European Society of Gynaecological Oncology

ADVANCED (STAGE III-IV) OVARIAN CANCER SURGERY

Quality Indicators

Complete report

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1 Introduction

Ovarian cancer is the leading cause of death among all gynecologic cancers and remains the most common cause of death for 15 years after diagnosis in women with stage III-IV tumours[1,2]. Surgery is the cornerstone in treatment of advanced ovarian cancer. Quality of surgical care as a component of a comprehensive regimen of multidisciplinary management has been shown to benefit the patient in other types of malignancies. Implementation of a quality improvement programme helped to reduce both morbidity and costs in other tumours where surgical interventions are also high risk. A mere implementation of a quality management programme could impact survival of patients with advanced ovarian cancer[3,4].

The European Society of Gynaecological Oncology ESGO) took a position to promote the training of gynaecological surgeons treating cancer for abdominal procedures including colorectal resection and upper abdominal surgery[5]. The aim of this project is to develop a list of quality indicators QIs for advanced ovarian cancer surgery that can be used to audit and improve the clinical practice in an easy and practical way. These QIs give practitioners and health administrators a quantitative basis for improving care and organizational processes. They also facilitate the documentation of quality of care, the comparison of performance structures, and the establishment of organizational priorities as a basis for accreditation.

The QIs and proposed targets are based on the standards of practice determined from scientific evidence and/or expert consensus. The key characteristics of an ideal indicator are clear definition, clinical relevance, measurability, feasibility in clinical practice, and a scientific basis. These QIs may have to be modified in the future.

The philosophy behind the project is to improve the average standard of surgical care by providing a set of quality criteria which can be used for self-assessment, for institutional quality assurance programs, for governmental quality assessment, and eventually to build a network of certified centres for ovarian cancer surgery. The mindset is not punitive but incentive. Certified centers can make the award known from doctors, patients, patient advocacy groups and lay persons. On the contrary, the targets defined by the workgroup can absolutely not be used to penalize or litigate doctors or institutions.

2 Acknowledgements

ESGO would like to thank the international development group for their constant availability, work, and for making possible the development of these QIs for the advanced ovarian cancer surgery. ESGO is also very grateful to the external panel of physicians and patients international reviewers for their participation. The names of the participants in each group are listed on Appendix 1.

ESGO also wishes to express sincere gratitude to the Institut National du Cancer INCa, France for providing the main funding for this work.

3 Method

QIs for advanced ovarian cancer surgery were developed using a four-step evaluation process **Figure 1.** The strengths of the process include creation of a multidisciplinary international development group, use of scientific evidence and/or international expert consensus to support the QIs, use of an international external review process physicians and patients , use of a structured format to present the QIs, and management of potential conflicts of interests.

It is inspired by published development processes and initiatives[6-117] identified from a literature search carried out 1 using a list of selected websites see Appendix 2, a nd 2 in Medline without any restriction in the search period indexing terms: consensus, development process, e vidence-based medicine, method, methodology, methodology research, program development, quality assurance, quality improvement, quality indicators, quality management). This development process involved 3 face to face meetings of the international experts panel, chaired by Professor Denis Querleu Institut Bergonié, Bordeaux, France convened in May 19, 2015 , in September 4, 2015, and January 25, 2016.

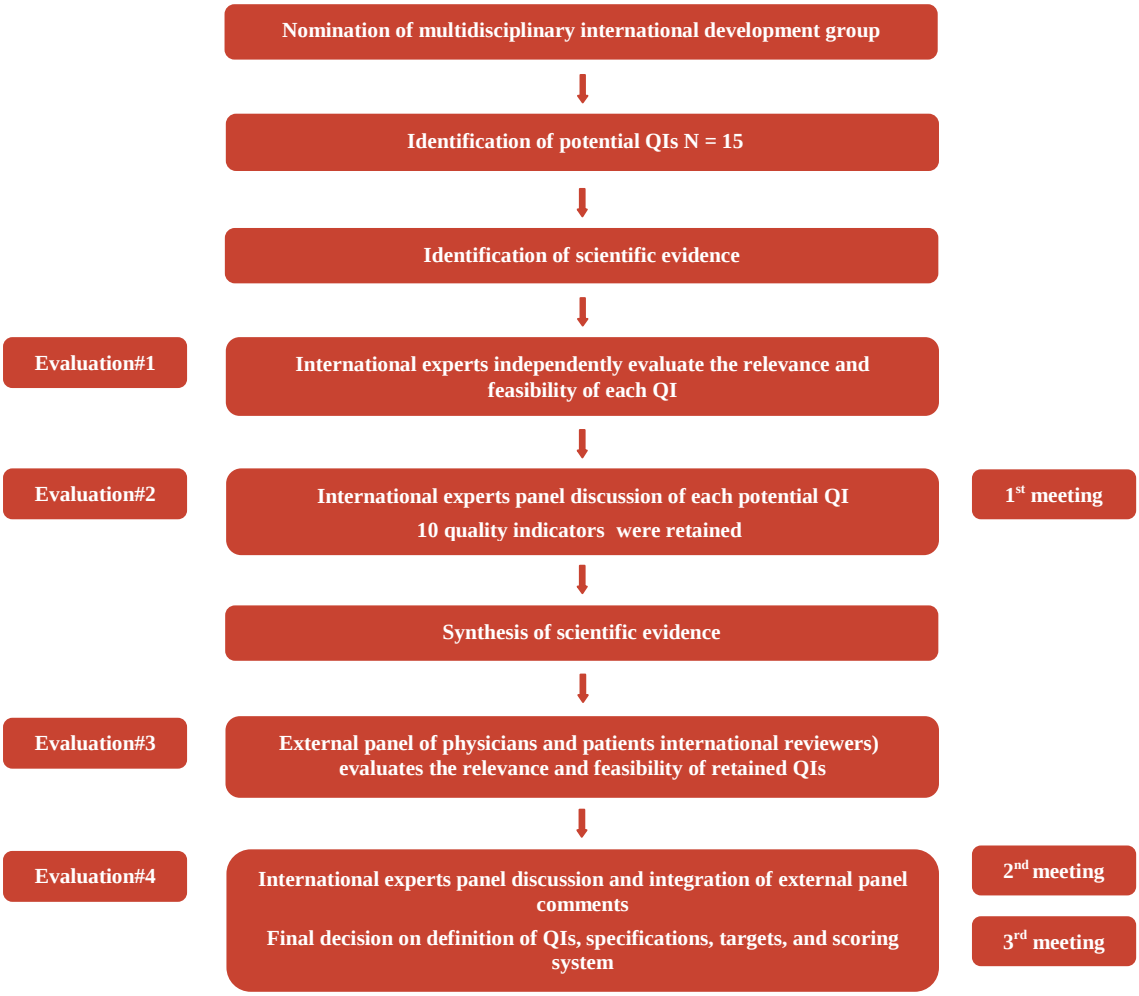

Figure 1. Development process - A four-step evaluation process

3.1 Nomination of multidisciplinary international development group

The ESGO Council nominated practicing clinicians that provide care to advanced ovarian cancer patients and had demonstrated leadership in quality improvement through research, administrative responsibilities, or committee membership to serve as experts panel. The objective was to assemble a multidisciplinary panel, including one surgical and one methodologic co-chairs. It was therefore essential to include professionals on the panel from relevant disciplines so that their multidisciplinary perspective would influence the validity and acceptability of the chosen indicators surgery, medical oncology, pathology, radiology, anaesthesiology, gynecology, radiation oncology. Another requirement was a balanced representativity of countries across Europe. The list of international experts development group is available in Appendix 1 .1.

3.2 Identification of potential QIs

All possible QIs for advanced ovarian cancer surgery were identified from existing guidelines and published indicators. A systematic literature search was conducted in MEDLINE without any restriction in the search period, using indexing terms as follows: quality indicators, ovarian cancer, surgery, methodology, guidelines, evidence-based medicine. An another bibliographic search was carried out using selected websites to identify guidelines. References were selected if they described indicators developed by other agencies or synthesized research evidence describing practice contributing to improved patient outcomes guidelines or consensus statements. Five previous initiatives publishing QIs for advanced ovarian cancer surgery were identified[26,46,53,64,118]. The surgical and methologic co-chairs compiled a list of 15 possible indicators:

1. Inclusion in the surgical team of a medical oncologist
2. Surgery performed by a gynecologic oncologist
3. Inclusion of patients in clinical trials
4. Delay between the decision to treat and treatment
5. Pelvic and para-aortic lymphadenectomy
6. Pretreatment multidisciplinary decision-making process
7. Anaesthetic management
8. Prospective reporting of complications
9. Midline laparotomy
10. Volume of ovarian surgery
11. Pathology report
12. Operative report
13. Intraoperative frozen sections
14. Complete surgical resection
15. Perioperative investigations

3.3 Identification of scientific evidence

A systematic literature search was conducted in MEDLINE to identify available scientific evidence which supports the 15 possible QIs research period: 2005/01/01 - 2015/04/01. This search used indexing terms as follows: anaesthesiology, clinical competence, clinical studies, clinical trials, complete resection, cytoreduction, cytoreductive surgery, debulking, decision making, delayed cytoreduction, delayed cytoreductive surgery, frozen sections, hospital teaching, hospital mortality, hospital volume, hospital university, in-hospital death, intensive care, intensive care unit, laparoscopy, laparotomy, length of stay, lymphadenectomy, lymph node dissection, medical audit, medical records, medical standards, mortality rate, mortality analysis, multidisciplinary team, multidisciplinary team approach, multivariate analysis, nutrition assessment, nutritional status, nutritional support, operation, operative report, operative report documentation, optimal cytoreduction, ovarian cancer, ovarian neoplasm, ovarian tumour, ovariectomy, para-aortic lymphadenectomy, pathology, pathology report, pathology report adequacy, pelvic lymphadenectomy, perioperative care, physician's role, physician specialty, postoperative care, postoperative complications, preoperative care, preoperative workup, primary cytoreduction, primary cytoreductive surgery, prognosis, quality of health care, quality of life, reoperation, repeat surgery, reporting, resection, residual disease, residual tumour, risk factors, specialization, suboptimal cytoreduction, surgeon volume, surgery, surgical management, surgical outcome, surgical outcome criteria, surgical procedures, surgical resection, survival rate, survival analysis, treatment outcome.

The literature search was limited to publications in English. Priority was given to high-quality systematic reviews and meta-analyses but lower levels of evidence were also evaluated. The search strategy excluded editorials, letters, case reports and *in vitro* studies. The reference list of each identified article was reviewed for other potentially relevant papers. The bibliography was also be supplemented by additional references provided by the international development group.

3.4 Evaluation of the potential QIs

The 15 possible QIs were formated as a questionnaire, and were sent by email to the international development group. Experts were asked to evaluate each indicator according to relevance and feasibility in clinical pratice evaluation #1. Responses were pooled and organized according to consens us about relevance and feasibility. The results of this first evaluation was sent to experts who convened during the first one-day meeting May 19, 2015. Acceptance, rejection or the need for further consideration of each indicator was discussed during th e meeting evaluation #2. Candidate QIs were retained if they were supported by sufficient high level scientific evidence and/or when a large consensus among experts was obtained. Finally, ten QIs for advanced ovarian cancer surgery were retained by the international development group. The 5 remaining indicators were not retained, as a result of lack of evidence, or of duplication of quality information:

1. Inclusion in the medical team of a medical oncologist: this potential QI has been incorporated in the number 5 QI;

2. Delay between the decision to treat and treatment: no evidence of impact was found and no consensus has been reached within the international experts panel;

3. Midline laparotomy: this potential QI will be considered in recommendations to avoid rupture of early ovarian cancer; in advanced ovarian cancer, midline laparotomy is the mainstay of comprehensive description of tumor extent and of complete surgery, which are two retained QIs number 1 and 8 ;

4. Intraoperative frozen sections: this potential QI will be considered in the management of suspicious adnexal masses; in advanced ovarian cancer, the differential diagnosis between peritoneal carcinomatosis secondary to genital tract malignancy and other conditions may be difficult ; however, availability of frozen section examination by a specialized pathologist is strongly encouraged;

5. Pelvic and para-aortic lymphadenectomy: removal of enlarged nodes is part of complete cytoreduction ; as the current literature does not provide evidence of increased overall survival OS when routine comprehensive node dissection is performed after complete intraperitoneal cytoreduction, the international experts panel concluded that it is more appropriate to wait for the publication of the results of ongoing clinical trials on this topic. Comprehensive pelvic and aortic lymph node dissection is the standard in patients with stage III based on lymph node involvement only.

