Impact of FDG-PET in optimizing patient selection for cytoreductive surgery in recurrent ovarian cancer

Yasuhiko Ebina[a,c], Hidemichi Watari,[b] Masanori Kaneuchi,[b] Mahito Takeda,[b] Masayoshi Hosaka,[b] Masataka Kudo,[b] Hideto Yamada,[a] Noriaki Sakuragi[b]

[a]Department of Obstetrics and Gynecology, Kobe University Graduate School of Medicine, Kobe 650-0017, Japan

[b]Department of Gynecology, Hokkaido University Graduate School of Medicine, Sapporo 060-8638, Japan, and

[c]Y.E. moved to Kobe University while he was preparing the manuscript.

Corresponding author, Yasuhiko Ebina MD, PhD

Associate professor

Department of Obstetrics and Gynecology,

Kobe University Graduate School of Medicine, Kobe 650-0017, Japan;

Tel: +81-78-382-6005, FAX: +81-78-382-6019

E mail: ebiyas@med.kobe-u.ac.jp

Abstract

Purpose. To investigate the impact of PET and PET-CT scanning on decision-making in the management plans and to identify the optimal setting for selecting candidate for surgery in suspicious recurrent ovarian cancer.

Methods. A retrospective chart review was performed on patients with possible recurrent ovarian cancer who underwent FDG-PET or FDG-PET/CT scans from July 2002 to August 2008. Forty-four patients had undergone primary optimal cytoreduction and taxane-carboplatin chemotherapy, and there were 89 occasions where PET/PET-CT scans were used to make treatment decisions for recurrent ovarian cancer. The positive PET scans were classified as follows. (1) Localized: one or two localized uptakes of FDG; (2) multiple: ≥3 uptakes of FDG; (3) diffuse: extensive low-grade activity outlining serosal and peritoneal surfaces.

Results. After PET scanning, the management plan was changed on 52 of 89 occasions (58.4%). The total number of cytoreductive surgeries selected as a treatment choice increased from 12 to 35. Miliary disseminated disease, which was not detected by PET scan, was found in 22.2% of surgeries. Miliary disseminated disease was detected in 6 of the 12 recurrent cases whose treatment-free interval (TFI) <12 months, whereas none of those with a TFI ≥12 months had such disease (p=0.0031).

Conclusions. PET or PET-CT is useful for selecting cytoreductive surgery candidates among patients with recurrent ovarian cancer. To avoid surgical attempts at miliary dissemination, patients with TFI ≥12 months are the best cytoreducive surgery candidates.

Keywords: ovarian cancer, recurrence, cytoreduction, FDG-PET

Introduction

The majority of women with advanced ovarian cancer eventually develop recurrent disease despite achieving clinical complete remission after initial treatment. With few exceptions, recurrent ovarian cancer patients are unlikely to be cured of their disease. Thus the goal of treatment is to improve the quality of life and lengthen the survival period. Most patients are offered further chemotherapy, although the response is limited. Alternatively, the role of secondary cytoreducive surgery for recurrent ovarian cancer is still controversial.

Several studies have reported factors associated with outcome in patients who have undergone secondary cytoreductive surgery. The treatment-free interval prior to secondary cytoreductive surgery and residual disease after it have been demonstrated to be associated with better outcome. [1, 2] However, the ratio of patients with optimal resection is as low as 70%.[3] This might be due to the difficulty of predicting the possibility of attaining optimal cytoreduction. The proper preoperative selection for the candidate remains unclear. The purposes of this study were to investigate the impact of PET scan findings (e.g., FDG uptake patterns) on decision-making for management plans and to identify the optimal setting for selecting candidates for surgery in suspicious recurrent ovarian cancer.

Patients and Methods

After obtaining Institutional Review Board approval, a retrospective chart review was performed on Hokkaido University Hospital patients with possible recurrent ovarian cancer, who had undergone FDG-PET or FDG-PET/CT scans between July 2002 and August 2008. This analysis includes 44 patients who underwent a total of 89

PET scans (60 FDG-PET, 29 FDG-PET/CT) during this period. All patients had histologically confirmed ovarian cancer and underwent primary optimal cytoreduction and taxane-carboplatin chemotherapy.

