
Histopathological correlation of splenic disease with radiological and surgical findings: should we incorporate splenectomy into standard procedures for disseminated Müllerian adenocarcinoma?

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Summary

Purpose of investigation: To determine the positive predictive value (PPV) of both preoperative radiological and intraoperative identification of splenic disease in cases of advanced and recurrent gynaecological malignancy. *Materials and Methods:* A retrospective study of all splenectomies performed during surgeries for disseminated gynaecological malignancy at the Pan Birmingham Gynaecological Cancer Centre between May 21st, 2008 and January 31st, 2015. *Results:* Forty-one women were identified, most of whom had Stage 3C, high grade, serous Müllerian adenocarcinomas. Thirty-seven (90.2%) spleens were removed because of intraoperative suspicion of disease and the remaining four (9.8%) were removed following inadvertent injury. No spleens were detected radiologically that did not have obvious macroscopic disease. The PPV for the preoperative and intraoperative detection of splenic disease were 88.9% and 91.9%, respectively. Half of the spleens removed following inadvertent injury had disease identified following histopathological examination. *Conclusion:* Intraoperative identification of splenic disease correlates well with histopathological examination. However, in 50% of splenectomies performed following inadvertent trauma and where disease was not suspected, metastases were identified.

Key words: Splenectomy; Gynaecological malignancy; Positive predictive value.

Introduction

Residual disease following cytoreductive surgery in ovarian, peritoneal, and tubal cancer has repeatedly been demonstrated to be the key modifiable determinant of survival [1-3]. Incorporating upper abdominal procedures into the surgical treatment of advanced gynaecological malignancy improves cytoreduction rates [2, 4]. Splenectomy is occasionally required during initial cytoreductive surgery, although the rates of it vary significantly between units [5, 6]. Beyond initial surgery, the spleen is a recognised site of recurrence and splenectomy may therefore be required in the context of secondary and subsequent cytoreductive surgeries [7, 8].

Splenic disease occurs following spread by blood, transcoelomic implantation or by direct invasion from adjacent tumour. Even if not affected by disease, due to its anatomical proximity to the supra-colic omentum, splenectomy may be required to achieve standard procedures in ovarian cancer surgery [9].

Intraoperative identification of disease has been shown to have a high positive predictive value with one centre correctly identifying disease in 86% of spleens which were removed [9]. Accurate intraoperative identification is important to reduce morbidity from inappropriate splenectomies. Although it is a relatively safe procedure [10], there are potential intra-

operative complications such as bleeding and the requirement for additional pancreatic surgery. Later complications such as overwhelming post-splenectomy infection (OPSI) [11] may also occur. Even without complications, splenectomy demands specific patient information, repeated vaccinations, and potentially lifelong antibiotic therapy [12].

The primary aim of this study was to elucidate the positive predictive value (PPV) of both preoperative radiological and intraoperative identification of splenic disease. Secondary aims were to determine the number of splenectomies performed, the indication for removal, and the occurrence of immediate and late morbidity in these patients.

Materials and Methods

The authors undertook a retrospective review of all splenectomies performed by sub-speciality trained gynaecological-oncologists during surgeries for disseminated gynaecological malignancy at the Pan Birmingham Gynaecological Cancer Centre between May 21st, 2008 and January 31st, 2015. This UK centre surgically treats approximately 65 Stage 3C/4 ovarian, tubal, and primary peritoneal cancers per year. Cases were identified from the gynaecological-oncology multi-disciplinary team database.

In the present Centre, the initial assessment of women with suspected disseminated serous Müllerian adenocarcinoma (ovarian, primary peritoneal, tubal or serous endometrial malignancy) con-

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sists of clinical examination, transvaginal ultrasound scan, and serum CA125 test. A CT scan of the abdomen and pelvis (and thorax if indicated) is performed in women in whom metastases are suspected. Following discussion in a multi-disciplinary team meeting women either underwent: primary surgery with the intention of complete cytoreduction, followed by six cycles of platinum-based adjuvant chemotherapy; a biopsy followed by three cycles of neoadjuvant chemotherapy plus surgery, with the intention of complete cytoreduction (delayed debulking surgery); or surgery to palliate symptoms or improve performance status followed by chemotherapy followed by surgery, with the intention of complete cytoreduction (interval debulking).