3.5 Synthesis of scientific evidence

For the 10 retained QIs, the systematic literature search as described above has been extended until July 1, 2015 in order to update the documentation for the 2nd one-day meeting. All retrieved articles have been methodologically and clinically appraised. After the selection and critical appraisal of the articles, a summary of the scientific evidence has been developed. To classify the risk of bias or confounding in the identified studies, we used the levels of evidence described in Appendix 3.

3.6 External evaluation of the retained QIs - International review

The ESGO Council established a large panel of practicing clinicians that provide care to advanced ovarian cancer patients and patients. These international reviewers were independent from the development group. Another requirement was a balanced representativity of countries across Europe. The 10 retained QIs were formated as a questionnaire, and were sent by email to the international reviewers who were asked to evaluate each indicator according to relevance and feasibility in clinical pratice only physicians.

Quantitative and qualitative evaluations of the 10 retained QIs were performed by 84 independent physicians and by 8 ovarian cancer patients between july 6, 2015 and August 31, 2015 evaluation #3. The list of international reviewers is available in Appendix 1.2.

3.7 Integration of international reviewers and finalization of the QIs

Responses were pooled and sent to experts who convened during the second one-day meeting September 4, 2015. The international development group discussed all comments evaluation #4. Final decision on definition of QIs, specifications, targets, and scoring system has been made by the international development group during the third one-day meeting January 25, 2016.

Each retained QI has a description which specifies what the indicator is measuring. The measurability specifications are then detailed. The latter highlight how the indicator will actually be measured in practice to allow audits. In this regard, the timeframe for assessment of criteria is the last calendar year. Further to measurement of the indicator, a target is indicated. This dictates the level which each unit/center should be aiming to achieve against each indicator. When appropriate, two or three targets were defined: an optimal target, expressing the best possible option for patients, a minimal target, expressing the minimal requirement when practical feasibility factors are taken into account, and intermediate target if necessary. Targets were based on evidence whenever available, on the personal experience or database of development group members, on expert consensus, and on feedback from the physicians external reviewers.

Each retained QI is categorized as structural indicators, process indicators, and outcome indicators as defined[1] below :

- "Structure" refers to health system characteristics that affect the system's ability to meet the health care needs of individual patients or a community. Structural indicators describe the type and amount of resources used by a health system or organization to deliver programs and services, and they relate to the presence or number of staff, clients, money, beds, supplies, and buildings. The assessment of structure is a judgment on whether care is being provided under conditions that are either conductive or inimical to the provision of good care;

- Process indicators assess what the provider did for the patient and how well it was done. Processes are a series of inter-related activities undertaken to achieve objectives. Process indicators measure the activities and tasks in patient episodes of care. Some authors include the patient's activities in seeking care and carrying it out in their definition of the health care process. Others limit this term to care that health care providers are giving. It may be argued that providers are not accountable for the patient's activities and these, therefore, do not constitute part of the quality of care, but rather fall into the realm of patient characteristics and behavior that influence patients' health outcomes;

- Outcomes are states of health or events that follow care, and that may be affected by health care. An ideal outcome indicator would capture the effect of care processes on the health and wellbeing of patients and populations. Outcomes can be expressed as 'The five Ds': i death: a bad outcome if untimely; ii) disease: symptoms, physical signs, and laboratory abnormalities; iii) discomfort: symptoms such as pain, nausea, or dyspnea; iv disability: impaired ability connected to usual activities at home, work, or in recreation; and v dissatisfaction: emotional reactio ns to disease and its care, such as sadness and anger. Intermediate outcome indicators reflect changes in biological status that affect subsequent health outcomes. Some outcomes can only be assessed after years e.g. 5 -year cancer survival). It is therefore important to assess intermediate outcome indicators. They should be evidence-based and reflect the final outcome. The final outcome criterion, such as cancer survival, which can be assessed only long after the completion of surgery, may have to be replaced by a surrogate outcome that can be assessed in a timely fashion. The surrogate indicator must be predictive of the final outcome.

[1]Mainz, J. Defining and classifying clinical indicators for quality improvement. *Int J Qual Health Care***15**, 523-530 2003).

4 Management of conflicts of interest

The experts of the multidisciplinary international development group were required to complete a declaration of interest form, and to promptly inform the ESGO council if any change in the disclosed information occurred during the course of this work.

5 QIs for advanced ovarian cancer surgery

5.1 QI 1 - Rate of complete surgical resection

5.1.1 Description of the QI

TYPE	Outcome indicator.
DESCRIPTION	Complete abdominal surgical resection is defined by the absence of remaining macroscopic lesions after careful exploration of the abdomen. Whenever feasible, localized thoracic disease is resected. Surgery can be decided upfront, or planned after neoadjuvant chemotherapy. However, the quality assurance program must take into account that patients who can be operated upfront with a reasonable complication rate benefit most from primary debulking surgery.
SPECIFICATIONS	i) Complete resection rate: • *Numerator*: number of patients with advanced ovarian cancer undergoing complete surgical resection. • *Denominator*: all patients with advanced ovarian cancer referred to the center. ii) Proportion of patients who are operated upfront : • *Numerator*: patients who are offered upfront surgery. • *Denominator*: all patients not previously treated.
TARGETS	i) Complete resection rate: • *Optimal target*: > 65%. • *Minimum required target:*> 50%. ii) Proportion of p rimary debulking surgeries: ≥50%
SCORING RULE	i) 5 if the optimal target is met, 3 if the minimum required target is met ii) 3 if the target is met.

5.1.2 Rationale

Surgery remains a key determinant of survival outcome in advanced ovarian cancer. The size of residual disease after cytoreductive surgery is estimated as the largest diameter of remaining tumor and is one of the most important prognostic factors.

According to the 4th international gynecologic cancer intergroup ovarian cancer consensus conference 2010 held in Vancouver[119], the term “optimal” cytoreduction should be reserved for those with no macroscopic residual disease. This corresponds to the definition of complete surgery.

Five previous initiatives[26,46,53,64,118] published a QI for this topic. No remaining macroscopic lesions was used as surgery criterion by three of these five previous initiatives[46,53,64]. An optimal primary cytoreduction as defined above is recommended by the six guidelines[120-125] identified for this subtopic and an optimal delayed cytoreduction is recommended by the two guidelines[124,126] identified for this subtopic.

5.1.3 Summary of available scientific evidence

<u>*Primary cytoreductive surgery*</u>: using the technique of meta-analysis, Elattar *et al.*[127] and Chang *et al.*[128] quantified the effect on survival of surgical outcome criteria among patients with advanced-stage ovarian cancer. Eleven studies[129-152] and 18 studies[3,130,136,139,142,144-149,151,153-158] were included in these meta-analyses, respectively. Six studies[130,136,139,142,144-149,151] were included in the 2 meta-analyses. **LoE 1-**

Elattar *et al.*[127] assessed the impact of various residual tumour sizes on survival. A subgroup meta-analysis of 4 studies[136-139,142,144-150], showed that women who were suboptimally debulked resi dual disease > 1 cm after primary cytoreductive surgery had more than 3 times the risk of death compared to women with only microscopic disease HR = 3.16, 95% CI = 2.26 -4.41, p < 0.05. An another subgroup meta-analysis of 6 studies[130-133,136-139,142,144-152], showed that women who were optimally debulked residual disease < 1 cm after primary cytoreductive surgery had more than twice the risk of death compared to women with only microscopic disease HR = 2.20, 95% CI = 1.90-2.54, p < 0.05. The authors reported that compl ete resection no visible residual disease is also associated with prolonged PFS compared to optimal resection 2 studies [144-152], HR = 1.96, 95% CI = 1.72-2.23, p < 0.05.

Chang *et al.*[128] performed separate multiple linear regression analyses using no gross residual disease or optimal residual disease ≤ 1 cm as the surgical outcome criteria. Although both criteria were significant and independent predictors of improved cohort survival after ajustement for stage and use of intraperitoneal chemotherapy, each 10% increase in the proportion of patients undergoing complete gross resection was associated with a 28% incremental improvement in the expected median survival time 2.3 months, 95% CI = 0.6 -4.0, p = 0.011 compared to the proportion of patients left with optimal residual disease 1.8 month, 95% CI = 0.6 -3.0, p = 0.004.

Twenty-six original studies[159-184] not included in the 2 meta-analyses mentioned above were also identified. All studies reported a significant benefit on survival to achieving an optimal cytoreduction. Twenty-three studies analyzed the independent prognostic value of optimal cytoreduction on OS or progression-free survival PFS using 3 optimal surgery criteria no gross, <1 cm and ≤1 cm. Multivariate analyses showed that optimal cytoreductive surgery was found to be independently prognostic for OS in 17 of 19 studies and in all studies N = 10 for PFS **Table 1**. According to data released by Everett *et al.*[176], Aletti *et al.*[177] and Kumpulainen *et al.*[178], optimal primary cytoreductive surgery is also a statistically independent prognostic factor for progression-free interval ≤1 cm [176], disease-specific OS <1 cm [177], disesase-specific survival no gross [184] and disease-free survival ≤1 cm [178]. **LoE 2-**

<u>*Delayed cytoreductive surgery*</u>: as part of a meta-regression analysis[185] including 21 studies[176,186-204], an increased rate of optimal cytoreduction significantly influenced median OS coeff. = 0.013, 95% CI = 0.003-0.023, p = 0.012. It should be noted that the results published by Kang *et al.*[185] have to be interpreted cautiously notably because there is severe heterogeneity between the included studies. **LoE 1-**

Four original studies[158,184,205,206] not included in the meta-analysis mentioned above were also identified. The four studies reported a significant benefit on survival to achieving an optimal cytoreduction. According to data released by three original studies[184,205,206], optimal delayed cytoreductive surgery surgery criteria: no gross, <1 cm and ≤1 cm is a statistically independent prognostic factor for OS, PFS, and DSS **Table 2**. **LoE 2-**

It should be noted that the available evidence presented above has to be interpreted cautiously notably because 1 a potential interobserver bias in assessing the diameter of residual disease may influence the results, 2 a limitation of the identified studies is that they were largely confined to younger women and those with a good performance status and the results might therefore not be generalisable to the wider patient population, and 3 the exact reasons for performing one type of

surgery over another were not well documented and it was likely that women in generally poor health would be subjected to less aggressive surgery and thus would be more likely to have larger residual disease.

Table 1. Original studies presenting survival multivariate analysis in patients with advanced ovarian cancer treated with primary cytoreductive surgery

Author[reference]	Year	N	Optimal	Residual	Multivariate analysis*		
		Total	criteria	disease	HR/OR	95% CI	p-value
Overall survival							
Akeson *et al.*[159]	2009	391[1]	no gross	≤ 20 mm	1.9	1.2-3.3	< 0.05
Akeson *et al.*[159]	2009	391[1]	no gross	> 20 mm	2.6	1.6-4.2	< 0.05
Fotopoulou *et al.*[160]	2010	101[2]	no gross	> 1 mm	4.99	2.3-10.85	< 0.001
Landrum *et al.*[161]	2013	428	no gross	≤ 5 mm	1.87	1.34-2.62	< 0.001
Landrum *et al.*[161]	2013	428	no gross	> 5 mm	2.03	1.31-3.15	0.001
Polterauer *et al.*[162]	2012	226[3]	no gross	> 1 mm	1.4	1.0-2.1	0.04
Wimberger *et al.*[163]	2010	573	no gross	≤ 10 mm	1.87	1.21-2.89	0.005
Wimberger *et al.*[163]	2010	573	no gross	> 10 mm	2.13	1.40-3.23	< 0.0001
Chang *et al.*[164]	2012	189	no gross	≤ 10 mm	2.25	1.25-4.03	0.01
du Bois *et al.*[165]	2009	3,126[5]	no gross	≤ 10 mm	2.12	1.85-2.43	< 0.0001
Cai *et al.*[166]	2007	95	<10 mm	≥ 10 mm	4.084	1.521-10.968	0.005
Fu *et al.*[167]	2014	251	<10 mm	NA	1.586	0.863-1.575	0.137
Gerestein *et al.*[168]	2009	118	<10 mm	≥ 10 mm	0.50	0.27-0.93	0.028
Kaern *et al.*[169]	2005	51	<10 mm	≥ 10 mm	19.5	1.5-249.9	< 0.05
Marth *et al.*[183]	2009	1,948	<10 mm	≥ 10 mm	1.5	1.25-1.81	< 0.001
Abaid *et al.*[170]	2011	75	≤ 10 mm	> 10 mm	1.18	0.36-3.87	> 0.05
Chang *et al.*[171]	2012	203	≤ 10 mm	> 10 mm	3.24	1.90-5.53	< 0.01
Gadducci *et al.*[172]	2005	315	≤ 10 mm	> 10 mm	1.985	1.307-3.015	0.0013
Pongsanon *et al.*[173]	2011	122	≤ 10 mm	> 10 mm	4.05	1.34-12.18	0.013
Eisenhauer *et al.*[174]	2006	140	≤ 10 mm	> 10 mm	2.99	1.64-5.45	< 0.001
Ayhan *et al.*[179]	2006	64[6]	≤ 10 mm	> 10 mm	0.30	0.14-0.66	0.003
Lydiksen *et al.*[182]	2014	650	≤ 10 mm	> 10 mm	0.22	0.18-0.28	< 0.01

* Cox regression analysis was used for multivariate analyses of prognostic variables, [1] 137 of the 391 included patients had FIGO stages I or II, [2] 14 of the 101 included patients had FIGO stages I or II, [3] 15 of the 226 included patients had FIGO stage II, [4] 95 of the 242 included patients had FIGO stages I or II, [5] 277 of the 3 126 included patients had FIGO stages IIB or IIC, [6] 8 of the 64 included patients had stage I-II disease at primary surgery, CI confidence interval, HR hazard ratio, NA data not available, OR odd ratio.