The images were reviewed by radiologists experienced with CT and nuclear medicine physicians experienced with PET. Whole-body 18F-FDG-PET imaging was performed with an ECAT EXACT 47 scanner (Siemens-CTI, Knoxville, TN, USA). Before the PET study, all of the patients fasted for at least 6 h, and serum glucose levels were checked before administration of 18F-FDG. The dose of 18F-FDG was 185 Mbq for each patient. Static emission scans were performed 60 min after 18F-FDG administration using the three-dimensional acquisition mode for a duration of 2 min per bed position. PET-CT imaging was performed using the Discovery LS (GE Medical Systems, Milwaukee, WI, USA). Patients fasted for a minimum of 4 h prior to PET acquisition. After confirmation of a blood glucose level <200 mg/dl, sterile FDG was administered intravenously (4.5 MBq/kg) followed by a tracer uptake phase of approximately 70 min. Positron emission data were acquired for five to seven bed positions, typically from the base of the skull to the mid-thigh. Emission data were acquired for 3 min for each bed position. PET images were reconstructed using CT for attenuation correction with the 2D OSEM algorithm. The CT scanner portion of the Discovery LS consisted of a multidetector helical CT. Imaging parameters were as follows for a five-bed-position acquisition: 140 mA, 60 mA, 0.6 s per CT rotation.

The standard surveillance protocol for patients with ovarian cancer consists of physical examination and evaluation of serum CA125 levels at 2～3-month intervals for the initial 24 months after completion of primary therapy and every 4 months thereafter. Abdominal and chest contrast-enhanced CT scans are performed every 6 months.

Patients who present an increase in serum CA 125 (20 U/ml or more) and a negative or equivocal CT scan receive a PET scan. The presence, region, and uptake pattern (e.g., nodular, diffuse) of FDG are fully reviewed. A management plan is then discussed. Close observation is recommended for patients who don't have distinct accumulation with PET scans despite a CA 125 rise. Systemic chemotherapy is given for patients who indicate a multiple or diffuse FDG uptake pattern. Otherwise, cytoreductive surgery is proactively considered for patients whose FDG uptake patterns are localized.

The positive PET scans were classified into three categories with FDG uptake patterns. (1) Localized: one or two localized uptakes of FDG, (2) Multiple: three or more uptakes of FDG. Each uptake is nodular, (3) Diffuse: extensive low-grade activity outlining serosal and peritoneal surfaces. Treatment-free interval (TFI) was defined as the time from completion of initial treatment or any previous recurrent treatment to the time of latest recurrence.

Statistical analyses were carried out using Statistica (StatSoft, OK, USA) software. Correlations between the variables were analyzed using Fisher's exact test and the Chi-square test. The Kruskal-Wallis test was used for non-parametric variables. $P<0.05$ was considered statistically significant.

Results

Forty-four patients underwent a total of 89 FDG-PET scans; 20 patients had one scan, 12 patients had two scans, and 12 patients had three or more scans. Indication for PET scanning was based on abnormal CT findings (48.3%), a rise in serum CA 125 (37.1%), suspicion of relapse at physical examination (10.1%), or clinical symptoms (4.5%). Most patients (95.5%) were asymptomatic at the time of PET scans.

Detailed characteristics of the patients are described in Table 1. The majority of patients had stage III (65.9%) and grade 3 (63.7%) disease at initial diagnosis. Most patients had serous histology (68.2%). A summary of the pre-PET and of the change in the post-PET management plans is shown in Figure 1. Positive FDG uptake was classified into 46 localized (51.7%), 18 multiple (20.2%), and 18 diffuse (20.2%) cases. In total, 58.4% (52/89) of PET scans led to changes in the patient's management plans. After the PET scans, the total number of candidates for whom surgery was planned increased from 12 to 35 (35/89; 39.3%).

Table 2 summarizes the association between treatment-free interval (TFI) and FDG uptake patterns in 82 patients in whom positive FDG uptake was detected. The ratios of patients with localized patterns in TFI<3 months, 3≤ TFI <6 months, 6≤ TFI < 12 months, and TFI ≥12 months were 36.0%, 52.9%, 58.8%, and 78.3%, respectively. The frequency was significantly higher in patients with TFI ≥6 months than in those with TFI <6 months (70.0% vs. 42.9%; p=0.012). As for patients with serous histology, the relationship between serum CA125 level and the FDG accumulation pattern was examined. The proportion of patients with a localized uptake pattern of FDG decreased as the CA125 level increased: 77.8% (14/18) in CA125≤50 U/ml, 66.7% (10/15) in 50<CA125≤100 U/ml, and 41.4% (12/29) in >100 U/ml (p=0.038).

