's intraoperative interpretation. An objective assessment could be the use of a durometer or histological examination.[40-42] Another important risk factor for POPF is a small pancreatic duct diameter.[35] A smaller duct diameter was observed in the preoperative therapy groups. Patients receiving preoperative therapy are expected to have a longer period of main pancreatic duct obstruction, especially when the tumor is in the pancreatic head. This difference may be due to the requirement of adequate biliary drainage before commencing PCT. Despite the smaller duct diameter in the preoperative therapy groups, a lower risk of POPF was observed.

The present study found a higher volume of intraoperative blood loss after preoperative therapy. This can potentially be explained by the higher rates of venous resections in these groups. However, no increase in the duration of surgery nor the rate of blood transfusions was observed.

The lower rate of POPF in the preoperative therapy groups did not translate into significantly fewer other postoperative complications (delayed gastric emptying, postpancreatectomy hemorrhage, or bile leakage) or lower in-hospital mortality. Future studies should assess the potential impact of POPF reduction on 90-day mortality and long-term survival.

This study also found that borderline resectable PDAC at the time of surgery was independently associated with a decreased risk of POPF in multivariable analysis. The resectability stage has not yet been described in relation to the risk of developing POPF. Subgroup analysis found the largest median (IQR) tumor diameter of 31 mm (25–40 mm) in the borderline resectable group compared with 29 mm (22–36 mm) in the resectable group and 30 mm (20–40 mm) in the locally advanced group ($P < .001$). The larger diameter of a borderline resectable tumor is more likely to cause a longer period of obstruction and parenchymal fibrosis, both factors known to be associated with a decreased risk of POPF.[35]

Study limitations

The results of this study should be interpreted in view of several limitations. First, the retrospective nature of this study may introduce confounding by indication. Second, the nationwide stepped-wedge cluster-randomized PORSCH trial was implemented during the study period.[43] Most likely, the increased use of radiological

Table II
Postoperative outcome of patients with pancreatic cancer after pancreatoduodenectomy

	Immediate surgery $N = 1,678$	Preoperative chemotherapy $N = 192$	Preoperative Chemoradiotherapy $N = 149$	*P* value
Clavien–Dindo classification ≥3	382 (23%)	38 (20%)	44 (30%)	.077
Missing	36	2	4	
POPF				.004
No or grade A/biochemical leak	1,529 (92%)	184 (96%)	146 (98%)	
Grade B/C	139 (8.3%)	8 (4.2%)	3 (2.0%)	
Missing	10	0	0	
Delayed gastric emptying				.624
No or grade A	1,426 (86%)	161 (84%)	124 (83%)	
Grade B/C	240 (14%)	31 (16%)	25 (17%)	
Missing	12	0	0	
PPH				.506
No or grade A	1,556 (94%)	184 (96%)	136 (93%)	
Grade B/C	101 (6.1%)	8 (4.2%)	10 (6.8%)	
Missing	21	0	3	
Bile leakage				.394
No or grade A	1,616 (97%)	189 (98%)	142 (96%)	
Grade B/C	47 (2.8%)	3 (1.6%)	6 (4.1%)	
Missing	15	0	1	
Blood transfusion	232 (14%)	32 (17%)	28 (19%)	.169
Missing	18	1	2	
Reintervention				
Reoperation	104 (6.3%)	11 (5.8%)	14 (9.6%)	.283
Radiologic intervention	210 (13%)	24 (13%)	20 (14%)	.932
Missing	25	1	2	
Readmission rate	254 (15%)	30 (16%)	28 (19%)	.493
Missing	21	1	2	
In-hospital/30-d mortality	52 (3.1%)	3 (1.6%)	3 (2.0%)	.494
Missing	21	1	2	

2018–2020	Immediate surgery $N = 612$	Preoperative chemotherapy $n = 165$	Preoperative chemoradiotherapy $n = 93$	
Operation time, min	321 (249–388)	337 (274–420)	329 (244–423)	.232
Missing	313	36	13	
Blood loss, mL	450 (200–842)	600 (400–1,091)	558 (300–1,000)	< .001
Missing	268	25	11	

