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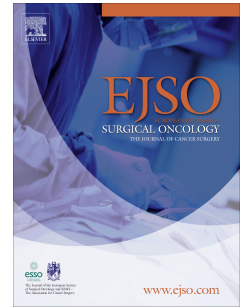


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Pseudomyxoma peritonei: a French multicentric study of 301 patients treated with cytoreductive surgery and intraperitoneal chemotherapy.

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Miniabstract :

The results obtained in 301 patients with pseudomyxoma peritonei treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy in 18 French-speaking centers confirms good results and that these procedures should be recommended in specialized centers.

STRUCTURED ABSTRACT**Objective :**

To analyze a large series of patients with pseudomyxoma peritonei (PMP) treated with cytoreductive surgery associated with perioperative intraperitoneal chemotherapy (PIC) in 18 French-speaking centers.

Patients and methods:

From March 1993 to December 2007, 301 patients with diffuse PMP were treated by cytoreductive surgery with PIC. Complete cytoreductive surgery was achieved in 219 patients (73%), and hyperthermic intraperitoneal chemotherapy (HIPEC) was performed in 255 (85%), mainly during the latter period of the study.

Results:

Postoperative mortality and morbidity were 4.4% and 40%, respectively. The mean follow-up was 88 months. The 5-year overall and disease-free survival rates were 73% and 56%, respectively. The multivariate analysis identified 5 prognostic factors : the extent of peritoneal seeding ($p=0.004$), the center ($p=0.0004$), the pathologic grade ($p=0.03$), gender ($p=0.02$), and the use of HIPEC ($p=0.04$). When only the 206 patients with complete cytoreductive surgery were considered, the extent of peritoneal seeding was the only significant prognostic factor ($p=0.004$).

Conclusion:

This large multicentric retrospective study confirms that cytoreductive surgery combined with PIC (with the use of hyperthermia) should be considered as the gold standard treatment of PMP and should be performed in specialized centers. It underlines the prognostic impact of the extent of peritoneal seeding, especially in patients treated by complete cytoreductive surgery. This prognostic impact appears to be greater than that of the pathologic grade.

Key-words: peritoneal pseudomyxoma, cytoreductive surgery, intraperitoneal chemotherapy, hyperthermia, prognosis;

Pseudomyxoma peritonei (PMP) is a clinico-pathologic entity characterized by the production of mucinous ascites (1,2) and mostly originates from appendiceal epithelial neoplasms. The tumor grows, obstructing the narrow lumen of the appendix and subsequently leading to appendiceal perforation (1,2). Then neoplastic cells progressively and slowly colonize the peritoneal cavity and copious mucin production builds up in the peritoneal cavity. Recently, pathologic enteric bacteria were shown to be present in all specimens and their density was correlated with the prognosis (3). Appendix tumors causing PMP range from a benign pathologic appearance (disseminated peritoneal adenomucinosis or DPAM), to malignant pathologic findings (peritoneal mucinous carcinomatosis or PMCA), with some intermediate pathologic grades (4). Clinically, this syndrome ranges from early PMP fortuitously discovered on imaging or during a laparotomy performed for another reason, to advanced cases with a distended abdomen, occlusive syndrome and starvation.

The conventional treatment of PMP is surgical debulking repeated, as necessary to alleviate pressure effects (5,6). However, this treatment is palliative, leaving visible or occult disease in the peritoneal cavity. Repeated debulking surgeries become ever more difficult due to progressively thickened intra-abdominal adhesions (7).

A combination of cytoreductive surgery (CRS) with perioperative intraperitoneal chemotherapy (PIC) was proposed by Sugarbaker (8). The rationale behind this strategy was to resect visible disease and any occult residual disease would be treated with a high concentration of chemotherapy and hyperthermia which mutually potentiate one another's effects (9,10). Fifteen years and 600 publications later (7), a systematic review of this novel treatment concluded that this combined approach was very probably superior to conventional therapy, even in the absence of controlled

randomized trials, and even with evidence from only five series of more than 100 cases (11-16). Each series reported the experience of only one team with various experiences, and there was no multicentric series reflecting “reality”.

This study aimed to collect patients with PMP treated with this combined approach in 18 different French-speaking centers, to analyze morbidity, mortality and survival results, and to identify the main prognostic factors for better patient selection.