Thirty-five cytoreductive operations were performed for 25 patients. The median patient age was 60 years (range, 35 - 78). The histological types were classified as: serous, 68%; clear cell, 20%; endometrioid, 8%; and mucinous, 4%. The initial FIGO stages were: FIGO stage I, 12%; stage II, 12%; stage III, 56%; and stage IV, 20%. The tumor grades were: grade 1, 24%; grade 2, 20%; grade 3, 56%. The median TFI prior to cytoreductive surgery was 10 months (range, 1-70 months). The surgical

procedures are listed in Table 3. The details of the cytoreductive operations are summarized in Table 4. In all patients, recurrent tumors preoperatively detected by PET scans were recognized during surgery. No macroscopic tumors that were undetectable by preoperative PET scan were discovered during surgery. However, 22.2% (6/27) of patients exhibited miliary disease in the abdominal cavity that could not be detected by a PET scan. The TFIs of the patients who had miliary disseminated disease were 6, 6, 6, 7, 8, and 10 months each. In addition, a small to modest amount of ascites (<500 mL) was recognized at the time of surgery in 11.1% (3/27) that could not be found preoperatively. All the patients with ascites had miliary disease. At the end of cytoreduction, macroscopically complete resection was achieved in 91.4% (32/35). On the other hand, 8.6% (3/35) of the patients had residual tumors less than 0.5 cm in diameter, and those were the patients that had miliary disease on the peritoneum surface. There were no patients who had residual tumors measuring more than 0.5 cm. Pathological examination confirmed recurrent disease in all patients. The median tumor diameter was 30 mm (range 10-72 mm). The mean estimated blood loss was 80 ml (range 10-580 ml). The median operative time was 125 min (range 50-450 min). There were no severe postoperative complications.

Regarding the 27 intraperitoneal operations, the factors that were related to peritoneal miliary dissemination are shown in Table 5. Miliary dissemination was detected in 6 (50.0%) of the 12 patients with a TFI <12 months, compared with 0 (0%) of those with a TFI ≥12 months (p=0.0031). Miliary dissemination was detected in 3 (12.5%) of the 24 patients with no ascites during the operation, compared with all 3 patients with measurable ascites (p=0.0068). In addition to these variables, none of the other variables analyzed (cytoreduction at secondary, tertiary, or quarterly, serous or

others, grade 1/2 or 3, CA125 <100 U/ml or ≥100 U/ml, lesions of recurrence 1 or 2, size of maximum tumor <30 mm or ≥30 mm) predicted miliary disease.

Discussion

In this study, we found that PET scan findings led to changes in management plans in 58% of cases. PET scanning was especially useful in selecting candidates for site-specific treatment (e.g., surgery, irradiation). As for cytoreductive surgery, the rate of complete resection was high, at 91%. Even if a PET scan indicates localized disease, patients with TFI≥12 months are the best candidates for complete resection due to the tumor size limitation.

For optimal management in recurrent ovarian cancer, it is necessary to consider the following factors: duration of the treatment-/platinum-free interval, possible second-line regimens, prior adverse effects experienced by the patient, and patient choice. Several studies have demonstrated that an elevation of serum CA 125 can precede the appearance of clinically or radiographically measurable recurrence by an average of 3 to 6 months.[4, 5] However, early reintroduction of treatment for asymptomatic patients is still controversial. OV05/EORTC 55955 trials have concluded that there was no survival benefit from early treatment based on an elevated serum CA 125 level alone.[6] On the contrary, recently investigators have reported that the detection of asymptomatic recurrence by routine surveillance testing was associated with a high likelihood of optimal secondary cytoreductive surgery and extended overall survival.[7]

During the course of recurrent treatment, several strategies can be used, namely: chemotherapy, cytoreductive surgery, and palliative irradiation. To avoid an accumulation of adverse effects of systemic cytotoxic agents (e.g., peripheral

neuropathy, myelosuppression), we considered that it would be preferable to offer site-specific therapy for recurrent patients when it was possible. Individualized approaches are slso essential for the long and comfortable survival of patients. For instance, patients who show symptoms or massive ascites need immediate treatment. On the other hand, in asymptomatic patients who exhibit only rising serum CA 125 levels and negative or equivocal CT scans, a PET scan is strongly recommended. The presence, region, and uptake pattern of FDG should be fully reviewed in order to make a decision. Management plans for the patient should then be discussed and confirmed. In some patients, close observation is recommended if there is no distinct accumulation with the PET scan despite elevated serum CA 125. Systemic chemotherapy is given for patients who indicate multiple or diffuse FDG uptake patterns. Otherwise, cytoreductive surgery is strongly considered for patients whose FDG uptake patterns are localized.