Original studies presenting survival multivariate analysis in patients with advanced ovarian cancer treated with primary cytoreductive surgery *continued*

Author[reference]	Year	N	Optimal	Residual	Multivariate analysis*		
		Total	criteria	disease	HR/OR	95% CI	p-value
Progression-free survival							
Landrum *et al.*[161]	2013	428	no gross	≤ 5 mm	1.64	1.19-2.26	0.002
Landrum *et al.*[161]	2013	428	no gross	> 5 mm	1.80	1.20-2.70	0.005
Polterauer *et al.*[162]	2012	226[1]	no gross	> 1 mm	1.6	1.3-2.1	< 0.001
Wimberger *et al.*[163]	2010	573	no gross	≤ 10 mm	1.51	1.05-2.19	0.028
Wimberger *et al.*[163]	2010	573	no gross	> 10 mm	1.82	1.28-2.59	0.001
Chang *et al.*[164]	2012	189	no gross	> 1 mm	2.03	1.25-3.31	< 0.01
du Bois *et al.*[165]	2009	3,126[2]	no gross	≤ 10 mm	2.03	1.81-2.27	< 0.0001
Fu *et al.*[167]	2014	251	< 10 mm	≥ 10 mm	2.371	1.221-4.606	0.011
Gerestein *et al.*[168]	2009	118	< 10 mm	≥ 10 mm	0.50	0.31-0.80	0.004
Pecorelli *et al.*[175]	2009	200	<10 mm	≥ 10 mm	1.91	1.21-3.03	< 0.05
Abaid *et al.*[170]	2011	75	≤ 10 mm	> 10 mm	2.30	1.19-4.45	0.013
Chang *et al.*[171]	2012	203	≤ 10 mm	> 10 mm	2.61	1.58-4.29	< 0.01
Progression-free interval							
Everett *et al.*[176]	2006	200[3]	≤ 10 mm	> 10 mm	2.96	NA	< 0.001
Disease-specific overall survival							
Aletti *et al.*[177]	2007	49	< 10 mm	≤ 20 mm	1.40	0.55-2.87	0.049
Aletti *et al.*[177]	2007	49	< 10 mm	> 20 mm	2.56	1.13-5.99	0.049
Disease-specific survival							
Rutten *et al.*[184]	2015	227	no gross	< 10 mm	2.04	1.11-3.76	0.02
Rutten *et al.*[184]	2015	227	no gross	> 10 mm	1.84	1.05-3.21	0.03
Disease-free survival							
Kumpulainen *et al.*[178]	2009	234	≤ 10 mm	> 10 mm	4.446	2.497-7.917	< 0.0001

* Cox regression analysis was used for multivariate analyses of prognostic variables, [1] 15 of the 226 included patients had FIGO stage II, [2] 277 of the 3,126 included patients had FIGO stages IIB and IIC, [3] 98 patients 49% had initial chemotherapy, CI confidence interval, HR hazard ratio, NA data not available, OR odd ratio.

Table 2. Original studies presenting survival multivariate analysis in patients with advanced ovarian cancer treated with delayed cytoreductive surgery

Author[reference]	Year	N	Optimal	Residual	Multivariate analysis*		
		Total	criteria	disease	HR/OR	95% CI	p-value
Overall survival							
Muraji *et al.*[206]	2013	124	no gross	< 10 mm	1.39	0.89-2.19	0.14
Muraji *et al.*[206]	2013	124	no gross	> 10 mm	3.78	2.06-6.94	< 0.001
Bilici *et al.*[205]	2010	52	< 10 mm	> 10 mm	0.28	0.003-0.37	0.002
Disease-specific survival							
Rutten *et al.*[184]	2015	462	no gross	< 10 mm	1.79	1.26-2.53	< 0.001
Rutten *et al.*[184]	2015	462	no gross	> 10 mm	3.11	2.01-4.81	< 0.001

* Cox regression analysis was used for multivariate analyses of prognostic variables, [1] 98 patients 49% had initial chemotherapy, CI confidence interval, HR hazard ratio, NA data not available.

5.2 QI 2 - Number of cytoreductive surgeries performed per center and per surgeon per year

5.2.1 Description of the QI

TYPE	Structural indicator number of upfront or interval cytoreductive surgeries performed per center. Process indicator number of surgeries per surgeon per year.
DESCRIPTION	Only surgeries with an initial objective of complete cytoreduction are recorded. Exploratory endoscopies, exploratory laparotomies, or surgeries limited to tissue biopsy that do not include at least a bilateral salpingo-oophorectomy if applica ble, hysterectomy if applicable, and a comprehensive peritoneal staging including omentectomy are not included.
SPECIFICATIONS	*Numerator*: i) number of cytoreductive surgeries as defined above performed per center per year. ii) number of cytoreductive surgeries as defined above performed per surgeon per year. Secondary and tertiary procedures are accepted. *Denominator*: not applicable.
TARGETS	i) Number of surgeries performed per center per year: • *Optimal target: N* ≥ 100. • *Intermediate target: N* ≥ 50. • *Minimum required target: N* ≥ 20 ii) ≥ 95% of surgeries are performed or supervised by surgeons operating at least 10 patients a year.
SCORING RULE	i) 5 if the optimal target is met, 3 if the intermediate target is met, 1 if the minimum required target is met. ii) 3 if the target is met.

5.2.2 Rationale

Although hospital volume and surgeon volume are not a sufficient guarantee of surgical quality, they are a major prerequisite. Patients treated in high volume hospitals have a higher chance of receiving standard treatment surgery conformed to recommended guidelines compared to patients treated in low volume hospitals [207]. The postoperative hospital stay is correlated with the number of surgical procedures done[208]. So, the hospital volume and surgeon volume must have to merged with outcome e.g. complete surgical resection and complications which must also be recorded. One previous initiative[26] published a QI for this topic.

5.2.3 Summary of available scientific evidence

LoE 2-

Impact of hospital volume on survival: du Bois *et al.*[209] performed a systematic review of the literature to evaluate notably whether hospital volume has any impact on outcome in ovarian cancer patients. The authors included 6 studies[112,210-214]. Hospital volume showed a significant impact on survival in multivariate analyses in 3 studies after adjustment for 1 age, stage, histological confirmation, year of diagnosis[212], 2 adjustment for age, stage, type of operation, period of operation[213], or 3 after adjustment for age, stage, histology [214]. In o ne of these studies, the only high-volume center was also the only center where a gynecologic oncologist was present in that region[212]. One out of the 6 studies included in the systematic review published by du Bois *et al.*[209] reported an association between volume and survival univariate analysis, but this association was

no longer significant in multivariate analysis[112]. Other studies[210,211] could not detect any association of higher hospital volume with better survival **Table 3**.

Eleven original studies[178,183,207,215-222] not included in the systematic review mentioned above were also identified. As part of large studies, Mercado *et al.*[215] 31,897 stage IIIC -IV patients and Bristow *et al.*[207,216,221] 10,641 stage IIIC -IV patients[216], 47,160 stage I-IV patients[221] and 9,933 stage I-IV patients[207], showed that the pati ent volume of the hospital have a significant impact on survival Cox regressions controlling for 1 age, comorbidity, hospital location [215], 2 stage, ethnicity, age, payer status, household income, and tumour grade[216], 3 adherence to NCCN guidelines, age, race, proportion with college degree, median household, primary payer at diagnosis, stage, grade and histology[221] or 4 age, stage, tumour size, and grade [207].

Another large study[222] was identified 36,624 patients. Authors suggest that women who undergo surgery for ovarian cancer at high-volume hospitals have superior outcomes. Patients treated at low-volume hospitals who experienced complications were more likely to die as a result of the complications. Among women who experienced a complication, the mortality rate was 8.0% at low-volume, 6.1% at intermediate-volume, and 4.9% at high-volume hospitals p = 0.001. After adjusting for age, year of surgery, race, comorbidity, urgency of operation, performance of extended cytoreduction, and hospital teaching status, the failure-to-rescue rate was 48% higher at low-volume compared with high-volume hospitals OR = 1.48, 95% CI = 1.11 -1.99. Similar trends were noted for medical and infectious complications 9.5% versus 5.8%, p < 0.001, adjusted OR = 1.49, 95% CI = 1.09-2.04 ; 14.3% versus 8.3%, p < 0.001, adjusted OR = 1.79, 95% CI = 1.21-2.64, respectively. It should be noted that these results have to be interpreted cautiously because 1 the groups were not comparable notably in terms of age, comorbidities, lymphadenectomies, extended cytoreductive surgeries, urgency of operation, and 2 the presence of an important under -reporting bias.

Marth *et al.*[183] and Ioka *et al.*[219] reported also an impact of hospital volume on survival after adjustment for stage, lymphadenectomy, age, grade, residual disease[183] and for sex, age, stage[219]. Other studies[178,217,218,220] could not detect any association of higher hospital volume with better survival.

Impact of hospital volume on surgical outcome: **LoE 2-**
among the studies included in the systematic review published by du Bois *et al.*[209], three studies[211,223,224] addressed the effect of hospital volume on surgical outcome. The reports used several residual postoperative tumor criteria no residual tumour, maximum diameter of residual tumor ≤ 1 cm, ≤ 2 cm. In one study, patients treated in hospitals managing more than 10 cases per year were more likely to be optimally debulked residual tumour < 2 cm, even after adjustment for age, stage, grade, and physician specialty[224]. The two other studies only performed univariate analyses[211,223]. Du Bois *et al.*[211] used a similar cut-off of 12 patients per year and found no evidence of any effect regardless of the surgical outcome criterion used. The third study described a non-systematically significant association between higher volume and poorer outcome **Table 4**. One original study[220] not included in the systematic review mentioned above was also identified and showed that hospital volume did not affected the results of cytoreductive surgery. It should be noted that these results concerning the impact of hospital volume on surgical outcome must take into account that a potential interobserver bias in assessing the diameter of residual disease may influence the results.

Impact of hospital volume on the likelihood of repeat surgery: Elit *et al.*[217] assessed whether the hospital procedure volume determined the likelihood of unnecessary repeated surgery. Univariate analysis showed that the hospital procedure volume was found to be significantly associated with risk of repeat surgery 16 -99/y vs. ≥ 100/y: RR = 1.89, 95% CI = 0.39-9.23, p < 0.05; 1-15/y vs. ≥ 100/y : RR = 5.70, 95% CI = 1.22-26.73, p < 0.05. However, this volume-outcome association lost **LoE 2-**

its statistical significance when other variables were included in the model.

It should be noted that the available evidence concerning the hospital volume presented above showed great heterogeneity and has to be interpreted cautiously notably because 1 there are variations in hospital volume definitions among identified studies, 2 th ere are variations in the sample sizes of the studies and the lack of adequate risk adjustment strategies made it difficult to distinguish between effects of separate variables, 3 none of the studies controlled for clustering i.e., the effects of the referral pattern of a given physician or institution that might distort the effects of selected variables, and 4 the decision to repeat a surgery is partially subjective, and the answer may lie in clinical decision-making. Factors that contribute to the decision to perform repeat surgery include the patient's age, other comorbidities, opportunity to avoid adjuvant therapy because of the information from a subsequent staging surgery, the strength of the conviction that optimal debulking improves survival, physician bias based on who performed the initial surgery and patient preference.