Surgery undertaken with the intention of achieving complete cytoreduction consists of basic and extensive (ultraradical) procedures, dependent on the sites of carcinomatosis. Basic procedures are performed in all women and include a midline laparotomy, peritoneal washings, total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and biopsies of any suspicious areas of peritoneum or enlarged lymph nodes. It may also include isolated recto-sigmoid resection if indicated. Extensive (ultraradical) procedures are performed when indicated (following pre- or intra-operative identification/suspicion of disease) depending on the patient's comorbidities/performance status. Extensive (ultraradical) procedures consist of: bowel resection(s), extensive peritoneal stripping; diaphragmatic stripping/resection; splenectomy, liver resection, gastric resection, and distal pancreatectomy.

Complete cytoreduction is accomplished when there is no macroscopic evidence of disease following completion of surgery. Optimal cytoreduction was defined as residual disease of less than one cm with greater than one cm residual disease being classified as sub-optimal cytoreduction. In the present Cancer Centre, during the past years the authors have moved towards the complete and suboptimal (> 0 cm) binary system.

Definitive histology (histological sub-type and grade) is obtained from the surgical specimens. Following surgery, all women undergo three to six cycles of adjuvant chemotherapy depending on previous chemotherapy exposure. All women are followed up for five years. Women with recurrent disease are considered on an individual basis for surgical resection (secondary debulking), chemotherapy or palliation following clinical assessment, cross-sectional imaging, and discussion at the multi-disciplinary meeting.

Data collection

The following data were retrospectively collected: age, FIGO stage, histological sub-type and grade, indication for splenectomy (removal following intraoperative suspicion of splenic disease or inadvertent splenic injury), histopathology results including the presence/absence of splenic disease and its location if present, type of initial surgery performed (primary, delayed, interval or secondary), degree of cytoreduction achieved (complete, optimal, sub-optimal), estimated blood loss during surgery, duration of surgery, length of hospital stay, additional procedures performed, and intra- and postoperative complications (graded according to the Dindo grading system) [13].

Statistical analysis

Both the preoperative suspicion of disease on cross-sectional imaging and the surgeon's intraoperative suspicion of disease following exploratory laparotomy was compared with the histopathological assessment and the corresponding PPVs were calculated. Categorical data were analysed using Chi-square where appropriate. Bonferroni corrections were applied for multiple comparisons. When $p < 0.05$, the difference was considered to be statistically significant.

Table 1. — Population characteristics and pathological findings.

Age (years) mean \pm SD	60.5 \pm 11.5
Stage	n (%)
Early	3 (7.3)
3C	29 (70.7)
4	9 (22.0)
Histological sub-type	n (%)
<i>Epithelial</i>	
Ovarian serous	25 (61.2)
Primary peritoneal serous	6 (14.6)
Tubal serous	6 (14.6)
Ovarian clear cell	1 (2.4)
Ovarian endometrioid + serous	1 (2.4)
<i>Non-epithelial</i>	
Ovarian yolk sac	1 (2.4)
Corpus serous	1 (2.4)
Grade	n (%)
Low	6 (14.6)
High	34 (82.9)
Unclassifiable	1 (2.5)
Indication for splenectomy	n (%)
Suspicion of disease	37 (90.2)
Incidental removal	4 (9.8)
Distribution of splenic disease	n (%)
Parenchyma	8 (19.5)
Capsule	19 (46.3)
Hilar	19 (46.3)
Hilar fat	7 (17.1)
Malignant cells in blood	1 (2.4)

Results

Overall, 41 women underwent splenectomy, the majority of whom had Stage 3C, high grade, serous Müllerian adenocarcinoma. The indication for splenectomy is illustrated in Table 1.

Identification of splenic disease

Splenic disease was suspected in 18 patients following preoperative CT. Of these, 16 were found to have splenic disease following histopathological examination (true positives) giving a PPV of 88.9% (Table 2). The remaining two spleens were incorrectly suspected of having disease (false positives). Splenic disease was not suspected in the remaining 23 patients following preoperative imaging. Of these, three did not have disease identified following histopathological examination (true negatives) while the remaining 20 spleens did have disease identified on histology (false negatives).

