Notable surgical trials in gynecologic oncology: a 10-year overview

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ABSTRACT

In the last decade, we have witnessed important advances in novel therapeutics in the management of gynecologic cancers. These studies have built on the findings from preexisting data and have provided incremental contributions leading to changes that have not only impacted the accuracy of cancer detection and its metastatic components but also led to improvements in oncologic outcomes and quality of life. Key landmark trials have changed the standard of care in cervix, uterine, and ovarian cancer. A number of these have been controversial and have generated significant debate among gynecologic oncologists. The main objective of this review was to provide an overview on each of these trials as a reference for immediate and consolidated access to the study aims, methodology, results, and conclusion.

INTRODUCTION

During the last decade, several groundbreaking trials have redefined the standard of care in patients with gynecologic malignancies. These trials have not only challenged established policies but have also resulted in significantly improved outcomes. They have paved the way for a novel approach to the decision-making process for cancer patients. According to global cancer statistics for 2020, gynecological malignancies accounted for 16.5% of the estimated 8.2 million new cancer cases in women worldwide.[1] Over the past 10 years, there has been a significant transformation in this field, notably due to improved surgical techniques and innovative therapeutic approaches resulting in major advancements. The main objective of this review is to provide an overview of each of these trials. This was done for each disease site in chronological order. A systematic review of key prospective studies of gynecological surgical oncology over the last 10 years was performed. The articles were selected based on a search in Medline, EMBASE, Web of Science, and the Cochrane Clinical Trials Database (Table 1).

VULVAR CANCER

GROINSS-V I (2016)

In 2008, the GROINSS-V[2] study, a prospective international observational study, demonstrated that in patients with early-stage squamous cell vulvar cancer with negative sentinel lymph node, it was safe to omit an inguinofemoral lymphadenectomy. GROINSS-V I[3] evaluated long-term follow-up of patients who underwent sentinel lymph node mapping during the GROINS-V study period (2000–2006). A total of 377 patients with unifocal squamous cell carcinoma of the vulva (T1, <4 cm) were included (253 with negative sentinel node and 124 with positive sentinel node). In patients with positive sentinel nodes, inguinofemoral lymphadenectomy was performed. The median follow-up was 105 months. The 5- and 10 year recurrence rates for sentinel node-negative patients were 24.6% and 33.2% (p=0.03), respectively. For patients with positive sentinel nodes and lymphadenectomy, the recurrence rates were 36.4% and 46.4%, respectively (p=0.03). The rate of isolated groin recurrence was 2.3% for patients with negative sentinel node and 8.0% for patients with positive sentinel node after 5 years. Disease-specific 10 year survival was 91% for sentinel node-negative patients compared with 65% for sentinel node-positive patients (p=0.0001). Among the study limitations, the exact location of each local recurrence was not prospectively recorded and the treatment of local recurrences was at the discretion of the treating gynecologist.

The authors concluded that the omission of lymphadenectomy is safe in patients with unifocal vulvar squamous cell carcinoma tumors <4 cm without suspicious inguinofemoral lymph nodes on clinical examination and imaging, in whom a negative sentinel lymph node was detected.

GROINSS-V II (2021)

GROINSS-V II[4] was a prospective multicenter phase-II single-arm trial investigating inguinofemoral radiotherapy as an alternative to inguinofemoral lymphadenectomy in patients with vulvar cancer and metastatic sentinel lymph node. The study included patients with early-stage vulvar cancer (<4 cm) without signs of lymph node involvement on imaging who had primary surgical treatment (local excision with sentinel lymph biopsy). When the sentinel lymph was involved (metastasis of any size), inguinofemoral radiotherapy was given (50 Gy). Patients were divided into two groups: those with sentinel node micrometastases (≤2 mm) received treatment with inguinofemoral radiotherapy (126 patients), and those

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Table 1 Summary of articles reviewed