Impact of physician volume on survival: among the studies included in the systematic review published by du Bois *et al.*[209], 3 studies[112,210,225] addressed the effect of surgeon volume on survival. Two studies[210,225] reported that surgeon volume did not impact survival in multivariate analyses. The third study[112] described an association between surgeon volume and survival after controlling for case mix **Table 5**. Two original studies [217,220] were also identified and showed that surgery by a high-volume surgeon did not reduce significantly the mortality risk in multivariate analyses. **LoE 2-**

Impact of physician volume on the risk of in-hospital death: Bristow *et al.*[226] reported that ovarian cancer surgery performed by a high-volume surgeon ≥ 10/y was independently associated with a 69% reduction in the risk of in-hospital death OR = 0.31, 95% CI = 0.16 -0.61, p = 0.001. **LoE 2-**

Impact of physician volume on surgical outcome: Goff *et al.*[227] described an advantage for high-volume surgeons ≥ 10/y in multivariate analysis after adjustment for age, race, stage, comorbidities, median household income, state, location of hospital, obstetrician/gynecologists per 100,000 population in country of residence, teaching status and hospital ovarian cancer volume **Table 6**. A second study [220] was identified and confirmed that high-volume surgeon > 12/y significantly affected the outcome of debulking residual tumour ≤ 1 cm, logistic regression analysis adjusted for stage and age. **LoE 2-**

It should be noted that these results concerning the impact of surgeon volume on surgical outcome must take into account that a potential interobserver bias in assessing the diameter of residual disease may influence the results.

Impact of surgeon volume on the likelihood of repeat surgery: Elit *et al.*[217] assessed whether the surgeon procedure volume determined the likelihood of unnecessary repeated surgery. Univariate analysis showed that the surgeon procedure volume < 10 per year was found to be significantly associated with a higher risk of repeat surgery 3 -9/y: RR = 7.63, 95% CI = 3.29-17.69, p < 0.05; 1-2/y: RR = 10.04, 95% CI = 4.44-22.71, p < 0.05. However, this volume-outcome association lost its statistical significance in when other variables were included in the model. **LoE 2-**

It should be noted that the available evidence concerning the surgeon volume presented above showed great heterogeneity and has to be interpreted cautiously notably because 1 there are variations in physician volume definitions among identified studies, 2 th ere are variations in the sample sizes of the studies and the lack of adequate risk adjustment strategies made it difficult to distinguish between effects of separate variables, and 3 none of the studies controlled for clustering i.e., the effects of the referral pattern of a given physician or institution that might distort the effects of selected variables, and 4 the decision to repeat a surgery is partially subjective, and the answer may lie in clinical decision-making. Factors that contribute to the decision to perform repeat surgery include the patient's age, other comorbidities, opportunity to avoid adjuvant therapy because of the

information from a subsequent staging surgery, the strength of the conviction that optimal debulking improves survival, physician bias based on who performed the initial surgery and patient preference.

Table 3. Original studies evaluating the impact of hospital volume on survival

Author[reference]	Year	FIGO stage	Hospital volume	N	Survival analysis			
					HR	95% CI	p-value	Type of analysis
Overall survival								
Elit *et al.* [210,a]	2002	I-IV	16-99/y vs. 1-15/y	1,378 vs. 985	0.81	0.70-0.94	> 0.05	multivariate
Elit *et al.* [210,a]	2002	I-IV	≥ 100/y vs. 1-15/y	1,378 vs. 987	0.85	0.72-1.00	> 0.05	multivariate
du Bois *et al.*[211,a]	2005	I-IV	≥ 12/y vs. 1-11/y	320 vs. 156	0.89	0.65-1.22	0.478	multivariate
Oberaigner *et al.*[212,a]	2006	I-IV	24-35/y vs. ≤ 11/y	453 vs. 458	0.79	0.65-0.95	≤ 0.05	multivariate
Kumpulainen *et al.*[213,a]	2002	I-IV	mean 8/y vs. mean 1/y	986 vs. 907	0.94	0.83-1.07	> 0.05	multivariate
Kumpulainen *et al.*[213,a]	2002	I-IV	mean 13/y vs. mean 1/y	968 vs. 907	1.03	0.91-1.16	> 0.05	multivariate
Kumpulainen *et al.*[213,a]	2002	I-IV	mean 28/y vs. mean 1/y	990 vs. 907	0.88	0.78-1.00	0.046	multivariate
Ioka *et al.*[214,a]	2004	I-IV	mean 2/y vs. < 1/y	726 vs. 626	0.86	0.75-0.97	≤ 0.05	multivariate
Ioka *et al.*[214,a]	2004	I-IV	mean 4/y vs. < 1/y	481 vs. 626	0.67	0.58-0.78	≤ 0.05	multivariate
Ioka *et al.*[214,a]	2004	I-IV	mean 9/y vs. < 1/y	617 vs. 626	0.62	0.54-0.72	≤ 0.05	multivariate
Schrag *et al.*[112,a]	2006	III-IV	13-28/8y vs. 1.12/8y	710 vs. 718	0.90	0.80-1.00	> 0.05	univariate
Schrag *et al.*[112,a]	2006	III-IV	29-93/8y vs. 1.12/8y	803 vs. 718	0.88	0.79-0.98	≤ 0.05	univariate
Mercado *et al.*[215]	2010	IIIC-IV	10-19 vs. 0-4/y	NA	0.89	0.86-0.93	< 0.0001	multivariate
Mercado *et al.*[215]	2010	IIIC-IV	≥ 20 vs. 0-4/y	NA	0.79	0.76-0.83	< 0.0001	multivariate
Elit *et al.*[217]	2008	I-IV	16-99/y vs. ≥ 100/y	721 vs. 104	1.05	0.84-1.31	> 0.05	univariate
Elit *et al.*[217]	2008	I-IV	1-15/y vs. ≥ 100/y	515 vs. 104	0.91	0.72-1.15	> 0.05	univariate
Brookfield *et al.*[218]	2009	I-IV	IVC vs. HVC[1]	NA	0.98	NA	0.69	multivariate
Brookfield *et al.*[218]	2009	I-IV	LVC vs. HVC[1]	NA	1.01	NA	0.11	multivariate
Bristow *et al.*[216]	2010	IIIC-IV	21-35/y vs. > 35/y	3,066 vs. 4,046	1.03	0.98-1.09	0.26	multivariate
Bristow *et al.*[216]	2010	IIIC-IV	9-20/y vs. > 35/y	1,936 vs. 4,046	1.08	1.01-1.15	0.03	multivariate
Bristow *et al.*[216]	2010	IIIC-IV	< 9/y vs. > 35/y	1,593 vs. 4,046	1.16	1.09-1.24	0.00	multivariate
Bristow *et al.*[221]	2013	I-IV	7-14/y vs. 1-6/y	11,868 vs. 11,742	0.96	0.92-1.00	> 0.05	multivariate
Bristow *et al.*[221]	2013	I-IV	15-25/y vs. 1-6/y	11,820 vs. 11,742	0.93	0.89-0.97	< 0.05	multivariate
Bristow *et al.*[221]	2013	I-IV	≥ 26/y vs. 1-6/y	11,730 vs. 11,742	0.92	0.88-0.97	< 0.05	multivariate
Marth *et al.*[183]	2009	I-IV	≤ 23/y vs. > 24/y	1,456 vs. 492	1.38	1.15-1.65	0.001	multivariate
Disease-free survival								
Kumpulainen *et al.*[178]	2009	I-IV	Continuous measure	234	0.994	0.978-1.009	0.412	multivariate
5-year ovarian cancer-specific mortality								
Kumpulainen *et al.*[178]	2009	I-IV	Continuous measure	238	0.998	0.981-1.016	0.857	multivariate
5-year survival								
Ioka *et al.*[219]	2007	I-IV	6/y vs. 18/y	285 vs. 261	1.3	1.0-1.7	> 0.05	multivariate
Ioka *et al.*[219]	2007	I-IV	3.6/y vs. 18/y	266 vs. 261	1.7	1.4-2.2	< 0.05	multivariate
Ioka *et al.*[219]	2007	I-IV	0.6/y vs. 18/y	267 vs. 261	2.0	1.6-2.5	< 0.05	multivariate
Ovarian cancer-specific survival								
Bristow *et al.*[207]	2015	I-IV	≥ 10/y vs. NCI CCC	4,654 vs. 800	1.18	1.04-1.33	< 0.05	multivariate
Bristow *et al.*[207]	2015	I-IV	< 10/y vs. NCI CCC	4,479 vs. 800	1.30	1.15-1.47	< 0.05	multivariate

[a] study included in the systematic review published by du Bois *et al.* 2009 [209], [1] medical facilities were grouped into tertiles based on number of surgeries with curative intent performed during the study period the upper one -third of institutions was classified as High-Volume Centers, the middle-third of institutions was classified as Intermediate-Volume Centers, the lower-third of institutions was classified as low-Volume Centers, CI confidence interval, HR hazard ratio, HVC high-volume centres, IVC intermediate-volume centres, LVC low-volume centres, NA data not available, NCI CCC national cancer institute comprehensive cancer center.

Table 4. Original studies evaluating the impact of hospital volume on surgical outcome

Author[reference]	Year	FIGO stage	Hospital volume	N	Survival analysis			
					HR	95% CI	p-value	Type of analysis
No residual tumour								
du Bois *et al.*[211,a]	2005	IIB-IV	≥ 12/y vs. 1-11/y	244 vs. 108	1.19	0.73-1.94	0.477	univariate
Obermair *et al.*[223,a]	2003	III	10-19/y vs. ≤ 9/y	154 vs. 176	0.46	0.28-0.78	0.004	univariate
Obermair *et al.*[223,a]	2003	III	≥ 20/y vs. ≤ 9/y	140 vs. 176	0.78	0.48-1.27	0.313	univariate
Residual tumour ≤ 1 cm								
du Bois *et al.*[211,a]	2005	IIB-IV	≥ 12/y vs. 1-11/y	244 vs. 108	1.27	0.80-2.01	0.311	univariate
Obermair *et al.*[223,a]	2003	III	10-19/y vs. ≤ 9/y	154 vs. 176	0.82	0.53-1.26	0.361	univariate
Obermair *et al.*[223,a]	2003	III	≥ 20/y vs. ≤ 9/y	140 vs. 176	0.53	0.34-0.83	0.006	univariate
Residual tumour ≤ 2 cm								
du Bois *et al.*[211,a]	2005	IIB-IV	≥ 12/y vs. 1-11/y	244 vs. 108	1.27	0.78-2.06	0.333	univariate
Olaitan *et al.*[224,a]	2001	I-IV	> 10/y vs. ≤ 10/y	NA	1.92	1.90-1.94	< 0.05	multivariate
Obermair *et al.*[223,a]	2003	III	10-19/y vs. ≤ 9/y	154 vs. 176	1.14	0.72-1.80	0.585	univariate
Obermair *et al.*[223,a]	2003	III	≥ 20/y vs. ≤ 9/y	140 vs. 176	0.85	0.53-1.34	0.473	univariate

[a] study included in the systematic review published by du Bois *et al.* 2009) [209], CI confidence interval, HR hazard ratio, NA data not available.

Table 5. Original studies evaluating the impact of physician volume on survival

Author[reference]	Year	FIGO stage	Physician volume	N	Survival analysis			
					HR	95% CI	p-value	Type of analysis
Woodman *et al.*[225,a]	1997	I-IV	≥ 6/2y vs. 1-5/2y	504 vs. 92	1.19	0.86-1.65	0.37	multivariate
Elit *et al.*[210,a]	2002	I-IV	3-9/y vs. 1-2/y	1,017 vs. 1,292	1.13	0.98-1.30	> 0.05	multivariate
Elit *et al.*[210,a]	2002	I-IV	≥ 10/y vs. 1-2/y	843 vs. 1,292	1.00	0.86-1.15	> 0.05	multivariate
Schrag *et al.*[112,a]	2006	III-IV	4-19/8y vs. 1-3/8y	614 vs. 1,044	0.93	0.84-1.04	> 0.05	univariate
Schrag *et al.*[112,a]	2006	III-IV	20-61/8y vs. 1.3/8y	573 vs. 1,044	0.87	0.77-0.98	0.03	multivariate
Vernooij *et al.*[220]	2009	III	> 12/y vs. ≤ 6/y	100 vs. 510	0.7	0.5-1.0	> 0.05	multivariate
Elit *et al.*[217]	2008	I-IV	3-9 vs. ≥ 10/y	403 vs. 496	0.73	0.62-0.86	< 0.05	univariate
Elit *et al.*[217]	2008	I-IV	1-2/y ≥ 10/y	425 vs. 496	0.92	0.79-1.06	> 0.05	univariate

[a] study included in the systematic review published by du Bois *et al.* 2009) [209], CI confidence interval, HR hazard ratio.