The sensitivity and specificity of CA 125 in recurrent ovarian cancer diagnosis is reported to be 57.6-92.1% and 71.9-96.7%, respectively. [8-10] And the sensitivity and specificity of PET-CT are 93.3-97.4% and 80-100%, respectively. [11, 12] A recent meta-analysis of 29 studies demonstrated that PET-CT had high sensitivity (89%) and specificity (90%).[13] Some reports have shown that management plans tended to change after examination of PET scans. [14, 15] Fulham mentioned that the management plans in 58.9% of patients changed based on PET scan findings. In that report, 38.9% of the patients finally underwent cytoreductive surgery.[16] In our study, management plans were changed in 58.4% of patients by PET results. Patients who were treated surgically increased from pre-PET, at 13.5%, to post-PET, at 39.3%. By introducing PET-CT for patients with elevated CA 125 levels, more patients would be

appropriately offered either chemotherapy or surgery.

Patients with localized uptake patterns of FDG are the best candidates for surgical therapy. The frequency of the patients with localized FDG uptake was higher in patients whose TFI was more than 6 months. Seventy-eight percent of patients who had a positive PET scan exhibited a localized pattern if TFI was more than 12 months. The association between TFI after second recurrence and outcome of the recurrent treatment are still controversial. And there is very limited data published for tertial surgical cytoreduction.[17] Notably, serum CA125 levels were lower in patients with localized FDG uptake than in those with multiple or diffuse patterns. Palomar reported that a PET scan is indicated when the CA 125 level is above 18 U/ml.[18] We observed that the rate for patients with a positive PET scan was significantly higher (29/35; 82.9%) when the CA125 level exceeded 20 U/ml, compared to those (4/27; 14.8%) less than 20 U/ml ($p<0.01$) (unpublished data). A localized FDG uptake pattern would likely be obtained when (a) TFI $\geq$6 months and (b) there is a successive elevation of serum CA 125 above 20-30 U/ml. In those cases, the choice of cytoreductive surgery should be evaluated.

A recent meta-analysis revealed that an optimal rate after secondary cytoreductive surgery is 70.3% (range, 22.2-100%) [3], although the definition of optimal cytoreduction varied (from <2.5 cm to no gross disease). The ratio of patients with complete resection was lower, with 52.2% (range, 9.4-100%). Multivariate analysis revealed that the proportion of patients undergoing complete cytoreduction and the year of publication were significant predictive factors for survival. Each 10% increase in the proportion of patients undergoing complete cytoreductive surgery was associated with a 3.00-month increase in median cohort survival time. However, there was no

statistical significance between the disease-free interval and survival.[3] As for tertiary cytoreduction, only residual disease after surgery retained prognostic significance.[17] Consequently, the selection of appropriate candidates is crucial for optimal cytoreduction. The results of our study suggest that the FDG uptake pattern is useful for selecting patients who are suitable for site-specific treatment. In this study, the rate of complete resection was as high as 91.4%, and median tumor size was small: 30 mm. Moreover, there were no severe complications or perioperative mortality. It is reasonable to suppose that we were able to choose optimal candidates using PET scanning and to perform cytoreduction earlier than in the previous studies. This may lead to a high complete resection rate and low morbidity.

FDG- PET scanning produces functional images that reflect increased rates of glucose metabolism in tumor, and it has many pit-falls in clinical use. Many papers in oncology have reported that PET scanning is of limited use in the detection of malignant tumors less than 1 cm in size. In the current study, 6 patients with localized macroscopic recurrence were also found to have miliary or multiple small diseases (< 5 mm). None of these lesions were detected by PET scans. All patients for whom complete resection was not possible had miliary disease. Size limitations in performing PET scans must be noted, since implants <10 mm are inconsistently identified owing to low concentrations and limited spacial resolution.[19] Miliary peritoneal dissemination was significantly associated with TFI<12 months and ascites at cytoreduction. Consequently, even if a PET scan indicates localized FDG uptake, we should carefully consider performing cytoreductive surgery for patients with TFI<12 months.