Patients and methods

Patient Population

The AFC (Association Française de Chirurgie) conducted a multicentric retrospective study in French (n=20), Belgian (n=2), Canadian (Quebec, n=2) and Swiss (n=1) centers. Patients were treated between March 1993 and December 2007. Inclusion criteria were 1) pathologic confirmation of PMP 2) patients treated with the intent of achieving an R-0 resection with cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) or early postoperative intraperitoneal chemotherapy (EPIC). Exclusion criteria were tumors originating from the colon, small bowel and appendiceal adenocarcinoma without a predominant mucinous component.

Treatment

Resection of PMP obeyed principles described elsewhere (17). In short, peritonectomy procedures which included a total anterior and lateral parietal peritonectomy, omentectomy and splenectomy, right and left sub-phrenic peritonectomy, pelvic peritonectomy and lesser omentectomy and cholecystectomy with stripping of the omental bursa were performed exclusively in the macroscopically pathologic areas.

More or less extended resections of the colon, rectum, small-bowel and stomach were associated, if invaded by PMP. Intraperitoneal chemotherapy was delivered immediately after cytoreductive surgery. EPIC was performed from day 1 to day 5 after surgery, and was used during the early period of this retrospective study. HIPEC was performed with an opened abdominal cavity (Coliseum technique), or a closed one and was used during the major second period of the study.

Data Forms

A standard data form was created to retrieve information on the primary colorectal tumor, on the status of the patient prior to the combined procedure, and on previous treatment with systemic chemotherapy. The extent of PC is assessed through intraoperative exploration using the Peritoneal Cancer Index (PCI) which scores from 0 to 3 each of the 13 defined areas of the abdominal cavity, and therefore ranges from 1 to 39. Four PCI subgroups were arbitrarily defined for the analysis : 1 to 6, 7 to 12, 13 to 19, and > 19. Information recorded about the combined procedure included the completeness of cytoreductive surgery, any simultaneous resection of the primary tumor and liver metastases, the presence or absence of lymph node metastases, the type of perioperative intraperitoneal chemotherapy (HIPEC or EPIC) and its modalities, and treatment with adjuvant systemic chemotherapy. Assessment of the completeness of the cancer resection (CCR) with cytoreductive surgery was done by the surgeon at the end of the procedure and classified into three categories: CCR-0 signified no macroscopic residual cancer, CCR-1, no residual nodules greater than 2.5 mm, and CCR-2, that the diameter of the residual nodules exceeded 2.5 mm. Information was obtained regarding the postoperative course, including postoperative deaths (within 30 postoperative days) and the cause of death. Major complications (grade 3 and 4

complications according to the National Cancer Institute's Common Toxicity Criteria) were considered and the reasons for re-operation were detailed.

PMP was classified into 3 pathological grades according to the Ronnett classification system (4): grade 1 corresponded to disseminated peritoneal adenomucinosis (DPAM), grade 2 to peritoneal carcinomatosis with intermediate features, and grade 3 to peritoneal mucinous carcinomatosis (PMCA).

Data recorded included the most recent follow-up information, the status of the patient (alive with disease, alive without disease, died with disease, died without disease), and the site of the initial recurrence.

Statistical Analysis

The descriptive analyses of the patients included in the registry, as well as the survival analyses were performed on a per-patient basis (one record per patient). However, all procedures were considered for the analyses of postoperative morbi-mortality events (death or major complications occurring within 30 days after surgery).

Categorical variables were described in terms of frequency and percentages. The distributions of continuous variables were described with the mean, standard error, median, 1st and 3rd quartiles. Patient, disease and treatment characteristics were correlated with postoperative morbi-mortality events using univariate and multivariate logistic regression models, adjusted on centers, because of their strong prognostic influence.