Table 6. Original studies evaluating the impact of physician volume on surgical outcome

Author[reference]	Year	FIGO stage	Physician volume	N	Survival analysis			
					HR/OR	95% CI	p-value	Type of analysis
Comprehensive surgical care								
Goff *et al.*[227,a]	2007	I-IV	2-9/y vs. 1/y	1,944 vs. 2,165	1.35	1.15-1.58	< 0.05	multivariate
Goff *et al.*[227,a]	2007	I-IV	≥ 10/y vs. 1/y	4,468 vs. 2,165	1.57	1.34-1.85	< 0.05	multivariate
Residual tumour ≤ 1 cm								
Vernooij *et al.*[220]	2009	III	7-12/y vs. ≤ 6/y	192 vs. 217	1.6	1.1-2.5	< 0.05	multivariate
Vernooij *et al.*[220]	2009	III	> 12/y vs. ≤ 6/y	44 vs. 217	2.8	1.4-5.7	< 0.05	multivariate

[a] study included in the systematic review published by du Bois *et al.* 2009) [209], CI confidence interval, HR hazard ratio, OR odd ratio.

5.3 QI 3 - Surgery performed by a gynecologic oncologist or a trained surgeon specifically dedicated to gynaecological cancers management

5.3.1 Description of the QI

TYPE	Process indicator.
DESCRIPTION	Surgery is performed by a certified gynecologic oncologist or, in countries where certification is not organized, by a trained surgeon dedicated to the management of gynecologic cancer accounting for over 50% of his practice or having completed an ESGO accredited fellowship. Skills to successfully complete abdominal and pelvic surgery procedures necessary to achieve complete cytoreduction must be available.
SPECIFICATIONS	*Numerator*: number of patients with advanced ovarian cancer operated by a specialist as defined above. *Denominator*: all patients undergoing surgery for advanced ovarian cancer.
TARGETS	≥ 90%.
SCORING RULE	3 if the target is met.

5.3.2 Rationale

In Europe, organization of gynecologic oncology differs among countries but there is a trend of centralization and subspecialization. The ESGO, in collaboration with the European Board and College of Obstetricians and Gynecologists, has developed a subspecialty training program in gynecologic oncology.

Three previous initiatives[26,53,118] published a QI for this topic. Furthermore, the three guidelines[122,123,125] identified for this topic suggest or recommend that the surgery should be performed by a gynecologic oncologist or a trained surgeon specifically dedicated to gynaecological cancers management.

5.3.3 Summary of available scientific evidence

LoE 2+

Impact of physician specialty on survival: Vernooij *et al.*[228] and du Bois *et al.*[209] performed systematic reviews of the literature to evaluate notably whether physician-related variables have any impact on outcome in advanced ovarian cancer patients. Vernooij *et al.*[228] included 11 studies[210,224,229-237]. du Bois *et al.*[209] also included 11 studies[229-231,233,234,237-242] 6 studies were included in the 2 systematic reviews[229-231,233,234,237].

Due to great heterogeneity of the studies, the authors could not quantitatively summarize the survival to determine whether surgery performed by a gynecologic oncologist led to an overall improved survival or not. Among the included studies, only 6 studies[229,231,234,237,239,242] analyzed the independent prognostic value of physician specialty on survival **Table 7**. Multivariate analyses showed that surgery performed by gynecologic oncologists was found to be independently prognostic for survival in 2 studies[229,237] after adjustment for 1 age, grade, histology, ascites, and socioeconomic status[229] or 2 age, grade, histology, ascites, performance status, CA 125, comorbidity, and residual disease[237].

Six studies[24,28-30,39,40,43] compared survival in patients with advanced ovarian cancer after treatment by general surgeon with survival after treatment by obstetricians/general gynecologists[229,231,234,237-239,243]. Three of these 6 studies[76,80,90] showed that survival was worse among patients treated by general surgeon and 2 studies[29,30] reported an independent significant impact of surgery performed by a general surgeon on survival[229,234] after adjustment for age, grade, histology, ascites, and

socioeconomic status[229] and adjustment for age, and comorbidity[234] **Table 7.**

Four original studies[8,10,13,16] not included in the systematic reviews mentioned above were also identified[178,215,217,220]. In a large cohort study 31,897 stage IIIC -IV ovarian cancer patients, Mercado *et al.*[215] showed that the hazard ratio for death for advanced stage patients was 1.63 when treated by a general surgeon as compared to a gynecologic oncologist/gynecologist Cox regression controlling for age, comorbidity, and hospital location. Treatment by a physician of another specialty was also associated with higher hazard of death as compared to treatment by a gynecologic oncologist/gynecologist. Like Mercado *et al.*[215], Elit *et al.*[217] reported that treatment by a physician of another specialty was associated with higher hazard of death as compared to treatment by a gynecologic oncologist association adjusted for age, comorbidity, residence location, stage, and grade **Table 7.**

In a study conducted by Vernooij *et al.*[220], gynecologists were classified according to their level of specialization as specialized, semi-specialized or general gynecologists. Specialized gynecologists have subspecialized during a mostly 2-year fellowship in a cancer center or have spent most of their career in gynecological oncology and are recognized as specialized gynecologists by the Dutch Society of Gynecological Oncology. Semi-specialized gynecologists are not formally trained in oncology but surgically treat the majority of ovarian and endometrial cancer patients in the semi-specialized hospital they work in. Furthermore in contrast to general gynecologists, semi-specialized gynecologists visit conferences and lectures on gynecologic cancer and take part in structured regional oncology consultations. The authors mentionned that specialization of the gynecologist did not influence survival significantly data not shown. Cox multivariate analyses reported by Kumpulainen *et al.*[178] indicated also that specialization of the gynecologist did not influence survival significantly **Table 7.**

LoE 2-

Impact of physician specialty on surgical outcome: among the studies included in the systematic review published by du Bois *et al.*[209], 10 studies[224,229,231,233,236,237,239,241,244,245] evaluated the surgical outcome with respect to residual postoperative tumor in advanced ovarian cancer. None of these studies performed multivariate analyses. Only 4 reports[233,236,237,239] used complete resection without residual tumor as outcome variable, others chose heterogeneous definitions of so-called optimal debulking including proportional measures e.g., debulking > 95%, met ric measures e.g. maximum diameter of residual tumor ≤ 1 mm, ≤ 2 mm or < 2 cm, or combined classes e.g., > 95 % debulking, residual < 15 mm.

All studies documented association in favor of gynecologic oncologist compared with obstetrician/general gynecologist or others regardless of the outcome variable used. However, only 4 associations reached statistical significance **Table 8**. Six studies included comparisons among disciplines general surgeon vs. obstetrician/general gynecologist . In 5 trials, the degree of cytoreduction was higher among patients treated by an obstetrician/general gynecologist regardless of the outcome variable used the associations reached statistical significance in 3 studies.

As part of a pooled analysis including two studies[233,236], Vernooij *et al.*[228] showed that stage III patients operated by a gynecologic oncologist were significantly more often debulked to no residual disease than patients treated by a general gynecologist RR = 2.3, 95% CI = 1.5 -3.5; p < 0.05. In another pooled analysis 5 studies [224,229,231,233,236], gynecologic oncologi sts achieved debulking to < 2 cm residual tumor among stage III patients 1.4 times more often than general gynecologist 95% CI = 1.2-1.5, p < 0.05.

In the study mentioned above and conducted by Vernooij *et al.*[220], the differences between general, semi-specialized and specialized gynecologists were small but statistically significant optimal debulking in 40%, 42%, and 45% of the patients respectively; p = 0.05. However, logistic regression analysis showed that there was no difference between gynecological specialties data not shown. The authors also mentioned that a collaboration between a gynecologist and a general

surgeon increased the chance of achieving optimal debulking OR = 1.8, 95% CI = 1.2 -2.8, $p < 0.05$; adjustment for age, stage and specialization of the gynecologist). Patients operated by both a general surgeon and a gynecologist underwent a bowel resection in 38% of the cases, compared to 5% of the patients treated by a gynecologist alone $p < 0.0001$.

It should be noted that these results concerning the impact of physician specialty on surgical outcome must take into account that a potential interobserver bias in assessing the diameter of residual disease may influence the results.

LoE 2-

Impact of physician specialty on the likelihood of repeat surgery: Elit *et al.*[217] assessed whether the specialty of the surgeon determined the likelihood of unnecessary repeated surgery. After adjustment for age, residence location, tumour grade, and stage, multivariate analysis showed that surgical discipline was found to be significantly associated with risk of repeat surgery. Patients who initially saw a general surgeon were 17 times more likely to undergo repeat surgery thant those who saw gynecologic oncologists RR = 16.97, 95% CI = 6.35 -45.32, $p < 0.05$. Those whose surgeries were performed by obstetricians were 6 times more likely than those who saw gynecologic oncologists to undergo repeat surgery RR = 6.54, 95% CI = 2.53 -16.93, $p < 0.05$. The authors mentioned that surgeon and hospital specialization were strongly correlated data not shown. After adjustment for hospital effects, patients operated by a general surgeon have an estimated likelihood of repeated surgery that was 6 times greater than that of patients who saw gynecologic oncologists RR = 5.7, 95% CI = 1.17-28.46, $p < 0.05$. The interpretation of these results must take into account that the decision to repeat a surgery is partially subjective, and the answer may lie in clinical decision-making. Factors that contribute to the decision to perform repeat surgery include the patient's age, other comorbidities, opportunity to avoid adjuvant therapy because of the information from a subsequent staging surgery, the strength of the conviction that optimal debulking improves survival, physician bias based on who performed the initial surgery and patient preference. Caution is still warranted because not all clinically relevant prognostic factors could be assessed through patient records by the authors.

Table 7. Original studies evaluating the impact of physician specialty on survival