Trial	Aim	Stage	Number of patients and interventions	Results
Vulvar Cancer				
GROINSS-V I (2016)[3]	Evaluate safety of omitting an inguinofemoral lymphadenectomy	Early stage unifocal squamous cell carcinoma of the vulva (<4 cm)	253 negative sentinel node 124 positive sentinel node – lymphadenectomy	The omission of lymphadenectomy is safe in early-stage unifocal squamous cell carcinoma of the vulva (T1, <4 cm) with negative SLN.
GROINSS-V II (2021)[4]	Evaluate if inguinofemoral radiotherapy is an alternative to inguinofemoral lymphadenectomy	Early-stage vulvar cancer (<4 cm) and metastatic sentinel lymph node	126 with micrometastases (≤2 mm) inguinofemoral radiotherapy 105 macrometastases (>2 mm) -lymphadenectomy	Inguinofemoral radiotherapy is a safe alternative in patients with sentinel node micrometastases. In patients with macrometastasis, lymphadenectomy is recommended
Cervical Cancer				
LACC (2018)[6]	Compare disease-free survival between minimally invasive and open radical hysterectomy	Early-stage cervical cancer (FIGO 2009 IA1 with LVSI to IB1)	319 minimally invasive surgery (laparoscopic or robotic) 312 open surgery	Minimally invasive surgery was associated with lower rate of disease-free and overall survival
UTERUS 11 (2020)[10]	Evaluate pre-treatment surgical vs clinical staging	Locally advanced cervical cancer (FIGO 2009 stage IIB-IVA)	130 surgical staging 125 clinical staging	No difference in disease-free survival and overall survival between surgical and clinical staging (except for FIGO stage IIB)
CONCERV (2021)[11]	Evaluate feasibility of cone or simple hysterectomy and lymph node staging	Early-stage (FIGO 2009 stage IA2–IB1) and low-risk cervical cancer	42 conization 36 conization followed by hysterectomy 16 inadvertent simple hysterectomy	Conservative surgery was safe and feasible in patients with early-stage and low-risk cervical cancer
SHAPE (2023)[12]	Compare disease-free survival for radical vs simple hysterectomy	Low-risk cervical cancer (FIGO 2009 stage 1A2 or 1B1 with lesion ≤2 cm and <10 mm stromal invasion)	350 to radical hysterectomy 350 to simple hysterectomy	No difference in pelvic recurrence–free survival, extrapelvic recurrence–free survival, recurrence-free survival, or overall survival for simple hysterectomy
Endometrial Cancer				
LACE (2017)[13]	Compare open vs total laparoscopic hysterectomy	Stage I endometrial cancer	353 open hysterectomy 407 laparoscopic hysterectomy	Total open abdominal hysterectomy compared with total laparoscopic hysterectomy resulted in equivalent disease-free survival and no difference in overall survival and recurrence.
Sentinel Lymph Node Mapping				
FIRES (2017)[16]	Compare sensitivity and negative predictive value of sentinel lymph node mapping with complete lymphadenectomy in detecting metastatic disease	Stage I endometrial cancer	340 received injection of dye with indocyanine green, attempted sentinel lymph node mapping, and lymphadenectomy. 97% had at least one mapped sentinel lymph node	Sentinel lymph nodes identified with indocyanine green have a high degree of diagnostic accuracy in detecting endometrial cancer metastases and may safely replace lymphadenectomy
FILM (2018)[17]	Evaluate if indocyanine green is non-inferior to isosulfan blue dye in detecting sentinel lymph nodes.	Stage I endometrial or cervical cancer	87 blue dye-indocyanine green 89 indocyanine green–blue dye	Indocyanine green dye is superior to isosulfan blue dye in detecting sentinel lymph nodes
SHREC (2019)[18]	Evaluate indocyanine green algorithm for the detection of pelvic lymph node metastases	Stage I-II high-risk endometrial cancer (FIGO grade 3 endometrioid histology, non-endometrioid histology, >50% myometrial tumor invasion, cervical stromal invasion	257 pelvic sentinel lymph node biopsy with pelvic lymph node dissection, and infrarenal para-aortic lymph node dissection.	Pelvic sentinel lymph node algorithm with indocyanine green may safely replace lymphadenectomy in stage I-II high-risk endometrial cancer.