The analysis of long-term mortality censored information after the cut-off date of December 31st 2007 since an active enquiry was performed in all centers to collect the status (dead/alive) of the patients at that date. The analysis of total mortality considered the interval from the first procedure to the date of death, the date of the

last news, or the cut-off date, whichever came first. The analysis of recurrence or death was based on the interval from the first procedure to the date of first recurrence, the date of death, the date of the last news, or the cut-off date, whichever came first. Postoperative deaths were not excluded from the survival analysis. Patients who had CCR-2 resections with residual tumor nodules exceeding 2.5 mm were considered as having immediate relapses. When the date of recurrence was unknown in patients who had died, the date of death was used instead. Kaplan-Meier survival estimates were calculated, and compared between strata with the log-rank test. The influence of baseline risk factors on the hazard of death was assessed using a multiple proportional hazard regression model stratified on centers. Stratification was justified due to considerable heterogeneity in hazards between centers, and to a strong potential confounding effect on other risk factors. In all multivariate analyses, age and PCI were entered as continuous variables. The completeness of cytoreduction was also entered as continuous when justified by a linear trend across categories. Risk factors with a trend of significance ($p \leq 0.10$) were retained in the final model. The SAS statistical software (Windows, V9.1) was used for all analyses.

Results

Patients

From March 1993 to December 2007, 301 patients with PMP were treated in 18 French-speaking centers with CRS plus PIC (5 centers did not treat PMP). The number of patients treated per center ranged from 130 to 1. There were 190 females and 111 males and the mean age was 52 years (1st-3rd quartile: 44-59; median: 52, range: 26-79).

PMP originated from the appendix in 91% of the cases (ovary in 7%, and the origin was unknown in 2%). The circumstances leading to the discovery of PMP were : unexplained ascites leading to laparoscopy or laparotomy (32%), abdominal pain (27%), increasing abdominal girth (15%), on imaging performed for another reason (15%), deterioration of general status (5%), wound hernia (4%), and appendicitis (2%).

Treatment Modalities

The mean peritoneal index was 18.5 (1st- 3rd quartiles: 11-26, median:18, range:9-39). Concerning the completeness of cytoreductive surgery, CCR-0 had been achieved in 73%, CCR-1 in 20%, and CCR-2 in 7%. Concerning intraperitoneal chemotherapy, 255 patients (85%) had been treated with HIPEC and 46 patients (15%) with EPIC. Hipec was done even with mitomycin C based-regimens during 60-120 min. at 41-42°C, even with oxaliplatin-based regimens during 30 min at 43°C. EPIC was done with mitomycinC during day 1 and 5-fluorouracyl from day 2 to day 5. Systemic chemotherapy had been administered before or after this combined treatment in 69 patients (23%), mainly those presenting severity of illness criteria (mean number of courses: 7.1).

Mortality and Morbidity

Thirteen patients (4.4%) had died postoperatively. The causes of death were septic shock (9 patients) linked to abdominal infection, respiratory complications (4 patients), hematological toxicity (2 patients), pulmonary embolism (1 patient), and acute renal insufficiency (1 patient).

Grade 3-4 complications had occurred in 119 patients (40%), and 17.5% (n=52) of all patients had been re-operated on; 8% (n=24) had a digestive fistula, 9% (n=27) a intraperitoneal abscess, 13% (n=38) hemorrhage, 14% (n=42) a pulmonary infection, and

20% (n=58) grade 3-4 hematological toxicity. The median duration of hospitalization was 21 days (mean duration 26 ± 14 days).

The logistic regression analysis of factors which significantly increased the risk of mortality and morbidity identified two main factors, the peritoneal index ($p=0.002$, correlated with the extent and duration of surgery), and the presence of a high pathologic grade (PMCA) ($p=0.03$).

Survival

With a mean follow-up of 88.4 months (1st - 3rd quartile: 28 - 125, median: 73), the overall 1-year, 3-year, and 5-year survival rates were respectively 89.4%, 84.8% and 72.6% (**figure 1**). The 10-year survival rate was 54.8%. Median survival had not yet been reached, but it will be longer than 100 months. The disease-free survival (DFS) rate was 56% at 5 years (**figure 1**) and the median duration of DFS was 78 months.

There was a strong center effect ($p=0.004$) that justified an analysis of the impact of other prognostic factors adjusted on centers (**figure 2**). Figure 2 shows 7 curves corresponding to the six centers which treated at least 10 patients and one curve (the lowest one) for the 11 remaining centers (which treated fewer than 10 patients per center).