Author[reference]	Year	FIGO stage	Specialties	N	Survival analysis			
					HR	95% CI	p-value	Type of analysis
Overall survival								
Nguyen *et al.*[238,a,b]	1993	I	OB/GYN reference vs. GS	907 vs. 279	1.26	0.84-1.90	> 0.05	univariate
Nguyen *et al.*[238,a,b]	1993	I	OB/GYN reference vs. GYO	907 vs. 191	1.06	0.63-1.78	> 0.05	univariate
Nguyen *et al.*[238,a,b]	1993	II	OB/GYN reference vs. GS	274 vs. 97	1.65	1.17-2.32	≤ 0.05	univariate
Nguyen *et al.*[238,a,b]	1993	II	OB/GYN reference vs. GYO	274 vs. 77	0.88	0.57-1.36	> 0.05	univariate
Junor *et al.*[229,a,b]	1999	I	OB/GYN reference vs. GS	318 vs. 24	1.01	0.40-2.57	> 0.05	multivariate
Junor *et al.*[229,a,b]	1999	I	OB/GYN reference vs. GYO	318 vs. 68	0.83	0.45-1.55	> 0.05	multivariate
Junor *et al.*[229,a,b]	1999	II	OB/GYN reference vs. GS	119 vs. 12	0.67	0.25-1.75	> 0.05	multivariate
Junor *et al.*[229,a,b]	1999	II	OB/GYN reference vs. G YO	119 vs. 32	1.00	0.56-1.80	> 0.05	multivariate
Grossi *et al.*[231,a]	2002	I-II	OB/GYN reference vs. GS	79 vs. 17	3.57	1.41-9.02	≤ 0.05	multivariate
Grossi *et al.*[231,a]	2002	I-II	OB/GYN reference vs. G YO	79 vs. 60	1.58	0.60-4.17	> 0.05	multivariate
Earle *et al.*[234,a]	2006	I-II	OB/GYN reference vs. G S	409 vs. 144	1.21	0.93-1.59	0.160	multivariate
Earle *et al.*[234,a]	2006	I-II	OB/GYN reference vs. G YO	409 vs. 198	0.97	0.75-1.24	0.788	multivariate
Engelen *et al.*[233,a]	2006	I-II	OB/GYN reference vs. GYO	135 vs. 64	0.50	0.26-0.94	0.03	univariate
Mayer *et al.*[246,a,b]	1992	I-II	Other reference vs. GYO	21 vs. 26	0.52	0.22-1.23	< 0.05[c]	univariate
Puls *et al.*[247,a,b]	1997	I	Other reference vs. GYO	25 vs. 29	0.25	0.07-0.94	0.04	univariate
Carney *et al.*[230,a,b]	2002	I-II	Other reference vs. GYO	195 vs. 124	1.29	0.69-2.39	0.421	univariate
Chan *et al.*[240,a]	2007	IC-II	Other reference vs. GYO	211 vs. 100	0.77	0.53-1.12	0.157	univariate
Elit *et al.*[217]	2008	I-IV	GYO reference vs. OB/GYN	485 vs. 664	1.00	0.86-1.16	> 0.05	multivariate
Elit *et al.*[217]	2008	I-IV	GYO reference vs. GS	485 vs. 158	1.19	0.94-1.50	> 0.05	multivariate
Elit *et al.*[217]	2008	I-IV	GYO reference vs. Other	485 vs. 15	1.52	1.18-1.95	< 0.05	multivariate
Nguyen *et al.*[238,a]	1993	III	OB/GYN reference vs. GS	656 vs. 382	1.32	1.18-1.48	≤ 0.05	univariate
Nguyen *et al.*[238,a]	1993	III	OB/GYN reference vs. GYO	656 vs. 317	1.06	0.94-1.20	> 0.05	univariate
Junor *et al.*[229,a,d]	1999	III	OB/GYN reference vs. GS	454 vs. 151	1.32	1.07-1.63	0.009	multivariate
Junor *et al.*[229,a,d]	1999	III	OB/GYN reference vs. GYO	454 vs. 192	0.75	0.62-0.92	0.005	multivariate
Paulsen *et al.*[237,a,d]	2006	IIIC	OB/GYN reference vs. GS	99 vs. 24	1.68	0.74-3.79	0.220	multivariate
Paulsen *et al.*[237,a,d]	2006	IIIC	OB/GYN reference vs. GYO	99 vs. 75	0.47	0.25-0.87	0.017	multivariate
Mercado *et al.*[215]	2010	IIIC-IV	GYO/GYN reference vs. GS	NA	1.63	1.56-1.71	< 0.0001	multivariate
Mercado *et al.*[215]	2010	IIIC-IV	GYO/GYN reference vs. Other	NA	1.56	1.52-1.61	< 0.0001	multivariate
Grossi *et al.*[231,a,d]	2002	III-IV	OB/GYN reference vs. GS	65 vs. 44	NA	NA	> 0.05	multivariate
Grossi *et al.*[231,a,d]	2002	III-IV	OB/GYN reference vs. GYO	65 vs. 142	NA	NA	> 0.05	multivariate
Earle *et al.*[234,a,d]	2006	III-IV	OB/GYN reference vs. GS	968 vs. 529	1.16	1.04-1.30	0.010	multivariate
Earle *et al.*[234,a,d]	2006	III-IV	OB/GYN reference vs. GYO	968 vs. 819	0.99	0.89-1.09	0.833	multivariate
Skirnisdottir *et al.*[239,a]	2007	III-IV	OB/GYN reference vs. GS	232 vs. 53	1.25	0.92-1.71	0.158	multivariate
Skirnisdottir *et al.*[239,a]	2007	III-IV	OB/GYN reference vs. GYO	232 vs. 137	1.03	0.83-1.30	0.772	multivariate
Engelen *et al.*[233,a,d]	2006	III-IV	OB/GYN reference vs. GYO	191 vs. 119	0.75	0.58-0.96	0.02	univariate
Carney *et al.*[230,a,d]	2002	III-IV	Other reference vs. GYO	243 vs. 172	0.69	0.54-0.87	0.002	univariate
Bailey *et al.*[242,a]	2006	III-IV	Other reference vs. GYO	145 vs. 216	0.98	0.74-1.31	0.911	multivariate
Chan *et al.*[240,a]	2007	III-IV	Other reference vs. GYO	692 vs. 398	0.77	0.67-0.88	< 0.001	univariate
Eisenkop *et al.*[241,a]	1992	IIIC-IVA	Other reference vs. GYO	129 vs. 121	0.53	0.39-0.71	< 0.001	univariate
Nguyen *et al.*[238,a]	1993	IV	OB/GYN reference vs. GS	473 vs. 429	1.22	1.09-1.36	≤ 0.05	univariate
Nguyen *et al.*[238,a]	1993	IV	OB/GYN reference vs. GYO	473 vs. 178	1.12	0.97-1.30	> 0.05	univariate
Junor *et al.*[229,a,d]	1999	IV	OB/GYN reference vs. GS	134 vs. 23	1.26	0.78-2.04	> 0.05	multivariate
Junor *et al.*[229,a,d]	1999	IV	OB/GYN reference vs. GYO	134 vs. 54	1.01	0.71-1.45	> 0.05	multivariate

[a] study included in the systematic review published by du Bois *et al.*[209], [b] study included in the systematic review published by Giede *et al.*[248], [c] the authors stated that the specialty of the surgeon attained statistical significance for survival p < 0.05) in the Cox regression analysis, but details were not reported. Thus, the presented numbers were estimated from the published survival curves. The upper limit of the confidence interval does not correspond with the reported p-value of p < 0.05, [d] study included in the systematic review published by Vernooij *et al.* 2007) [228], CI confidence interval, GS general surgeon, GYO gynecologic oncologist, HR hazard ratio, OB/GYN obstetrician/general gynecologist, NA data not available.

Original studies evaluating the impact of physician specialty on survival *continued*

Author[reference]	Year	FIGO stage	Specialties		N	Survival analysis			
						HR	95% CI	p-value	Type of analysis
Disease-free survival									
Kumpulainen *et al.*[178]	2009	I-IV	GYO reference	vs. GYN	98 vs. 136	0.861	0.573-1.295	0.473	multivariate
5-year ovarian cancer specific mortality									
Kumpulainen *et al.*[178]	2009	I-IV	GYO reference	vs. GYN	102 vs. 136	1.237	0.752-2.03	0.403	multivariate

CI confidence interval, GYO gynecologic oncologist, GYN general gynecologist, HR hazard ratio.

Table 8. Original studies evaluating the impact of physician specialty on surgical outcome

Author[reference]	Year	FIGO stage	Specialties	N	Survival analysis			
					HR	95% CI	p-value	Type of analysis
No residual tumour								
Engelen *et al.*[233,a,b,c]	2006	III	OB/GYN reference vs. GYO	142 vs. 98	2.45	1.20-5.01	0.014	univariate
Kumpulainen *et al.*[236,a,b,d]	2006	III	OB/GYN reference vs. GYO	92 vs. 53	3.40	1.51-7.65	0.003	univariate
Paulsen *et al.*[237,a,b,d]	2006	IIIC	OB/GYN reference vs. GS	99 vs. 24	1.17	0.41, 3.30	0.771	univariate
Paulsen *et al.*[237,a,b,d]	2006	IIIC	OB/GYN reference vs. GYO	99 vs. 75	1.19	0.59-2.40	0.632	univariate
Skirnisdottir *et al.*[239,a,c]	2007	III-IV	OB/GYN reference vs. GS	233 vs. 46	0.14	0.00-0.83	0.026	univariate
Skirnisdottir *et al.*[239,a,c]	2007	III-IV	OB/GYN reference vs. GYO	233 vs. 137	1.12	0.56-2.23	0.742	univariate
Residual tumour ≤ 1 mm								
Eisenkop *et al.*[241,a,c]	1992	IIIC-IVA	Other reference vs. GYO	137 vs. 126	10.86	6.06-19.45	< 0.001	univariate
Residual tumour ≤ 2 mm								
Grant *et al.*[245,a,c]	1992	IIB-IV	OB/GYN reference vs. GS	14 vs. 13	0.06	0.01-0.62	0.018	univariate
Kumpulainen *et al.*[236,a,b,d]	2006	III	OB/GYN reference vs. GYO	92 vs. 53	1.36	0.69-2.69	0.373	univariate
Residual tumour < 20 mm								
Junor *et al.*[229,a,b,c]	1999	III	OB/GYN reference vs. GS	432 vs. 146	0.33	0.19-0.57	< 0.001	univariate
Engelen *et al.*[233,a,b,c]	2006	III	OB/GYN reference vs. GYO	277 vs. 163	1.30	0.87-1.93	0.198	univariate
Olaitan *et al.*[224,a,b,d]	2001	III-IV	OB/GYN reference vs. GS	148 vs. 5	0.30	0.03-2.77	0.290	univariate
Grossi *et al.*[231,a,b,c]	2002	III-IV	OB/GYN reference vs. GS	65 vs. 44	0.41	0.16-1.02	0.055	univariate
Skirnisdottir *et al.*[239,a,c]	2007	III-IV	OB/GYN reference vs. GS	233 vs. 46	0.12	0.03-0.50	0.004	univariate
Skirnisdottir *et al.*[239,a,c]	2007	III-IV	OB/GYN reference vs. GYO	233 vs. 137	1.44	0.92-2.26	0.114	univariate
Debulking > 95 % and residual tumour < 15 mm								
Chen *et al.*[244,a,c]	1985	III-IV	OB/GYN ref erence vs. GYO	37 vs. 47	75.57	9.35-610.74	< 0.001	univariate

[a] study included in the systematic review published by du Bois *et al.* 2009) [209], [b] study included in the systematic review published by Vernooij *et al.* 2007) [228], [c] retrospective study, [d] prospective study, CI confidence interval, GS general surgeon, GYO gynecologic oncologist, HR hazard ratio, OB/GYN obstetrician/general gynecologist, NA data not available.

5.4 QI 4 - Center participating in clinical trials in gynecologic oncology

5.4.1 Description of the QI

TYPE	Structural indicator.
DESCRIPTION	The center actively accrues patients in clinical trials in gynecologic oncology.
SPECIFICATIONS	*Numerator*: not applicable. *Denominator*: not applicable.
TARGETS	Not applicable.
SCORING RULE	3 if the center actively accrues patients in clinical trials in gynecologic oncology

5.4.2 Rationale

Institutions participating in clinical research contribute to improve quality of care. Patients treated in study hospitals have a higher chance of receiving standard treatment compared to patients treated in hospitals not participating in cooperative clinical studies[211]. Furthermore, study centers do not only recruit patients but tend to have infractructures associated with clinical trials participation. They have physicians interested in ovarian cancer and motivated to perform studies. They also might participate more often in quality assurance programs. The benefit could not be limited to patients enrolled in active protocols. The positive effects could also be observed in patients where no protocol has been active[211]. Thus, patients treated in these centers but who are not enrolled in clinical trials might receive quality of care above average as well. Finally, two previous initiatives[26,53] published a QI for this topic.

5.4.3 Summary of available scientific evidence

Impact of participation in clinical studies on survival: as part of this national German survey, du Bois *et al.*[211] reported that non-participation in clinical studies was independently associated with an 82% increase of risk of death HR = 1.82, 95% CI = 1.27 -2.61, p = 0.001 after ajustment for stage, performance status, ascites, comorbidity, age, histology, grading and hospital volume. Survival advantages observed in this survey cannot be attributed to patients enrolled in study protocols authors compared all patients treated in institutions participating in trials versus all patients treated in institutions that do not participate.

Another study[249] determined the effect of participation in clinical trials on survival. The on-study subjects were similar to off-study subjects for age, ethnicity, residence location, stage, histology, proportion of optimally debulked or completely staged surgically, proportion of patients receiving recommended treatment. The authors reported that median OS was significantly superior in on-study subjects 46 vs. 25 months, p = 0.03. A nonsignificant trend toward improved median PFS was also observed in on-study patients 23 vs. 9 months, p = 0.087 .

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Impact of participation in clinical studies on surgical outcome: as part of the national German survey mentioned above, authors[211,250] observed also that debulking performed in hospitals participating in clinical studies were significantly more optimal residual tumour < 1 cm as compared to those performed in centers do not participate OR = 1.63, 95% CI = 1.05 -2.53, p = 0.030 univariate analysis.

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5.5 QI 5 - Treatment planned and reviewed at a multidisciplinary team meeting

5.5.1 Description of the QI

TYPE	Process indicator.
DESCRIPTION	The decision for any major therapeutic intervention has been taken by a multidisciplinary team MDT including at least a surgical specialist as defined above QI 2 and QI 3, a radiologist, a pathologist if a biopsy is available, and a physician certified to deliver chemotherapy a gynecologic oncologist in countries where the subspecialty is structured and/or a medical oncologist with special interest in gynecologic oncology.
SPECIFICATIONS	*Numerator*: number of patients with advanced ovarian cancer for whom the decision for therapeutic interventions has been taken by a MDT. *Denominator*: all patients with advanced ovarian cancer undergoing therapeutic interventions.
TARGETS	≥ 95%
SCORING RULE	3 if the target is met.

5.5.2 Rationale

Multidisciplinary care is recognized as best practice in treatment planning and care for patients internationally. In several cancer types, there is evidence that decisions made by a MDT are more likely to be in accord with evidence-based guidelines than those made by individual clinicians and the role of multidisciplinary approach in the quality of care is recognized[220,228,251-257].

Three previous initiatives[26,46,53] published a QI for this topic. Furthermore, the only guideline[120] identified for this topic recommends that treatment should be individualized to the patient after full discussion at MDT.

5.5.3 Summary of available scientific evidence

No directly applicable clinical studies have been identified.

5.6 QI 6 - Required preoperative workup

5.6.1 Description of the QI

TYPE	Process indicator.
DESCRIPTION	Unresectable parenchymal metastases have been ruled out by imaging. Ovarian and peritoneal malignancy secondary to gastrointestinal cancer has been ruled out by suitable methods e.g. plasma CA 125 and CEA levels, and/or by biopsy under radiologic or laparoscopic guidance.
SPECIFICATIONS	*Numerator*: number of patients with advanced ovarian cancer who had undergone cytoreductive surgery and who were offered minimum preoperative workup as defined above. *Denominator*: all patients with suspected advanced ovarian cancer who underwent cytoreductive surgery.
TARGETS	≥ 95%
SCORING RULE	3 if the target is met.