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Table 1 Continued

Trial	Aim	Stage	Number of patients and interventions	Results
SENTOR (2021)[19]	Evaluate sensitivity of the sentinel lymph node biopsy algorithm in detecting metastatic disease.	Stage I intermediate- and high-grade (FIGO grade 2 or 3 endometrioid, serous, carcinosarcoma, clear cell, undifferentiated or dedifferentiated, and mixed) endometrial cancer	156 sentinel lymph node and lymphadenectomy 101 (with high-grade) also para-aortic lymph node dissection	Sentinel lymph node biopsy is comparable in diagnostic accuracy and prognostic ability to lymphadenectomy in patients with intermediate- and high-grade endometrial carcinoma.
Ovarian Cancer				
NACT vs primary cytoreductive surgery				
CHORUS (2015)[20]	Compare primary surgery vs neoadjuvant chemotherapy with primary endpoint of overall survival.	Stage III or IV ovarian cancer	276 primary surgery 274 neoadjuvant chemotherapy	Primary chemotherapy is non-inferior to primary surgery in overall survival and progression-free survival
JCOG0602 (2020)[23]	Compare overall survival between primary surgery and neoadjuvant chemotherapy	Stage III or IV ovarian cancer	149 primary surgery 152 neoadjuvant chemotherapy	Compared with primary surgery a survival noninferiority of neoadjuvant chemotherapy was not confirmed.
SCORPION (2020)[24]	Investigate whether neoadjuvant chemotherapy followed by surgery is superior to primary debulking surgery and chemotherapy in terms of progression-free survival	Stage IIIC-IV ovarian cancer	84 primary surgery 87 neoadjuvant chemotherapy	No difference in overall and progression-free survival, with neoadjuvant chemotherapy and primary cytoreductive surgery in patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer (stage IIIC-IV)
OVHIPEC1 (2018)[25]	Determine whether hyperthermic intraperitoneal chemotherapy (HIPEC) at interval cytoreductive surgery after neoadjuvant chemotherapy improved recurrence-free survival and overall survival	Stage III epithelial ovarian cancer	123 surgery without HIPEC 122 surgery with HIPEC	HIPEC with interval cytoreductive surgery led to improved recurrence-free survival and overall survival compared with surgery alone
LION (2019)[31]	Assess efficacy of systematic pelvic and para-aortic lymphadenectomy in patients with advanced ovarian cancer and intra-abdominal complete debulking	Stage IIB-IV ovarian cancer	323 lymphadenectomy 324 non-lymphadenectomy	In patients with macroscopically complete resection and clinically negative lymph nodes, systematic pelvic and para-aortic lymphadenectomy was not associated with better overall survival and progression-free survival compared with no lymphadenectomy
Secondary cytoreduction				
GOG-213 (2019)[28]	Assess whether secondary cytoreduction would increase overall survival among women with platinum sensitive, recurrent ovarian cancer	Platinum-sensitive recurrent ovarian cancer with investigator-determined resectable disease	240 secondary cytoreduction plus chemotherapy 245 chemotherapy alone (84% received bevacizumab)	Secondary cytoreductive surgery followed by chemotherapy in patients with platinum-sensitive, recurrent ovarian cancer did not result in longer overall survival than chemotherapy alone
SOC-1 (2021)[29]	Assess the efficacy of secondary cytoreduction plus chemotherapy vs chemotherapy alone	Platinum-sensitive recurrent ovarian cancer with resectable disease according to iMODEL score and PET-CT	182 secondary cytoreduction plus chemotherapy 175 chemotherapy alone (1% received bevacizumab)	Secondary cytoreductive surgery follow by chemotherapy improved progression-free survival with acceptable morbidity compared with chemotherapy alone. No statistically significant difference in overall survival.

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Table 1 Continued

Trial	Aim	Stage	Number of patients and interventions	Results
DESKTOP III (2021)[30]	Compared overall survival in recurrent ovarian cancer patients who underwent surgery and chemotherapy vs chemotherapy alone	Platinum-sensitive recurrent ovarian cancer with resectable disease according to AGO score	206 secondary cytoreduction plus chemotherapy 201 chemotherapy alone (23.1% received bevacizumab)	Secondary cytoreductive surgery followed by chemotherapy resulted in longer overall survival than chemotherapy alone, especially in patients with complete resection.

AGO, Arbeitsgemeinschaft Gynaekologische Onkologie; FIGO, International Federation of Gynecology and Obstetrics; LVSI, Lymphovascular space invasion; PET-CT, Positron emission tomography-computed tomography; SLN, Sentinel lymph node.

with sentinel node macrometastases (>2 mm) underwent lymphadenectomy (105 patients).

In patients with sentinel node micrometastases, the ipsilateral isolated groin recurrence rate at 2 years was 1.6%. The isolated groin recurrence rate with sentinel node macrometastases at 2 years was 22% in those who underwent radiotherapy and 6.9% in those who underwent inguinofemoral lymphadenectomy (p=0.011). Lymphedema was less frequent in the radiotherapy group compared with inguinofemoral lymphadenectomy (11% vs 23% at 12 months, p<0.001). Regarding the limitations, no pretreatment quality control was conducted for radiotherapy design and planning, the use of concurrent chemotherapy for treatment was at the treating physician's discretion, and the protocol was modified during the study to exceed the recurrence rate in patients with sentinel node-positive macrometastases.