In summary, PET scanning is helpful in optimizing the management plans for

recurrent ovarian cancer patients and in aiding in the selection of appropriate candidates for attempted surgical resection.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Figure legend:

Figure 1 Treatment plans pre- and post-PET in patients with suspected recurrent ovarian cancer

Fig.1

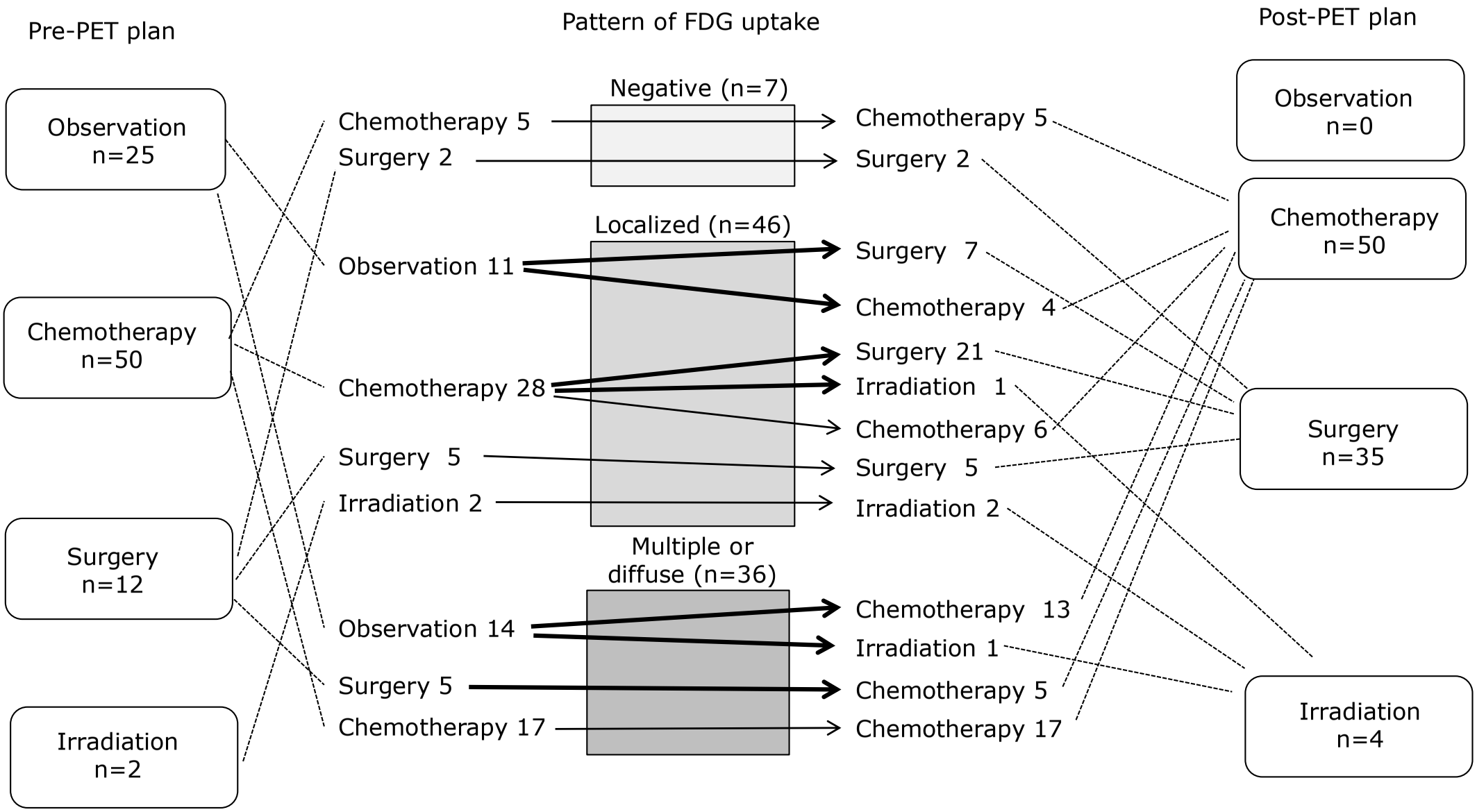
Pre-PET plan
Pattern of FDG uptake
Post-PET plan
Observation n=25
Chemotherapy n=50
Surgery n=12
Irradiation n=2
Negative (n=7)
Chemotherapy 5
Surgery 2
Localized (n=46)
Observation 11
Chemotherapy 28
Surgery 5
Irradiation 2
Multiple or diffuse (n=36)
Observation 14
Surgery 5
Chemotherapy 17
Chemotherapy 5
Surgery 2
Surgery 7
Chemotherapy 4
Surgery 21
Irradiation 1
Chemotherapy 6
Surgery 5
Irradiation 2
Chemotherapy 13
Irradiation 1
Chemotherapy 5
Chemotherapy 17
Observation n=0
Chemotherapy n=50
Surgery n=35
Irradiation n=4