5.6.2 Rationale

An accurate diagnosis guides patient management and informs prognosis. It is crucial to determine whether peritoneal infiltration and/or omental masses in patients with prior malignancy represent recurrent disease or a new disease process[258]. A great proportion of women with newly diagnosed ovarian cancer have peritoneal carcinomatosis. Ovarian and peritoneal malignancy secondary to gastrointestinal cancer has to be ruled out by suitable methods. In case of possible gastro-intestinal tract origin, colonoscopy and gastroscopy should be performed before surgery. Furthermore, parenchymal metastases have to be ruled out by imaging. One previous initiative[53] published a QI for this topic.

5.6.3 Summary of available scientific evidence

No directly applicable clinical studies have been identified.

5.7 QI 7 - Pre-, intra-, and post-operative management

5.7.1 Description of the QI

TYPE	Structural indicator.
DESCRIPTION	The minimal requirements are: 1 intermediate care facility, and access to an intensive care unit in the center are available, 2 an active perioperative management program is established[1] .
SPECIFICATIONS	*Numerator*: not applicable. *Denominator*: not applicable.
TARGETS	Not applicable.
SCORING RULE	3 if the minimal requirements are met.

[1)] Details of perioperative management includes non -exhaustive list: preoperative hemoglobin optimization and iron deficit correction; correction of denutrition and immunonutrition according the current guidelines; fluid management, involving a Goal Directed Therapy GDT policy rather than liberal fluid therapy without hemodynamic goals. However, the superiority of GDT compared to restrictive fluid strategy remains unclear. There is no recognized standard method of monitoring; pain management, including in the absence of contra-indication the use of epidural analgesia in order to avoid opioids; while routine premedication is no longer recommended, prevention of postoperative nausea and vomiting should be systematic.

5.7.2 Rationale

Malnutrition has been demonstrated to affect two third of ovarian cancer patients at the time of diagnosis and portends poor surgical outcomes[259]. Malnutrition at the time of surgery is an important contributor to perioperative morbidity. It makes patients more vulnerable to surgical site infections. Malignancy related malnutrition causes alterations in immune function that impairs a patient's response to surgical stress and places malnourished surgical patients at increased risk for the development of surgical site infections[260,261]. Immunomodulating diets in ovarian cancer patients could provide an effective way to minimize the post-operative morbidity associated with surgical site infections.

The overall reduction of mortality and morbidity rates after surgery has consistently decreased over the last decade with the introduction of innovative perioperative care, which has made difficult to assess the independent role of each single perioperative intervention. However, the high morbidity of ovarian cancer surgery, which increases with complexity[71,131,262], justifies the implementation of the concept of "fast-track surgery" or "enhanced recovery programs" involving procedure-specific evidence-based care principles which has been demonstrated to result in enhanced recovery with reduced of stay and morbidity[263].

While no specific research on this topis has been carried out in ovarian cancer surgery, the abundant available literature concerning open colorectal surgery provides compelling data which can reasonably be transposed[264]. Perioperative management includes: 1 preoperative hemoglobin optimization [265] and iron deficit correction[266], 2 correction of denutrition according the current guidelines [267], 3 fluid management, involving a GDT policy rather than liberal fluid therapy without hemodynamic goals; however, the superiority of GDT compared to restrictive fluid strategy remains unclear[268]; there is no recognized strandard method of monitoring[269]. While routine premedication is no longer recommended[270], prevention of postoperative nausea and vomiting should be systematic[271].

One previous initiative[53] published a QI for this topic.

5.7.3 Summary of available scientific evidence

No directly applicable clinical studies have been identified.

5.8 QI 8 - Minimum required elements in operative reports

5.8.1 Description of the QI

TYPE	Process indicator.
DESCRIPTION	Operative report is structured. Size and location of disease at the beginning of the operation must be described. All the areas of the abdominal cavity[1)] must be described. If applicable, the size and location of residual disease at the end of the operation, and the reasons for not achieving complete cytoreduction must be reported.
SPECIFICATIONS	*Numerator*: number of patients with advanced ovarian cancer undergoing cytoreductive surgery who have a complete operative report that contains all required elements as defined above. *Denominator*: all patients with advanced ovarian cancer undergoing cytoreductive surgery.
TARGETS	90%.
SCORING RULE	3 if the target is met.

[1)] ovaries, tubes, uterus, pelvic peritoneum, paracolic gutters, anterior parietal peritoneum, mesentery, peritoneal surface of the colon and bowel, liver, spleen, greated and lesser omentum, porta hepatis, stomach, Morrison pouch, lesser sac, undersurface of both hemidiaphragms, pelvic and aortic nodes and if applicable pleural cavity.

5.8.2 Rationale

In another pathology, there is evidence that standardized operative reports result in more complete and reliably interpretable operative data compared with non-standardized operative reports[272]. Furthermore, compliance with the standardized operative report improves over time. In the absence of international validated standardized operative report in ovarian cancer, some required elements must be reported. Size and location of disease at the beginning of the operation must be described. All the areas of the abdominal cavity must be described ovaries, tubes, uterus, pelvic peritoneum, paracolic gutters, anterior parietal peritoneum, mesentery, peritoneal surface of the colon and bowel, liver, spleen, greated and lesser omentum, porta hepatis, stomach, Morrison pouch, lesser sac, undersurface of both hemidiaphragms, pelvic and aortic nodes and if applicable pleural cavity . If applicable, the size and location of residual disease at the end of the operation, and the reasons for not achieving complete cytoreduction must be reported.

Three previous initiatives[26,53,64] published a QI for this topic. Furthermore, the only guideline[125] identified for this topic recommends that operative reports sould include some required elements e xtent of initial disease before debulking pelvis, midabdomen, or upper abdomen cutoffs: pelvic brim to lower ribs; amount of residual disease in the same areas after debulking; complete or incomplete resection; if incomplete, indicate the size of the major lesion and total number of lesions. Indicate if miliary or small lesions.

5.8.3 Summary of available scientific evidence

No directly applicable clinical studies have been identified.

5.9 QI 9 - Minimum required elements in pathology reports

5.9.1 Description of the QI

TYPE	Process indicator.
DESCRIPTION	Pathology report contains all the required elements listed in the international collaboration on cancer reporting ICCR histopathology reporting guide [1) 2)] .
SPECIFICATIONS	*Numerator*: number of patients with advanced ovarian cancer undergoing cytoreductive surgery who have a complete pathology report that contains all required elements as defined in ICCR histopathology reporting guide. *Denominator*: all patients with advanced ovarian cancer undergoing cytoreductive surgery.
TARGETS	≥90%. The tolerance within this target reflects situations where it is not possible to report all components of the data set due to poor quality of specimen.
SCORING RULE	3 if the target is met.

[1)] https://www.rcpa.edu.au/Library/Practising-Pathology/ICCR/Cancer-Datasets.

[2)] McCluggage, W.G., et al. Data set for reporting of ovary, fallopian tube and primary peritoneal carcinoma: recommendations from the international collaboration on cancer reporting ICCR. Mod Pathol 2015).

5.9.2 Rationale

An accurate pathology report is critical for the optimal management of advanced ovarian cancer patients. The link between the absence of standardized reporting guide and deficiencies among reports is described for other tumour types[273-275]. The report is essential for communication to treating physicians, data collection within clinical trials, review by a second pathologist or when unforeseen problems arise and a reassessment is needed later on. The distinction between primary ovarian and metastatic tumours is based on the interpretation of a complex combination of macroscopic, microscopic and biochemical data and requires pathological expertise. Histological reports must provide prognostic indicators which inform treatment planning for women diagnosed with epithelial ovarian cancer. Three previous initiatives[26,46,53] published a QI for this topic.

In 2015, an international panel of pathologists and clinicians developed a common, internationally agreed upon, evidence-based ovarian cancer data set[276]. It contains “required” mandatory/core and “recommended” non - mandatory/noncore elements. Required elements were defined as those that had agr eed evidentiary support and that were unanimously agreed upon by the review panel to be essential for clinical management. Recommended elements were those considered to be clinically important and recommended for good practice but with lesser degrees of supportive evidence. The data set has been developed for resection specimens of primary borderline and malignant epithelial tumours of the ovary, fallopian tubes and peritoneum. It does not include non-epithelial ovarian neoplasms such as germ cell or sex cord stromal tumours or other primary peritoneal neoplasms such as mesothelioma.

The international development group considers that a widespread utilization of this internationally agreed upon, evidence-based, structured pathology data set for advanced ovarian cancer will lead not only to improved patients management but is a prerequisite for research and for international benchmarking in health care.

5.9.3 Summary of available scientific evidence

Only one study[116] was identified. As part of an audit, Vernooij *et al.*[116] assessed the quality of 479 surgical pathology reports of advanced stage ovarian, fallopian tube and primary peritoneal cancer from 40 institutions in 11 different countries. In absence of standardized pathology reports used in

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the different institutions, minimal standards for the pathology reports were identified in the literature macroscopic description of all specimens, measuring and weighing of major specimens, description of tumour origin and differentiation. Although only minimal requirements were checked, this audit showed that in a substantial number of reports, basic pathologic data are missing with potential adverse consequences for the quality of care:

- Macroscopic description of all specimen: 7.7%;
- Measuring and weighing of major specimens: 40.1%;
- Description of tumour origin: 22%;
- Description of differentiation: 15.4%.

The authors also mentionned that important deficiencies for all items were correlated with country of origin, and type of hospital academic vs. non -academic hospitals data n ot shown. It should be noted that a potential bias in the assessment of reports cannot be excluded and it must be considered in interpreting the results of this audit. Indeed, there was no dual independent assessment of reports even if, for internal quality control, a randomly selected 10% of the reports were also assessed by a second author, showing only minor discrepancies.

5.10 QI 10 - Existence of a structured prospective reporting of postoperative complications

5.10.1 Description of the QI

TYPE	Outcome indicator.
DESCRIPTION	Data to be recorded are reoperations, interventional radiology, readmissions, secondary transfers to intermediate or intensive care units, and deaths.
SPECIFICATIONS	*Numerator*: number of recorded serious postoperative complications or deaths occurred among patients with advanced ovarian cancer who have undergone cytoreduction. *Denominator*: all complications occurred among patients with advanced ovarian cancer who have undergone cytoreduction.
TARGETS	*Optimal target*: 100% of complications are prospectively recorded. *Minimum required target*: selected cases are discussed at morbidity and mortality conferences.
SCORING RULE	3 if the optimal target is met, 1 if the minimum required target is met.

5.10.2 Rationale

The absence of consensus within the surgical community on the way to report surgical complications has hampered proper evaluation of the surgeon's work and possibly progress in the surgical field. The therapy used to correct a specific complication remains the cornestone to rank a complication. Conclusive assessments of surgical procedures remained limited by the lack of consensus on how to define complications and to stratify them by severity. One previous initiative[53] published a QI for this topic.

The Clavien-Dindo classification[277,278], a proposed morbidity scale based on the therapeutic consequences of complications, consisted of 5 severity grades and focused on the medical perspectives, with a major emphasis on the risk and invasiveness of the therapy used to correct a complication:

- Grade I: any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are as follows: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside;
- Grade II: requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included;
- Grade III: requiring surgical, endoscopic or radiological intervention:
    - Grade IIIa: intervention not under general anesthesia;
    - Grade IIIb: intervention under general anesthesia.
- Grade IV: life-threatening complication including central nervous system complications brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks requiring intermediate care/intensive care unit management:
    - Grade IVa: single organ dysfunction including dialysis;

- Grade IVb: multiorgan dysfunction.

- Grade V: death of a patient;

- Suffix “d”: if the patient suffers from a complication at the time of discharge, the suffix “d” for “disability” is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication and the outcome and related long-term quality of life.

In 2013, Slankamenac *et al.*[279] developed a comprehensive complication index that takes into account all complications after a procedure and their respective severity. The development of this comprehensive complication index was based on the adapted Clavien-Dindo classification system. The complications were weighed with different severities by adopting an “operation risk index” approach.

The international development group considers that a widespread utilization of a simple, objective and reproducible approach for comprehensive surgical outcome assessment will lead to improve patients management. It should be easily applicable and usable by surgeons who are less experienced.

5.10.3 Summary of available scientific evidence

No directly applicable clinical studies have been identified.