Thirty-four of the 37 splenectomies performed following intraoperative suspicion of splenic disease had splenic disease confirmed on histopathology, giving an overall PPV of 91.9%. The PPV ranged from 50% to 100% depending on the type of surgery performed (Table 2).

Of the four splenectomies that were performed follow-

Table 2. — PPVs for the preoperative and intraoperative detection of splenic disease.

Suspicion of disease	No. of spleens suspected of having disease (n)	No. of spleens with disease (n)	PPV (%)
Preoperative (CT)	18	16	88.9
Intraoperative			
<i>All surgery</i>	37	34	91.9
Primary	6	6	100
Delayed	25	23	92.0
Interval	2	1	50.0
Delayed+interval	27	24	88.9
All initial	33	30	90.9
Secondary	4	4	100

ing inadvertent injury, histopathological examination identified splenic disease in two (50%).

The most common sites of disease following histopathological examination of the 41 removed spleens are illustrated in Table 1. Two of the seven spleens with disease identified in the hilar fat had diseased fat intimately involved with the splenic hilum, but no other splenic disease. Of the two diseased spleens that were removed following inadvertent injury, one had capsular disease and the other had malignant cells identified in splenic parenchymal vessels. Eight spleens were found to have parenchymal metastases following histopathological examination. Of these, two were suspected of having parenchymal disease following preoperative imaging. A further five were suspected of having splenic disease, but not specifically parenchymal disease. One was not suspected preoperatively but was suspected intraoperatively. Sixteen (43%) spleens had disease at more than one location. No splenic specimens were noted to have incidental pancreatic tissue.

Cytoreduction rates

Cytoreduction rates are illustrated in Table 3. The patient who was optimally cytoreduced had residual disease on the right hemi-diaphragm and gall bladder. Excision of this disease was considered to be inappropriate due to morbid adherence of the diaphragm to the liver surface. Of those patients who were sub-optimally cytoreduced, one had irresectable disease identified in the lesser sac only after splenectomy had been performed and the other had surgery prematurely terminated due to anaesthetic concerns.

Additional procedures and postoperative complications

Thirteen women underwent basic procedures plus splenectomy only. The remaining 28 women underwent a variety of other additional procedures (Table 3). Some women underwent more than one additional procedure. Twelve (29.3%) women experienced no postoperative complications and 22 (53.7%) had grade 1 or 2 complications. Only seven (17%) women had grade 3 or higher complica-

Table 3. — Type of surgery, surgical outcomes and post-operative morbidity.

Type of surgery	n (%)
Primary	6 (14.6)
Delayed	28 (68.3)
Interval	3 (7.3)
Delayed + interval	31 (75.6)
All initial	37 (90.2)
Secondary	4 (9.6)
Cytoreduction	n (%)
Complete	38 (92.7)
Optimal	1 (2.4)
Sub-optimal	2 (4.9)
Estimated blood loss (ml)	
Mean ± SD	816 ± 484.9
Operating time (minutes)	
Mean ± SD	338.7 ± 116.9
Length of stay	
Median (IQR)	8 (7-11)
Additional procedures	n (%)
Recto-sigmoid resection	24 (58.5)
Other bowel resection	12 (29.3)
Diaphragmatic stripping	13 (31.7)
Liver resection	3 (7.3)
Distal pancreatectomy	4 (9.8)
Lymphadenectomy	2 (4.9)
Gastric resection	3 (7.3)
Highest grade* of complication	n (%)
None	12 (29.3)
Grade 1	6 (14.6)
Grade 2	16 (39.0)
Grade 3a/3b	3 (7.3)
Grade 4a/4b	3 (7.3)
Grade 5	1 (2.4)

* According to Dindo's grading system (Dindo *et al.*, 2004 [13]).

tions (Table 2).

There was a significant difference in the number of women who experienced grade 3+ complications amongst women who underwent basic procedures plus splenectomy, only compared to women who underwent basic procedures plus splenectomy plus any other additional procedure ($p < 0.05$). In the 13 women that underwent basic procedures plus splenectomy only, six experienced no complications and the remaining seven experienced grade 1 or 2 complications only. In the 28 women who underwent basic procedures plus splenectomy plus additional procedures, recto-sigmoid or any other bowel resection were both found to be significantly associated with grade 3+ complications ($p < 0.05$). There were no recorded cases of OPSI. The majority of complications occurred while the women were still in hospital. Only four (9.8%) patients were readmitted to hospital following discharge.