This study concluded that inguinofemoral radiotherapy is a safe alternative in patients with sentinel node micrometastases. However, in patients with macrometastasis, lymphadenectomy continues to be the recommended treatment. Based on these, the European Society of Gynaecological Oncology (ESGO) guidelines recommend that micrometastasis and isolated tumor cells can be treated with postoperative radiotherapy.[5]

CERVICAL CANCER

LACC (2018)

LACC[6] was aphase 3 multicenter noninferiority randomized trial designed to assess the rate of disease-free survival at 4.5 years comparing minimally invasive and open radical hysterectomy among patients with early-stage cervical cancer. The study population were patients with International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IA1 with lymphovascular invasion to IB1 cervical cancer and a histologic subtype of squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma.

A total of 319 patients were randomized to minimally invasive surgery (laparoscopic or robotic) and 312 patients to open surgery. The rate of disease-free survival at 4.5 years was 86.0% with minimally invasive surgery and 96.5% with open surgery, a difference of −10.6 percentage points (95% confidence interval (CI), −16.4 to −4.7). Minimally invasive surgery was associated with a lower rate of disease-free survival than open surgery (3 year rate, 91.2% vs 97.1%; HR for disease recurrence or death from cervical cancer, 3.74; 95% CI, 1.63 to 8.58, p=0.002) and was also associated with a lower rate of overall survival (3 year rate, 93.8% vs 99.0%), a higher rate of death from cervical cancer (3 year rate, 4.4% vs 0.6%) and a higher rate of locoregional recurrence-free survival (3 year rate, 94.3% vs 98.3%). The results of this trial cannot be generalized to patients with "low-risk" cervical cancer because the trial was not powered to evaluate the oncologic outcomes of the two surgical approaches in that context. In addition, the study was not designed to determine if there was a difference between the laparoscopic and robotic approaches.

Based on the results of the LACC trial, guidelines in gynecologic oncology (the European Society of Gynaecological Oncology (ESGO), European Society for Medical Oncology (ESMO), and the National Comprehensive Cancer Network (NCCN)[7–9] recommended the open abdominal approach for radical hysterectomy.

UTERUS 11 (2020)

UTERUS 11[10] was a prospective international multicenter study evaluating pre-treatment surgical staging vs clinical staging on disease-free survival in patients with locally advanced cervical cancer. The secondary endpoint was overall survival. The design included patients FIGO 2009 stage IIB-IVA, subtypes squamous cell carcinoma, adenocarcinoma, or adenosquamous who were randomized 1:1 to surgical or clinical staging followed by primary platinum-based chemoradiation. All patients underwent pre-treatment imaging, including abdominal CT and/or abdominal magnetic resonance imaging (MRI). A total of 255 patients (surgical arm, n=130; clinical arm, n=125) were randomized. After a median follow-up of 90 months, there was no difference between the groups in disease-free survival (p=0.084) and overall survival (p=0.071). It should be noted that positron emission tomography-computed tomography (PET-CT) was not used routinely in the preoperative workup due to lack of reimbursement, patients with stage IB2 (FIGO 2009) could not be included in the protocol and some patients included in the surgical staging arm showed macroscopic disease in the para-aortic region.

The authors concluded that in patients with locally advanced cervical cancer, there is no difference in disease-free survival and overall survival between surgical and clinical staging. However, a post-hoc analysis showed a benefit in disease-free survival for patients with FIGO stage IIB. Currently, PET-CT or chest/abdomen computed tomography (if PET-CT is not available) is recommended to assess nodal and distant disease.[7]

CONCERV (2021)

CONCERV[11] was a prospective, single-arm, multicenter study to evaluate the feasibility of conservative surgery in patients with early-stage (FIGO 2009 stage IA2–IB1), low-risk cervical cancer.

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The inclusion criteria were squamous cell (any grade) or adenocarcinoma (grade 1 or 2) histology; tumor size <2 cm; no lymphovascular space invasion; depth of invasion <10 mm; negative imaging for metastatic disease; and negative conization margins. Eligible patients desiring fertility preservation underwent a conization with pelvic lymph node assessment. Those not desiring fertility preservations underwent simple hysterectomy with lymph node assessment.

A total of 100 patients were included in the study. The median follow-up was 36.3 months. The rate of positive lymph nodes was 5%, and the rate of residual disease in the hysterectomy specimen following conization was 2.5%. The 2 year recurrence rate was 3.5% overall; 2.4% (1/42) among patients who had conization, 0% (0/36) among patients who had conization followed by hysterectomy, and 12.5% (2/16) among patients who had an inadvertent simple hysterectomy.