N (%). Pearson's χ^2 test; Fisher exact test, based on complete case analysis.
PPH, postpancreatectomy hemorrhage; *POPF*, postoperative pancreatic fistula.

drainage (grade B POPF according to the ISGPS criteria) in this trial resulted in higher POPF rates over time. However, because that trial was implemented on a nationwide level, it is unlikely that the results of the present study were influenced. Third, although the groups of patients receiving PCT and PCRT are relatively large, we cannot exclude a type II error given the effect of PCT on POPF in multivariable analysis. Fourth, because no data on long-term survival were available, the impact of PCRT on the reduction of POPF on 90-day mortality could not be assessed. Fifth, intention-to-treat analysis could not be performed as data on the duration and completeness of preoperative therapy are lacking. The main strength of the present study is its nationwide design, including all patients after pancreatoduodenectomy for pancreatic ductal adenocarcinoma, providing a more robust assessment of the impact of preoperative chemo- and chemoradiotherapy on the rate of POPF after pancreatoduodenectomy.

Further studies are needed to investigate whether the decrease in POPF is driven by radiotherapy alone. Therefore, the pre-emptive use of radiotherapy targeting the intended pancreatic transection margin is currently being investigated in the FIBROPANC trial (NCT05641233). This multicenter phase 2 trial includes patients with a high risk of POPF (ie, patients scheduled for pancreatoduodenectomy for indications other than PDAC). Although reduced POPF rates could result in more patients initiating adjuvant treatment, potentially leading to better overall survival, early and adequate treatment of POPF is just as important.[43–45] Despite this, tumor characteristics are expected to remain the determining factor for the type of preoperative treatment. In situations where a decision has to be made between preoperative chemotherapy and chemoradiotherapy in patients at high risk of POPF (ie, nondilated pancreatic duct), the findings of this study could be taken into account.

In conclusion, in this nationwide audit-based study in patients undergoing pancreatoduodenectomy for PDAC, PCRT, but not PCT, was associated with a reduced rate of POPF. This may be related to increased pancreatic fibrosis due to the radiotherapy.

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Conflict of interest/Disclosure

The authors have no conflicts of interests or disclosures to report.

Table III
Univariable and multivariable analysis for the effect of preoperative chemotherapy and preoperative chemoradiotherapy on grade B/C postoperative pancreatic fistula

	Univariable				Multivariable (N = 1,651/2,056)		
	N	OR	95% CI	*P* value	OR	95% CI	*P* value
Sex (female)	1,993/2,056	0.82	0.58–1.14	< .001	0.69	0.46–1.02	.064
Age (≥70 y)	2,056/2,056	0.94	0.68–1.31	.725			
Charlson comorbidity index (0)	2,056/2,056						
1–2		0.93	0.61–1.41	.753			
>2		1.09	0.74–1.60	.649			
BMI <20 kg/m^2	1,993/2,056						
20–25		1.09	0.57–2.28	.813	1.08	0.52–2.54	.848
>25		2.36	1.25–4.95	.014	2.20	1.06–5.16	.048
Biliary drainage (yes)	1,997/2,056	0.57	0.41–0.80	.001	0.56	0.38–0.83	.004
Resectability (resectable)	1,966/2,056						
Borderline resectable		0.39	0.22–0.64	.001	0.47	0.25–0.84	.016
Locally advanced		0.63	0.28–1.25	.226	0.93	0.36–2.07	.863
Pancreatic duct diameter (>3 mm)	1,839/2,056						
≤3 mm		3.73	2.50–5.64	< .001	3.47	2.26–5.40	< .001
Unknown		1.66	0.95–2.83	.068	1.57	0.87–2.75	.123
Octreotide	2,029/2,056	1.52	1.08–2.19	.019	1.28	0.86–1.92	.236
Preoperative therapy (none)	2,009/2,056						
Chemotherapy		0.48	0.21–0.93	.047	0.59	0.25–1.25	.199
Chemoradiotherapy		0.23	0.06–0.61	.012	0.21	0.03–0.69	.033

P value based on complete case analysis unless unknown is displayed.

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