Grade 3-5 morbidity included: pelvic collection requiring image guided drainage, bronchoscopy and chest drain insertion for a hydro/pneumothorax, acute renal failure requiring

Table 4. — PPVs for the intraoperative detection of splenic disease in primary (P) and secondary (S) surgeries in published cohorts and the numbers of incidental (I) splenectomies performed.

Author	Year	P	S	Total	I	PPV (%)		Overall
						P	S	
Morris	1991	-	-	24	-	-	-	75.0
Nicklin	1995	-	-	16	2	-	-	83.3
Scarabelli	1998	12	22	34	6	-	-	94.1
Ayhan	2004	34	-	34	-	79.4	-	79.4
Bilgin	2005	-	-	9	3	-	-	100
Uzan	2010	40	15	55	3	80.0	93.0	86.0
McCann	2011	44	-	44	-	84.1	-	84.1
Phillips	2015	33	4	37	4	90.9	100.0	91.9

ITU support, return to theatre following postoperative gastric perforation and multi-organ support on ITU, respiratory failure requiring ventilation assistance, early postoperative death from a massive pulmonary embolus, and return to theatre for small bowel obstruction secondary to herniation through mesh dehiscence used to repair a relocated stoma.

With respect to splenectomy associated complications, 20 infections and three thrombo-embolic events were recorded. Only one patient had a left sided pleural effusion requiring intervention. All patients had a full blood count test performed at some point during the postoperative period: 27 (65.9%) had a white cell count greater than $11.0 \times 10^9/l$ and 20 (48.8%) had a platelet count greater than $450 \times 10^9/l$.

Discussion

This is a retrospective review of all women who underwent a splenectomy during treatment for advanced or recurrent gynaecological malignancy at the Pan Birmingham Gynaecological Cancer Centre between May 21st, 2008 and January 31st, 2015. It is one of the very few studies comparing surgically presumed macroscopic disease with histopathologically confirmed microscopic findings in both initial and secondary surgery.

Excluding the present study, the intraoperative suspicion of splenic disease during initial/primary surgeries in other cohorts has PPVs ranging between 79.4% [14] and 84.1% [15] (Table 4) [9, 14-19]. Only one other study [9] considered secondary debulking surgery as a separate entity and it found that the intraoperative suspicion of splenic disease was associated with a PPV of 93.0%. The present study is therefore the first to demonstrate such high PPVs of 90.9% and 100% for the intraoperative suspicion of splenic disease during initial and secondary debulking surgeries, respectively, and it confirms that intraoperative suspicion of splenic disease is highly suggestive of splenic involvement. The overall PPVs (including all initial/primary and secondary debulking surgeries) range from 83.3% [17] to

Table 5. — Incidence of splenectomies performed during initial surgeries for advanced ovarian/tubal/primary peritoneal malignancy in published cohorts.

Author	Year	Country	Minimum Stage	Size of Cohort	Splenectomies n (%)
Guidozzi	1994	South Africa	3	148	8 (5.4)
Nicklin	1995	USA	3C	210	11 (5.2)
Kuhn	1998	Germany	3	107	17 (15.9)
Eisenkop	2006	USA	3C	404	49 (12.1)
Goff	2006	USA	3	6375	121 (1.9)
Aletti	2006	USA	3C	194	12 (6.2)
Eisenhauer	2006	USA	3C	262	17 (6.5)
Magtibay	2006	USA	3C	194	12 (6.1)
Sehouli	2009	Germany	3	186	3 (1.6)
Chi	2009	USA	3C	210	26 (12.4)
Kommos	2010	Germany	3B	267	32 (12.0)
Vergote	2010	Europe	3C (NACT)	322	13 (4.0)
			3C (Primary)	310	18 (5.8)
McCann	2011	USA	3	660	44 (6.7)
Luyckx	2012	France	3C	527	50 (9.5)
Tanner	2013	USA	3B	576	97 (16.8)
Phillips	2015	UK	3C	412	39 (9.5)

100% [19] and this variation is likely to be due to the size of the cohort and the proportion of secondary debulking surgeries included.