It is important to mention that lymph node evaluation and the choice of surgical approach was based on surgeon preference and training. The inclusion criteria were modified during the trial, prompted by three patients who developed recurrent disease, adding requirements for depth of invasion <10 mm and negative cone margins for high-grade dysplasia.

This study was the first of three (SHAPE[12] and GOG 278 NCT01649089) showing the feasibility and safety of conservative surgery in patients with early-stage (FIGO 2009 stage IA2–IB1) and low-risk cervical cancer.

SHAPE (2023)

SAPHE[12] was a phase 3, multicenter, noninferiority, randomized trial comparing radical hysterectomy with simple hysterectomy including lymph-node assessment in low-risk cervical cancer. Patients were eligible if they had squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma; FIGO 2009 stage 1A2 or 1B1 with lesion ≤2 cm and limited stromal invasion (<10 mm on LEEP/cone or <50% on preoperative MRI). The primary outcome was pelvic recurrence rate at 3 years. Secondary outcomes included pelvic recurrence-free survival, extrapelvic recurrence-free survival, recurrence-free survival, overall survival, adverse events, and quality of life.

A total of 700 patients underwent randomization, 350 to radical hysterectomy and 350 to simple hysterectomy. With a median follow-up of 4.5 years, the incidence of pelvic recurrence at 3 years was 2.2% in the radical hysterectomy group and 2.5% in the simple hysterectomy group (an absolute difference of 0.35 percentage points; 90% CI, −1.62 to 2.32). There was no apparent association between treatment group and pelvic recurrence–free survival, extrapelvic recurrence–free survival, recurrence-free survival, or overall survival. Radical hysterectomy was associated with a significantly higher incidence of urinary incontinence (p=0.003) and urinary retention (p=0.0001). Quality of life scores showed a significant difference between the two groups in favor of simple hysterectomy. The trial was designed before the results of the LACC trial and was not designed to determine the safety of the surgical approach (minimally invasive vs open) in this very low-risk population. In addition, the surgical approach was chosen by the surgeons.

Based on these findings, simple hysterectomy is not inferior to radical hysterectomy in patients with low-risk cervical cancer (FIGO 2009 stage 1A2 or 1B1 with lesion ≤2 cm and limited stromal invasion). Fewer urinary tract complications, better quality of life, and sexual-function were observed with simple hysterectomy.

ENDOMETRIAL CANCER

LACE (2017)

LACE [13] was a was a multinational, phase 3, randomized equivalence trial. Patients with clinical stage I endometrial cancer were randomized to undergo open abdominal hysterectomy (with or without lymphadenectomy) or total laparoscopic hysterectomy (with or without lymphadenectomy). The primary outcome was disease-free survival. Secondary outcomes included disease recurrence, patterns of recurrence, and overall survival. Patients were followed for a median of 4.5 years.

Of 760 randomized patients (353 to open abdominal hysterectomy and 407 to laparoscopic hysterectomy), 679 (89%) completed the trial. The disease-free survival was 81.3% in the open abdominal hysterectomy group and 81.6% in the total laparoscopic hysterectomy group (difference: 0.3% [95% CI, −5.5% to 6.1%], favoring total laparoscopic hysterectomy, p=0.007). There were no statistically significant differences between groups in terms of recurrence (difference: 0.2% [95% CI, −3.7% to 4.0%]; p=0.93) or overall survival (difference: 0.6% [95% CI, −3.0% to 4.2%]; p=0.76).

Some weaknesses of the study were that the randomization was performed before the patient was scheduled for surgery. Moreover, performance of pelvic and aortic retroperitoneal node dissection was left to the discretion of the surgeons. Otherwise, the study only included patients with endometrial tumors with endometroid histology.

The authors concluded that total open abdominal hysterectomy compared with total laparoscopic hysterectomy in stage I endometrial cancer resulted in equivalent disease-free survival and no difference in overall survival and recurrence. This study supported those of the previously published landmark study (GOG-LAP2),[14] confirming the standard being laparoscopic hysterectomy for patients with stage I endometrial cancer.[15]

Sentinel lymph node mapping

FIRES (2017)

FIRES[16] was a multicenter, prospective cohort study comparing the sensitivity and negative predictive value of sentinel lymph node mapping with complete lymphadenectomy in detecting metastatic disease for endometrial cancer.