In the univariate analysis (**table 1**), age did not exert an impact on survival unlike gender ($p=0.02$, in favor of females), the extent of peritoneal seeding ($p<0.001$), the completeness of CRS ($p<0.001$), the pathologic grade ($p<0.001$) and the presence of invaded lymph nodes ($p<0.001$). Two other prognostic factors must be underlined: HIPEC seemed more efficient than EPIC ($p=0.001$) and the results were different

according to the centers ($p=0.0004$). The prognosis was worse ($p=0.01$) for patients who had received systemic chemotherapy (because it was given in advanced and high-grade cases).

The multivariate analysis identified five factors with an independent influence on survival (**table 2**). First, the center effect ($p<0.01$), second, the extent of peritoneal seeding ($p=0.004$) (**figure 3**) with a significant decline in survival when the peritoneal index was greater than 20. This index was strongly correlated with the completeness of the CRS : CCR1 and CCR-2 were only observed when the peritoneal index was high. Thirdly, the pathologic grade ($p=0.03$) was a poor prognostic factor for PMCA. No significant difference in survival was found between DPAM and intermediate grades. The other two factors were gender ($p=0.02$) in favor of females, and the use of HIPEC rather than EPIC ($p=0.04$).

Multivariate analysis of disease-free survival identified two significant factors: the extent of the peritoneal seeding ($p<0.001$) (strongly correlated with the CCR-status), and the center's experience ($p=0.006$).

In the group of 206 patients with a CCR-0 resection, the 5-year and 10-year survival rates were 84% and 61% respectively. It is noteworthy that two factors became non-significant in the univariate analysis : gender and the pathologic grade. Only one factor continued to exert a prognostic impact : the extent of peritoneal seeding ($p=0.004$), while HIPEC was marginally better ($p=0.07$) than EPIC.

Discussion

This study reports the results of the first multicentric retrospective analysis of 301 patients with diffuse PMP treated by cytoreductive surgery combined with

perioperative intraperitoneal chemotherapy. Postoperative mortality was 4%, and grade 3-4 morbidity was 40 %. The 5-year survival rate was 72.6% and median disease-free survival was 78 months. Median survival has not yet been attained but was longer than 100 months.

Survival. This study reports on the largest series of patients with PMP ever published after the monocentric series of 501 cases reported by Sugarbaker (11). Compared to the exceptional expertise of Sugarbaker, it presents results from 18 French-speaking centers, and adequately reflects the management of PMP in real-life settings where the experience of such treatment is very unequal from one center to another. It is always difficult to extrapolate results from a monocentric experience to other centers, due to considerable heterogeneity in selection criteria, in CRS and intraperitoneal chemotherapy techniques. Our study effectively underlines the importance of the experience of the center in the survival results. Due to a healthy degree of scepticism among some oncologists, any multicentric study collecting data from a large number of centers is particularly useful, even if the experience and the techniques differ considerably from one center to another. This trial concerns a collaborative effort of 25 French-speaking centers, which included 1290 patients with primary or digestive peritoneal carcinomatosis treated by CRS combined with PIC to evaluate the efficiency of this combined approach (18 of them have treated PMP). Due to its retrospective nature, this study suffers from many potential biases in the selection of patients and in treatments. Nonetheless, it has allowed us to present a large number of patients treated in many centers and to draw conclusions.

Also, the 5-year overall survival rate of 72.6% for PMP represents the worst results that can be obtained with CRS combined with PIC because it takes into account the learning curves of 18 centers, and because progress in patient selection and in the quality of

surgery increases with experience. This overall survival rate is identical to the 72% reported by Sugarbaker in his cohort of 501 patients (11). Thus, our multicentric study corroborates the results of the largest monocentric study. If we analyze the other four trials which included more than 100 patients treated with this combined approach, our survival results are better than those reported by Zoetmulder (13) and Loggie (14), close to those of Chua et al. (16) but worse than those reported by Elias (15) who included only patients whose resection was complete or sub-complete (CCR-0 or CCR-1).

Moreover, a mortality rate of 4% and a morbidity rate of 40% for this combined approach are the sort of rates that would be obtained with any kind of complex oncologic surgery such as oesophagectomy or duodeno-pancreatectomy. These rates are therefore acceptable face to benefits for overall and disease-free survival.