Preoperative imaging with CT was also found to have a high PPV (88.9%) in the present cohort. Unlike a surgeon's intraoperative suspicion of disease, preoperative radiological suspicion of disease is usually tempered by the surgeon's findings and as such not all spleens that have radiological suspicion of disease will necessarily be removed rendering the PPV an unreliable marker. In order to determine the true PPV of preoperative imaging with CT for splenic involvement in gynaecological malignancy, all CT-suspicious spleens would need to be removed (regardless of the surgeon's intraoperative level of suspicion) and histopathology obtained. Furthermore, while we may rely on CT to identify splenic disease preoperatively, the present study demonstrates that it does not reliably identify parenchymal metastases with only 25% of cases being correctly identified preoperatively. However, in this study, as well as in others [6, 20], histopathology revealed that no parenchymal metastases existed in isolation of other splenic disease, which was identified in 62.5% of cases preoperatively.

Alongside the variability in PPVs, there is considerable variability in the incidence of splenectomies performed during surgery for advanced and recurrent gynaecological malignancy. This variation is observed both between (Table 5) [2, 4-6, 10, 15, 17, 21-28] and within units (Figure 1). Among the units, the percentage of splenectomies performed ranges between 1.6% [5] and 16.8% [6]. Within the present unit, over time, the percentage of splenectomies ranged from 3.1% in 2008-2009 to 16.4% in 2012-

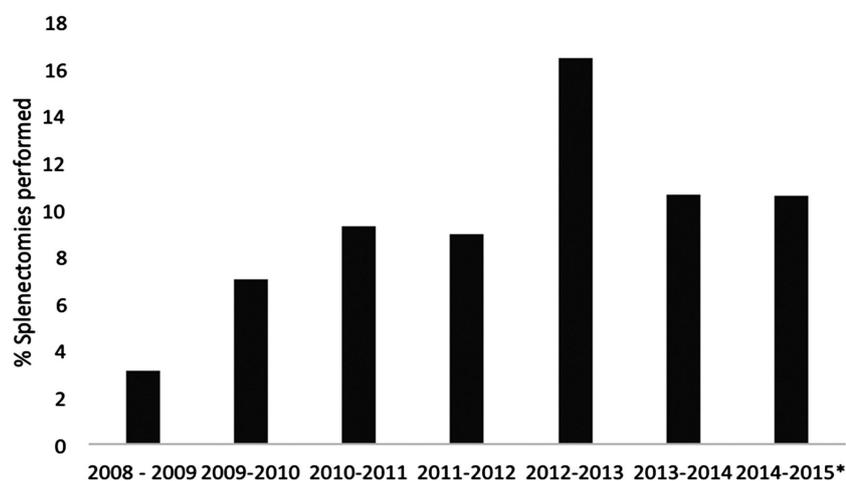


Figure 1. — Percentage of splenectomies performed (during all surgeries for Stage 3C/4 disease) annually between May 21st, 2008 and January 31st, 2015 at the Pan Birmingham Gynaecological Cancer Centre.

2013. More recently, the incidence of splenectomy has plateaued at a rate of approximately 10%.

Splenectomy for advanced gynaecological malignancy remains an uncommon procedure in the UK being performed in only 0.6% of patients with Stage 3/4 ovarian/tubal/primary peritoneal malignancies [29]. This is considerably lower than the splenectomy rate of 9.5% reported in the present UK series, and indeed all other published cohorts (Table 5) raising the concern that perhaps elsewhere in the UK we are underperforming splenectomies and consequently under-treating women with advanced gynaecological malignancy. The wide variation in the rates of splenectomies may be explained by: geographical variations in the distribution of Stage 3/4 disease, use of neoadjuvant chemotherapy, extent of supracolic omentectomy to allow inspection of the splenic hilum, surgical incision and exposure of the spleen, and surgical ethos towards debulking surgery, en-bloc omentectomy, and splenectomy.