A total of 385 patients with clinical stage I endometrial cancer of all histologic subtypes and grades undergoing robotic staging were included. Of those, 340 patients received injection of dye with indocyanine green, attempted sentinel lymph node mapping, and lymphadenectomy. Of these, 41 (12%) patients had positive nodes. Nodal metastases were identified in the sentinel lymph nodes of 35/36 (97%) patients who had at least one mapped sentinel lymph node, yielding a sensitivity to detect node-positive disease of 97.2% (95% CI 85 to 100). Twenty-one (60%) of 35 patients with positive sentinel lymph nodes had disease limited to the sentinel lymph nodes, and 14 (40%) patients had additional positive nodes in their nonsentinel lymph node specimens. Among the 258 patients with negative sentinel lymph nodes, 257 had truly negative nonsentinel lymph nodes, resulting in a negative predictive value of 99.6%

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(95% CI 97.9 to 100). Some limitations of the study were that only 28% of patients had high-grade histologic subtypes, the study was unable to determine morbidity or oncological outcomes, and performing para-aortic lymphadenectomy was at the discretion of each surgeon.

Based on this study, sentinel lymph nodes identified with indocyanine green have a high degree of diagnostic accuracy in detecting endometrial cancer metastases and may safely replace lymphadenectomy in the staging of endometrial cancer. Although sentinel lymph node biopsy did not identify metastases in 3% of patients with node-positive disease, it may expose fewer patients to the morbidity of a complete lymphadenectomy.

FILM (2018)

FILM[17] was a international, multicentre, randomized, open-label, phase 3, non-inferiority study. A total of 180 patients with clinical stage I endometrial or cervical cancer undergoing surgery were randomized 1:1 to lymphatic mapping with isosulfan blue dye (visualized by white light) followed by indocyanine green (visualized by near-infrared imaging) or indocyanine green followed by isosulfan blue dye, of whom 176 patients received the intervention and were evaluable. In total, 169 (96%) of 176 patients had uterine cancer, and seven (4%) had cervical cancer. The primary endpoint was the efficacy of intraoperative indocyanine green with near-infrared fluorescence imaging vs that of blue dye in identifying lymph nodes.

In total, 471 (97%) of 485 lymph nodes were identified with the green dye and 226 (47%) with the blue dye (difference 50%, 95% CI 39 to 62; p<0.0001). The rate of detection of at least one sentinel node showed a difference of 22% (95% CI 17 to 32; p<0.0001), and the rate of bilateral sentinel nodes detection showed a difference of 49% (41–57; p<0.0001) in favor of green dye. Only 16 (9%) of 176 patients had metastatic disease in 21 sentinel nodes; 13 (62%) detected both blue and green, and eight (38%) only with green. No allergic reactions or adverse events were attributable to either isosulfan blue dye or indocyanine green. Among the weaknesses of the study were the inability to determine sensitivity, negative predictive value, and oncologic outcomes for lymphatic mapping and sentinel node biopsy.

The authors concluded that indocyanine green is superior to isosulfan blue dye in detecting sentinel lymph nodes. The use of indocyanine green dye and isosulfan blue together was unnecessary because adding isosulfan blue dye to indocyanine green was not shown to identify more nodes beyond those identified with indocyanine green alone. Based on these findings, the US Food and Drug Administration (FDA) approved the use of green dye in lymphatic mapping in gynecologic oncology.

SHREC (2019)

SHREC[18] was a prospective non-randomized trial evaluating the diagnostic accuracy of a surgically and anatomically defined sentinel lymph node indocyanine green algorithm and overall sentinel lymph node algorithm for the detection of pelvic lymph node metastases in women with high-risk endometrial cancer. A total of 257 patients with stage I-II high-risk endometrial cancer (FIGO grade 3 endometrioid histology, non-endometrioid histology, >50% myometrial tumor invasion, cervical stromal invasion or, until February 14, 2017, a non-diploid cytometry) were assessed for eligibility. Patients underwent robotic hysterectomy, pelvic sentinel lymph node biopsy with pelvic lymph node dissection, and infrarenal para-aortic lymph node dissection.