6 Acronyms and abbreviations

ACPG Alberta clinical practice guidelines

AGDH Australian government department of health

AHRQ agency for healthcare research and quality

AQuAS agència de qualitat i avaluació sanitàries de Catalunya

ASCO American society of clinical oncology

BCCA British Columbia cancer agency

CA 125 cancer antigen 125

CADTH Canadian agency for drugs and technologies in health

CCO cancer care Ontario

CEA carcinoembryonic antigen

CEPO comité de l'évolution des pratiques en oncologie

CI confidence interval

CoCanCPG coordination of cancer clinical practice guidelines in Europe

COMPAQ-HPST coordination pour la mesure de la performance et l'amélioration de la qualité, hôpital, patient, sécurité, territoire

ESGO European society of gynaecological oncology

ESMO European society of medical oncology

GDT Goal Directed Therapy

GIN guidelines international network

GS general surgeon

GYN general gynecologist

GYO gynecologic oncologist

HAS haute autorité de santé

HR hazard ratio

HVC high-volume centres

ICCR international collaboration on cancer reporting

INAHTA international network of agencies for health technology assessment

INCa institut national du cancer

INESSS institut national d'excellence en santé et en services sociaux

IVC intermediate-volume centres

KCE centre fédéral d'expertise des soins de santé

LVC low-volume centres

MDT multidisciplinary team

MSAC medical services advisory committee

NA data not available

NCCN national comprehensive cancer network

NCI CCC national cancer institute comprehensive cancer center

NHMRC national health and medical research council

NHS national health service

NICE national institute for health and care excellence

NZGG New Zealand guidelines group

OB obstetrician

OR odd ratio

OS overall survival

PFS progression-free survival

QI quality indicator

RCT randomized controlled trial

RR relative risk

SIGN Scottish intercollegiate guidelines network

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8 Appendices

8.1 Appendix 1 - People involved in the production of the QIs

8.1.1 Appendix 1.1 - List of the international development group

Name	Specialty	Affiliation
Denis Querleu	Surgeon chair	Institut Bergonié, Bordeaux France
François Planchamp	Methodologist co -chair	Institut Bergonié, Bordeaux France
Giovanni Aletti	Gynecologic Oncologist	European Institute of Oncology, Milan Italy
Desmond Barton	Gynecologic Oncologist	Royal Mardsen Hospital, London United Kingdom
Silvestro Carinelli	Pathologist	European Institute of Oncology, Milan Italy
Luis Chiva	Gynecologic Oncologist	Anderson Cancer Center, Madrid Spain
David Cibula	Gynecologic Oncologist	Charles University Hospital, Prague Czech Republic
Karen Creutzberg	Radiation Oncologist	Leiden University Medical Center, Leiden Netherlands)
Ben Davidson	Pathologist	Norwegian Radium Hospital, Olso Norway
Andreas du Bois	Gynecologic Oncologist	Kliniken Essen-Mitte, Essen Germany
Christina Fotopoulou	Gynecologic Oncologist	Imperial College London, London United Kingdom
Philip Harter	Gynecologic Oncologist	Kliniken Essen-Mitte, Essen Germany
Eric Leblanc	Surgeon	Centre Oscar Lambret, Lille France
Lene Lundvall	Gynecologic Oncologist	Rigshospitalet, Copenhagen Denmark
Christian Marth	Gynecologic Oncologist	Innsbruck Medical University, Innsbruck Austria
Philippe Morice	Surgeon	Institut Gustave Roussy, Villejuif France
Sébastien Pierre	Anesthesiologist	Institut Universitaire du Cancer de Toulouse, Toulouse France
Arash Rafii	Clinical scientist	Weill Cornell Medical College in Qatar, Doha Qatar
Isabelle Ray-Coquard	Medical Oncologist	Centre Léon Bérard, Lyon France
Andrea Rockall	Radiologist	Imperial College London, London United Kingdom
Christiana Sessa	Medical Oncologist	Oncology Institute of Southern Switzerland, Bellinzona Swizerland
Ate van der Zee	Gynecologic Oncologist	University Medical Center, Groningen Netherlands)
Ignace Vergote	Gynecologic Oncologist	University Hospitals, Leuven Belgium

8.1.2 Appendix 1.2 - List of external panel of physicians and patientsinternational reviewers

Name	Physician/Patient	Country
Azra Abazari	Patient	Sweden
Lukas Angleitner Boubenizek	Gynecologic oncologist	Austria
Jana Barinoff	Gynecologic oncologist	Germany
Christer Borgfeldt	Gynecologic oncologist	Sweden
Tatjana Bozanovic	Gynecologist	Serbia
Line Bjørge	Gynecologist	Norway
Simon Alastair Butler-Manuel	Gynecologic oncologist	United Kingdom
Angelo Cagnacci	Gynecologist	Italy
Eduardo Cazorla Amoros	Gynecologist	Spain
Elisabeth Chereau	Gynecologic oncologist	France
Nicoletta Colombo	Gynecologic oncologist	Italy
Hannelore Denys	Medical oncologist	Belgium
Marcia Donziger	Patient	United States of America
Anna Fagotti	Gynecologic oncologist	Italy
Scott Fegan	Gynecologic oncologist	United Kingdom
Paz Ferrero	Patient	Spain
Anne Floquet	Medical oncologist	France
José Alberto Fonseca Moutinho	Gynecologic oncologist	Portugal
Michael Friedrich	Gynecologist	Germany
Laurence Gladieff	Medical oncologist	France
Mikel Gorostidi	Gynecologic oncologist	Spain
Andreas Guenthert	Gynecologic oncologist	Switzerland
Frederic Guyon	Gynecologic oncologist	France
Bjørn Hagen	Gynecologic oncologist	Norway
Dimitrios Haidopoulos	Gynecologic oncologist	Greece
Annette Hasenburg	Gynecologic oncologist	Germany
C. William Helm	Gynecologic oncologist	United Kingdom
Christoph Honegger	Gynecologic oncologist	Switzerland
Ahmet Cem Iyibozkurt	Gynecologic oncologist	Turkey
Ibon Jaunarena	Gynecologic oncologist	Spain

Name *continued*	**Physician/Patient**	**Country**
Rachel Jones	Medical oncologist	United Kingdom
Pascale Jubelin	Patient	France
Matias Jurado	Gynecologist	Spain
Päivi Kannisto	Gynecologic oncologist	Sweden
Sean Kehoe	Gynecologic oncologist	United Kingdom
Vesna Kesic	Gynecologic oncologist	Serbia
Preben Kjölhede	Gynecologic oncologist	Sweden
Petra Kohlberger	Gynecologic oncologist	Austria
Jacob Korach	Gynecologic oncologist	Israel
Gunnar Kristensen	Gynecologic oncologist	Norway
Maria Kyrgiou	Gynecologic oncologist	United Kingdom
Birthe Lemley	Patient	Denmark
Christianne Lok	Gynecologic oncologist	Netherlands
Tito Lopes	Gynecologic oncologist	United Kingdom
Domenica Lorusso	Gynecologic oncologist	Italy
Tiziano Maggino	Gynecologic oncologist	Italy
Sven Mahner	Gynecologic oncologist	Germany
Gemma Mancebo	Gynecologic oncologist	Spain
Frederik Marmé	Gynecologist	Germany
Leon Massuger	Gynecologic oncologist	Netherlands
Mohamed Mehasseb	Gynecologic oncologist	United Kingdom
Usha Menon	Gynecologic oncologist	United Kingdom
Lucas Minig	Gynecologic oncologist	Spain
Miloš Mlyn ek	Gynecologic oncologist	Slovakia
Ole Mogensen	Gynecologic oncologist	Denmark
Sara Morales Sierra	Gynecologist	Spain
Tim Mould	Gynecologic oncologist	United Kingdom
Hans Nijman	Gynecologic oncologist	Netherlands
Andrew Nordin	Gynecologic oncologist	United Kingdom
Ernst Oberlechner	Gynecologic oncologist	Germany
Maaike Oonk	Gynecologic oncologist	Netherlands

Name *continued*	**Physician/Patient**	**Country**
Peter Oppelt	Gynecologic oncologist	Austria
Maja Pakiž	Gynecologic oncologist	Slovenia
Janine Panier	Patient	France
Fedro Alessandro Peccatori	Medical oncologist	Italy
Jacobus Pfisterer	Gynecologic oncologist	Germany
Jurgen Piek	Gynecologic oncologist	Netherlands
Alexander Reinthaller	Gynecologic oncologist	Austria
Maria de los Reyes Oliver Perez	Gynecologist	Spain
Lukas Rob	Gynecologic oncologist	Czech Republic
Alexandros Rodolakis	Gynecologic oncologist	Greece
Henk W.R Schreuder	Gynecologic oncologist	Netherlands
Jalid Sehouli	Gynecologic oncologist	Germany
Philippe Simon	Gynecologic oncologist	Belgium
Piero Sismondi	Gynecologic oncologist	Italy
Špela Smrkolj	Gynecologic oncologist	Slovenia
Erik Soegaard-Andersen	Gynecologic oncologist	Denmark
Eva Maria Strömsholm	Patient	Finland
Sudha Sundar	Gynecologic oncologist	United Kingdom
Karl Tamussino	Gynecologic oncologist	Austria
Cagatay Taskiran	Gynecologic oncologist	Turkey
Ingrid Thranov	Gynecologic oncologist	Denmark
Catherine Transler	Patient	Germany
Dimitrios Tsolakidis	Gynecologist	Greece
Daiva Vaitkiene	Gynecologic oncologist	Lithuania
Eleonora van Dorst	Gynecologic oncologist	Netherlands
René Hewnricus Maria Verheijen	Gynecologic oncologist	Netherlands
Ingvild Vistad	Gynecologist	Norway
Pauline Wimberger	Gynecologic oncologist	Germany
Alain Zeimet	Gynecologic oncologist	Austria
Paolo Zola	Gynecologist	Italy
Cristina Zorrero	Gynecologic oncologist	Spain

8.2 Appendix 2 - List of evidence-based medicine websites consulted

Organism/agency	Website
ACPG	http://www.topalbertadoctors.org/home/
AGDH	http://www.health.gov.au/
AHRQ	http://www.guideline.gov/
AQuAS	http://aquas.gencat.cat/ca/
ASCO	http://www.asco.org/
BCCA	http://www.bccancer.bc.ca/default.htm
CADTH	http://www.cadth.ca/
CCO	https://www.cancercare.on.ca/
CEPO	http://www.msss.gouv.qc.ca/index.php
COMPAQ-HPST	http://www.compaqhpst.fr/fr/
CoCanCPG	http://www.cocancpg.eu/
ESMO	http://www.esmo.org/
GIN	http://www.g-i-n.net/
HAS	http://www.has-sante.fr/portail/jcms/fc_1249588/fr/accueil
INAHTA	http://www.inahta.org/
INESSS	http://www.inesss.qc.ca/
INCa	http://www.e-cancer.fr/
KCE	https://kce.fgov.be/fr
MSAC	http://www.msac.gov.au/
NCCN	http://www.nccn.org/
NHMRC	http://www.nhmrc.gov.au/
NHS	http://www.nhs.uk/Pages/HomePage.aspx
NICE	http://www.nice.org.uk/
NZGG	http://www.health.govt.nz/
SIGN	http://www.sign.ac.uk/

ACPG Alberta clinical practice guidelines, AGDH Australian government department of health, AHRQ agency for healthcare research and quality, AQuAS agència de qualitat i avaluació sanitàries de Catalunya, ASCO American society of clinical oncology, BCCA British Columbia cancer agency, CADTH Canadian agency for drugs and technologies in health, CCO cancer care Ontario, CEPO comité de l'évolution des pratiques en oncologie, CoCanCPG coordination of cancer clinical practice guidelines in Europe, COMPAQ-HPST coordination pour la mesure de la performance et l'amélioration de la qualité, hôpital, patient, sécurité, territoire, ESMO European society of medical oncology, GIN guidelines international network, HAS haute autorité de santé, INAHTA international network of agencies for health technology assessment, INCa institut national du cancer, INESSS institut national d'excellence en santé et en services sociaux, KCE centre fédéral d'expertise des soins de santé, MSAC medical services advisory committee, NCCN national comprehensive cancer network, NHMRC national health and medical research council, NHS national health service, NICE national institute for health and care excellence, NZGG New Zealand guidelines group, SIGN Scottish intercollegiate guidelines network.

8.3 Appendix 3 - Key to evidence statements[2]

1++ High quality meta-analyses, systematic reviews of randomized controlled trials RCTs, or RCTs with a very low risk of bias

1+ Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias

1- Meta-analyses, systematic reviews, or RCTs with a high risk of bias

2++ High quality systematic reviews of case control or cohort studies

High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2+ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal

2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal

3 Non-analytic studies, eg case reports, case series

4 Expert opinion

[2] http://www.sign.ac.uk/guidelines/fulltext/50/annexoldb.html

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