Table 1. Characteristics of the patients who had PET or PET-CT to evaluate localization of recurrent ovarian cancer

Characteristic	N (%)
Age at initial diagnosis	
Median (range)	54.5 (31-74)
Stage at initial diagnosis	
Ⅰ	4 (9.1)
Ⅱ	6 (13.6)
Ⅲ	29 (65.9)
Ⅳ	5 (11.4)
Tumor grade	
1	6 (13.6)
2	10 (22.7)
3	28 (63.7)
Histology	
Serous	30 (68.2)
Clear	7 (15.9)
Endometrioid	4 (9.1)
Others	3 (6.8)
Number of scans	
1	20 (45.4)
2	12 (27.3)
>3	12 (27.3)

Table 2
The association between treatment-free interval (TFI) and FDG uptake pattern

TFI (months)	N	Localized (%)	Multiple or diffuse (%)	
<3	25	9 (36.0)	16 (64.0)	
3 - <6	17	9 (52.9)	8 (47.1)	
6 - <12	17	10 (58.8)	7 (41.2)	
>=12	23	18 (78.3)	5 (21.7)	
<6	42	18 (42.9)	24 (57.1)	P=0.012
>=6	40	28 (70.0)	12 (30.0)	

Table 3 . Surgical procedures used in treatment of recurrent ovarian cancer

Procedures	N
Tumor cytoreduction alone	6
Bowel resection	9
rectal resection	3 *
other large-bowel resection	4
small-bowel resection	2
Hepatic resection	5
Splenectomy	3
Distal pancreatectomy	1
Diaphragm resection	3
Cholecystectomy	1
Para-aortic node dissection	3
Cervical node dissection	3
Axillary node dissection	2
Inguinal node dissection	1
Video-assisted thoracoscopic surgery	2
Chest wall resection	1
Upper vaginectomy	1
Partial cystectomy	1

* Colostomy 2

Table 4. Results of cytoreductive surgeries for recurrent ovarian cancer

Characteristic	N (%)
Age at cytoreduction(years)	
Median (range)	60 (35-78)
Secondary cytoreduction	24 (68.5)
Tertiary cytoreduction	8 (22.9)
Quaternary cytoreduction	3 (8.6)
Treatment-free interval (months)	
Median (range)	10 (1-70)
Numbers of recurrent lesions	
1	27 (77.1)
2	8 (22.9)
Size of largest recurrence (mm)	
Median (range)	30 (10-72)
Dissemination	
Yes	6 (22.2)
No	21 (77.8)
Ascites at operation	
Yes	3 (11.1)
No	24 (88.9)
Residual after cytoreductive surgery	
No gross	32 (91.4)
<0.5cm	3 (8.6)
>0.5cm	0 (0.0)
Operation time (min)	
Median (range)	125 (50-450)
Bleeding in operation (g)	
Median (range)	80 (10-580)

Table 5. Factors predicting peritoneal dissemination in case of recurrent ovarian cancer

Variable	N	Dissemination N (%)	p
Secondary cytoreduction	21	4 (19.0)	0.608
Tertiary cytoreduction	4	1 (25.0)	
Quartery cytoreduction	2	1 (50.0)	
Histology			
Serous	20	6 (30.0)	0.155
Others	7	0 (0.0)	
Grade			
1/2	9	1 (11.1)	0.381
3	18	5 (27.8)	
TFI (months)			
<12	12	6 (50.0)	*P=0.0031*
≧12	15	0 (0.0)	
CA 125 (U/ml)			
<100	19	4 (21.1)	0.773
≧100	8	2 (25.0)	
Number of recurrent lesions			
1	19	2 (10.5)	0.136
2	8	4 (50.0)	
Size of largest tumor (mm)			
<30	14	4 (28.6)	0.648
≧30	13	2 (15.4)	
Ascites at the operation			
No	24	3 (12.5)	*P=0.0068*
Yes	3	3 (100.0)	