Fifty-four patients (21%) of 257 had pelvic lymph node metastases, and 52 (20%) were correctly identified by the sentinel lymph node indocyanine green algorithm. This had a sensitivity to identify pelvic lymph node metastases of 98% (95% CI 89 to 100) and a negative predictive value of 99.5% (95% CI 97 to 100). The corresponding values for the sentinel lymph node overall algorithm were 100% (95% CI 92 to 100) and 100% (95% CI 98 to 100). Before and after reinjection, the bilateral mapping rate was 82% and 95%, respectively. The para-aortic lymph node dissection was performed in 208 (81%) patients, and only two (1%) patients had isolated para-aortic metastases. No adverse events occurred during the sentinel lymph node procedure. It should be noted that only 49% of patients had high-grade histologic subtypes and that algorithm should, in the author's opinion, be performed at high-volume centers by high-volume surgeons.

The authors concluded that pelvic sentinel lymph node algorithm may safely replace lymphadenectomy in stage I-II high-risk endometrial cancer without the need for para-aortic dissection. The pelvic sentinel lymph node algorithm is supported by a lower rate of isolated para-aortic metastases (1%).

SENTOR (2021)

SENTOR[19] was a prospective, multicenter cohort study to evaluate the sensitivity of the sentinel lymph node biopsy algorithm in patients with intermediate- and high-grade (FIGO stage I, grade 2 or 3 endometrioid, serous, carcinosarcoma, clear cell, undifferentiated or dedifferentiated, and mixed) endometrial cancer. Only 28% in the FIRES[16] trial and 49% in the SHREC[18] trial had high-grade histologic subtypes. The primary endpoint was the sensitivity of the sentinel lymph node biopsy algorithm in detecting metastatic disease.

Patients received a standard algorithm for sentinel lymph node and then underwent the reference standard of lymphadenectomy; grade 2 endometrioid endometrial cancer required bilateral pelvic lymph node dissection, and high-grade endometrial cancer required bilateral pelvic lymph node dissection and para-aortic lymph node dissection. Patients with grade 2 endometrioid endometrial cancer underwent para-aortic lymph node dissection only when a sentinel lymph node mapped to the para-aortic region or when the surgeon deemed it necessary.

Sentinel lymph node detection rates were 97.4% per patient (95% CI, 93.6% to 99.3%), 87.5% per hemipelvis (95% CI, 83.3% to 91.0%), and 77.6% bilaterally (95% CI, 70.2% to 83.8%). Of 27 patients (17%) with nodal metastases, 26 patients were correctly identified by the sentinel lymph node biopsy algorithm, yielding a sensitivity of 96% (95% CI, 81% to 100%), a false-negative rate of 4% (95% CI, 0% to 19%), and a negative predictive value of 99% (95% CI, 96% to 100%). Only one patient (0.6%) was misclassified by the sentinel lymph node biopsy algorithm. Fourteen patients with node-positive disease (52%) had metastatic disease in sentinel lymph nodes only, and seven cases (26%) were found outside lymphadenectomy boundaries or required immunohistochemistry for diagnosis. These patients would not have been identified by pelvic lymph node dissection and para-aortic lymph node dissection alone. The estimates of diagnostic accuracy may not be generalizable to less experienced surgeons and centers, to sentinel lymph node biopsy with different types of tracers, or to patients

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in whom pelvic lymph node dissection or para-aortic lymph node dissection may not be feasible.

The study concluded that sentinel lymph node biopsy is comparable in diagnostic accuracy and prognostic ability to lymphadenectomy in patients with intermediate- and high-grade endometrial carcinoma.

OVARIAN CANCER

Neoadjuvant therapy vs primary cytoreductive surgery

CHORUS (2015)

CHORUS[20] was a phase 3, non-inferiority, randomized, controlled trial comparing primary chemotherapy followed by delayed surgery vs surgical debulking followed by chemotherapy in patients with suspected stage III or IV ovarian cancer. The primary outcome measure was overall survival. Inclusion criteria were patients with clinical or imaging evidence of a pelvic mass with extrapelvic disease compatible with FIGO 1988 stage III or IV ovarian, fallopian tube, or primary peritoneal cancer who were candidates for surgery and chemotherapy. Of the 550 eligible patients, 276 were assigned to primary surgery and 274 to primary chemotherapy.

Median overall survival was 22.6 months in the primary surgery group vs 24.1 months in primary chemotherapy. The HR for death was 0.87 in favor of primary chemotherapy (with the upper bound of the one-sided 90% CI 0.98 [95% CI 0.72 to 1.05]). Progression-free survival was similarly in favor of the primary chemotherapy group, with medians of 12.0 months vs 10.7 months for the primary surgery group. The HR for progression-free survival was 0.91 (95% CI 0.76 to 1.09). The primary surgery group had more grade 3 or 4 adverse events than the primary chemotherapy group (60 [24%] vs 30 [14%], p=0.007). Additionally, there were more postoperative deaths in the primary surgery group within 28 days than in the primary chemotherapy group (14/255 patients [6%] vs 1/219 patients [<1%], p=0.001). It is important to mention that 59% of patients had suboptimal primary surgery, moreover, the rate of complete resection was low in both groups.