The results of the conventional treatment of PMP mainly based on repeated surgical debulking have been reported in two series (5,6). Gough et al. (5) reported a 5-year survival rate of 53%, with a 97% recurrence rate at 10 years in 56 PMP patients who underwent serial debulking and were selectively treated with intraperitoneal radiotherapy or chemotherapy between 1957 and 1983. Minner et al. (6) reported an 88% recurrence rate at 5 years in 97 PMP patients treated with serial debulking, systemic chemotherapy and/or delayed intraperitoneal 5-fluorouracil over a 22-year period. The 3% and 12% disease-free survival rates are well below the 56% rate we observed in our series. Sugarbaker and Zoetmulder also reported higher rates, 47% and 61%, respectively. All these results are probably due to the superiority of the combined over the conventional approach. In France, this combined approach has become the gold standard treatment when feasible (18).

Prognostic factors. The multivariate analysis of our series identified four significant and independent prognostic factors, adjusted on centers: the extent of the disease, the pathologic grade, gender, and the use of hyperthermia. One of these factors, namely the extent of the disease, was not identified in the five earlier series of more than 100 patients treated with the combined approach. In contrast, the completeness of cytoreduction was statistically significant in three (12,14,16). The pathologic grade was not retained in three series (12-15), but selected in two (13,16) which reported only 31 CCR-0 resections in 103 treated patients and 73 CCR-0 resections in 106 treated patients for the first and the second study respectively.

Thus, new information is emerging from our multicentric study.

First, this multicentric study underlines the influence of the center in which the procedure was performed and this led us to perform a multivariate analysis adjusted on centers. Centers with less experience had a lower rate of complete cytoreduction and poorer survival results. The fact that incomplete cytoreduction in the 174 patients reported by Glehen et al (23), resulted in only 15% of patients alive at 5 years argues in favor of exclusively entrusting this approach to experienced, good quality centers in the future.

Second, the extent of peritoneal seeding has a potent prognostic impact, even if this impact is probably lower than for patients with colorectal peritoneal carcinomatosis (18-21). In our series, the 5-year survival rate was only 57% for patients with a peritoneal index exceeding 19, whereas it was 83% for the other patients. We also established that the completeness of cytoreduction was strongly correlated with the disease extent (peritoneal cancer index), and also with the pathologic grades (data not shown). Finally, extensive PMP with high pathologic grades are the most frequently incompletely resected lesions and mainly in inexperienced centers.

Third, the pathologic grade had a significant prognostic impact on the whole series, but it disappeared when only the 206 patients with a complete CCR-0 resection were considered. Thus complete cytoreductive surgery is able to reduce the negative prognostic impact of the pathologic grade as previously pointed out by Elias et al. (15). Fourth, survival was better among female patients in the whole series, but gender was not statistically significant when only CCR-0 patients were taken into account. Thus, male patients more frequently presented with extended and incompletely resectable PMP than female patients.

Fifth, survival results were better with HIPEC than with EPIC. Glehen et al. (23) already reported the superiority of HIPEC over EPIC in a retrospective study evaluating patients treated with incomplete CRS. Our results could stem from a bias because EPIC was mainly used during the earlier period of the study. Although experimental studies are also in favor of the use of hyperthermia (24), its benefit should be confirmed in a prospective study.

Finally, it is noteworthy that the extent of peritoneal seeding was the only prognostic factor identified in the multivariate analysis in the group of patients with a CCR-0 resection.

In conclusion, this multicentric study of 301 patients with PMP confirms the promising results reported earlier by Sugarbaker and a few other experienced teams using the combination of cytoreductive surgery with perioperative intraperitoneal chemotherapy to treat PMP. It also establishes that the extent of peritoneal seeding and the completeness of cytoreduction exert a greater impact on survival than the pathologic grade.

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Table 1 : Univariate analysis of prognostic factors.