Recognising that the incidence of splenectomies performed during surgery for advanced and recurrent gynaecological malignancy varies significantly both between and within units, the present authors propose that the splenectomy rate and the PPV of the surgeon's intraoperative suspicion of disease are potential markers of the quality of abdominal exploration. For many reasons splenic disease is challenging to detect. Firstly, the spleen, in contrast to other abdominal organs, is less well-visualised via a limited midline incision. Once adequate access has been achieved, the spleen then demands careful handling, making inspection of it more difficult than in other more resilient organs such as the bowel. Additionally, the spleen has various crevices that make an ideal hiding place for malignant cells, similar to the hepato-renal recess of Morrison or the insertion of the ligamentum teres in the liver. This is exemplified in the present study by the fact that 46% of spleens had disease located at the splenic hilum. Units too aggressive in their surgery will perform more

splenectomies but potentially have a lower positive predictive value i.e. they would remove more spleens than perhaps necessary. More conservative units on the other hand, where only spleens with obvious disease are removed, would have higher PPVs but perform fewer splenectomies in total and may potentially not remove all affected spleens. The correct benchmarks for both the rate of splenectomy and the PPV required would need to be set by the gynaecological oncology community at large prior to implementing this approach.

The difficulty with setting a benchmark level for the splenectomy rate is that the prevalence of splenic metastases in advanced gynaecological malignancy is variable. Few studies have looked specifically at the prevalence of splenic disease in advanced gynaecological malignancy prior to cytoreductive surgery, but those that have, report a marked difference between the observed prevalence of splenic disease and the splenectomy rate. Sehouli *et al.* found that of women undergoing surgery for advanced gynaecological malignancy, 8.1% exhibited macroscopic splenic disease but only 1.6% of women actually had their spleens removed [5]. Similarly, during primary surgery, Vergote *et al.* report both a higher prevalence of splenic disease (16.8%) and a higher rate of splenectomies undertaken (5.8%), but still a marked discrepancy between the two. Even in women who have undergone neoadjuvant chemotherapy, 7.1% of women exhibited splenic disease and yet only 4% underwent splenectomy [27], suggesting that while the use of neoadjuvant chemotherapy clearly reduces the prevalence of macroscopic splenic disease (by 57.7%) it has a relatively smaller effect on reducing the splenectomy rate (by 31.0%). To complicate the matter even further, in these studies the prevalence of splenic disease was determined by the intraoperative assessment of the surgeon, not by histopathology results. In the present study, 50% of the spleens removed following inadvertent injury had histopathologically confirmed splenic disease

suggesting that the true prevalence of splenic disease may be considerably higher than that reported in these studies. This is supported by the fact that three other studies [9, 17, 18] which collectively incorporate 11 incidental splenectomies found disease upon histopathology in eight (72.7%) spleens.

Introducing splenectomy to basic procedures, although controversial, would allow us to answer certain questions not addressed by this study, specifically the diagnostic accuracy of intraoperative splenic disease detection as well as the prevalence of occult splenic parenchymal metastases. One of the problems with incorporating splenectomy into basic procedures for gynaecological malignancy is the concern that it is associated with significant additional morbidity. This is not supported by the present data. In the present authors' experience, morbidity associated with splenectomy was comparable to other studies [10] but in this study, splenectomy itself was not responsible for any serious (grade 3+) complications. All patients who experienced grade 3+ complications had received a recto-sigmoid resection in conjunction with their splenectomy and it is this procedure that was significantly associated with serious morbidity. This finding is consistent with the literature [9]. The perioperative 30-day mortality rate in the present study was 2.4% and this is comparable to rates of 2.8% and 1.7% reported elsewhere [9, 30]. Another potential problem with incorporating splenectomy into basic procedures for gynaecological malignancy is the theoretical concern that splenectomy may have a detrimental effect on subsequent disease progression, but more evidence is needed regarding this phenomenon [31].

In conclusion, intraoperative identification of macroscopic splenic lesions correlates well with the microscopic findings following histopathological examination. The present authors suggest that such correlation may be in part due to surgical experience and ethos, but additionally may be due to an unrecognised higher prevalence of splenic disease. Further studies are needed to identify the diagnostic accuracy of intraoperative splenic disease detection in gynaecological malignancy. Incorporating splenectomy into basic procedures would help answer these questions but is controversial. While basic procedures plus splenectomy alone does not appear to contribute to the experience of significant postoperative morbidity, it is not without lifelong consequences. With such varied rates of splenectomies being performed, the present authors suggest that rates of splenectomies undertaken and the corresponding PPVs from individual units could be used as predictors of adequate abdominal examination. At present, the question of whether a patient has been completely, optimally or sub-optimally cytoreduced, is subjective. Adopting this approach would lend some objectivity to proceedings.

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