Variable	Number	3-y survival (%)	5-y survival (%)	p
Gender				
Female	190	88	77	0.02
Male	111	84	66	
Age				
< 53 y	162	87	71	0.09
≥ 53 y	139	82	73	
IV chemotherapy				
No	229	88	78	0.01
Yes	72	72	68	
Extent of Peritoneal Disease ¹				
1-6	34	92	79	< 0.001
7-12	47	92	83	
13-19	59	92	84	
> 19	117	74	57	
Size of remaining tumor ²				
0 mm	201	90	84	< 0.001
< 2.5 mm	55	71	58	
> 2.5 mm	19	67	25	
Lymph node involvement ³				
No	243	88	78	< 0.001
Yes	7	0	0	
Pathologic grade ⁴				
DPA	136	93	85	< 0.001
Intermediate	71	90	84	
PMC	59	69	47	
Type of intraperitoneal chemo				
HIPEC	255	90	79	0.001
EPIC	46	63	54	
Center				
Best results	36	87	77	0.02
Worst results	9	47	45	

¹According to the peritoneal index, 44 were not reported²After cytoreductive surgery (= completeness of the resection), 26 were not reported³51 were not reported, ⁴35 were not reported

DPA = diffuse peritoneal adenomucinosis

PMC = Peritoneal mucinous carcinomatosis

HIPEC = hyperthermic intraperitoneal chemotherapy

EPIC = Early postoperative intraperitoneal chemotherapy

Table 2: Multivariate analysis of prognostic factors for overall survival of 301, patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy

Variable	p	Hazard ratio	95% CI
Peritoneal index (1)	0.004	1.042	1.013 - 1.072
Center	< 0.001	0.469	0.286- 0.797
Histologic grade (2)	0.02	0.338	0.133 - 0.859
Sex	0.02	0.554	0.330 - 0.931
HIPEC vs EPIC	0.04	4.476	1.051 - 19.053

- (1) For each point in the peritoneal index. Each additional point increases the relative risk of death, i.e. by 4.2%.
- (2) In three categories: . Passing from DPA or intermediate category to PMC increases the risk of death by 33.8.% .

Figure Legends:

Figure 1: Overall and disease-free survival of the 301 patients with PMP treated with CRS + HIPEC

Figure 2: Overall survival according to the centers ($p < 0.001$) (the names of centers are censored).

Figure 3: Overall survival according to the peritoneal index ($p = 0.004$)

Figure 1:

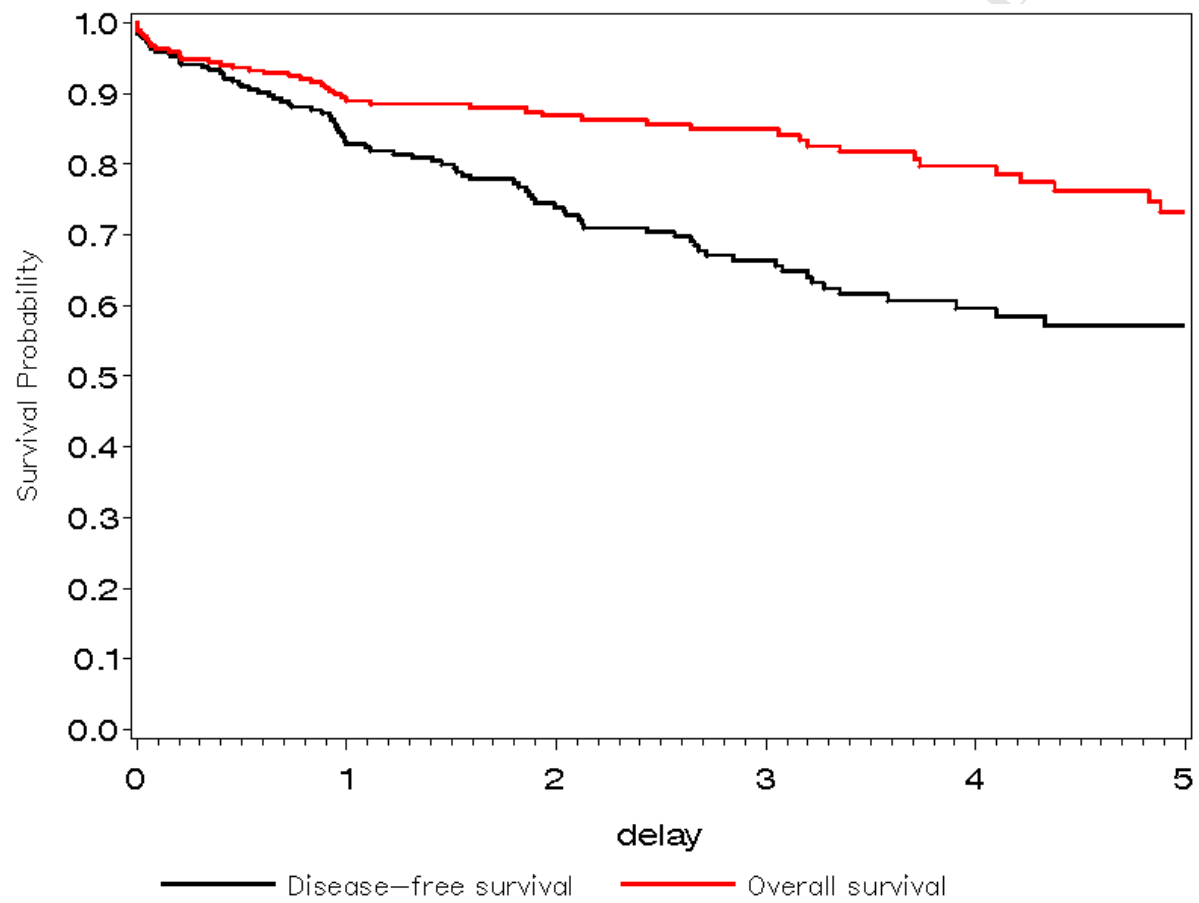


Figure 2 :

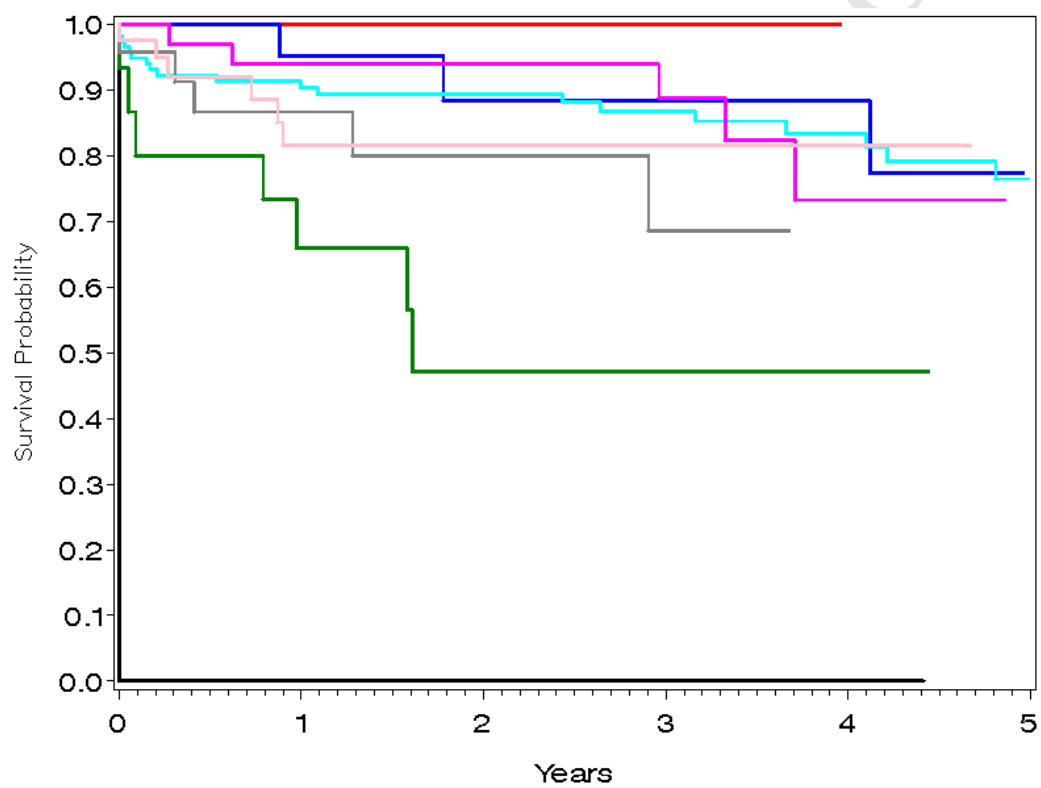


Figure 3 :