This study was the second prospective trial (after EORTC 55971[21] to investigate the timing of surgery in the first-line treatment of advanced ovarian cancer. These two trials confirmed that in patients with stage III or IV ovarian cancer, primary chemotherapy is non-inferior to primary surgery, and surgical morbidity and mortality were significantly reduced.[22]

JCOG0602 (2020)

JCOG602[23] was a open-label phase III noninferiority randomized trial designed to compare primary debulking surgery and neoadjuvant chemotherapy in patients with stage III/IV ovarian, tubal, and peritoneal cancers with overall survival as the primary objective. A total of 301 patients were randomized, with 149 undergoing primary debulking surgery and 152 receiving neoadjuvant chemotherapy. The median overall survival was 49.0 months in primary debulking surgery and 44.3 months in neoadjuvant chemotherapy (HR of neoadjuvant chemotherapy compared with primary surgery was 1.05 [95% CI 0.84 to 1.33], p=0.24). The median progression-free survival was 15.1 months in the primary debulking surgery and 16.4 in the neoadjuvant chemotherapy (HR: 0.96 [95% CI 0.75 to 1.23]). Among the study limitations, the protocol did not require histological confirmation, and the sample size was smaller than in previous studies. Complete resection was achieved in only 12% of patients in the primary surgery group and in 64% of patients in the neoadjuvant group.

This study is the third (EORTC 55971[21] and CHORUS[20] to assess the role of neoadjuvant therapy for stage III/IV ovarian, tubal, and peritoneal cancers. The study authors did not confirm the noninferiority of neoadjuvant chemotherapy and suggested that it may not always be a substitute for primary debulking surgery.

SCORPION (2020)

SCORPION[24] was a open-label, randomized phase III trial designed to investigate whether neoadjuvant chemotherapy followed by interval debulking surgery was superior to primary debulking surgery in terms of perioperative complications and progression-free survival in advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer. The study included patients with FIGO stage IIIC-IV with high tumor load assessed by a standardized laparoscopic predictive index, (ECOG) performance status 0–2, and chemotherapy naïve.

A total of 171 patients were randomly 1:1 assigned to primary debulking surgery (n=84) vs neoadjuvant chemotherapy, followed by interval debulking surgery and adjuvant chemotherapy (n=87). Complete resection rates (R0) were 47.6% in the surgery arm vs 77.0% in the neoadjuvant arm (p=0.001). In total, 53 major postoperative complications were registered, 25.9% in the surgery arm vs 7.6% in the neoadjuvant arm (p=0.0001). With an overall median follow-up of 59 months, the median progression-free and overall survival were 15 and 41 months for patients assigned to primary debulking surgery, compared with 14 and 43 months for patients assigned to neoadjuvant chemotherapy, respectively (HR 1.05, 95% CI 0.77 to 1.44, p=0.73; HR 1.12, 95% CI 0.76 to 1.65, p=0.56). It should be noted that the sample size was smaller than in previous studies, BRCA status was not recorded, some patients received treatment with bevacizumab once the trial started, and some patients received four cycles of neoadjuvant chemotherapy.

This is the fourth study (EORTC 55971,[21] CHORUS,[20] and JCOG0602[23] to assess this topic and the third (EORTC 55971[21] and CHORUS[20] to show no difference in overall and progression-free survival, with neoadjuvant chemotherapy and primary cytoreductive surgery in patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer (stage IIIC-IV).

Hyperthermic intraperitoneal chemotherapy (HIPEC)

OVHIPEC1 (2018)

OVHIPEC1[25] was a multicenter, open-label, phase 3 trial to determine whether hyperthermic intraperitoneal chemotherapy (HIPEC) at interval cytoreductive surgery after neoadjuvant chemotherapy improved recurrence-free survival and overall survival in patients with stage III epithelial ovarian cancer. Disease recurrence or death occurred in 110 of 123 patients (89%) who underwent cytoreductive surgery without HIPEC (surgery group) and in 99 of 122 patients (81%) who underwent cytoreductive surgery with HIPEC (surgery-plus-HIPEC group) (HR for disease recurrence or death, 0.66 [95% CI 0.50 to 0.87] p=0.003). Adverse events (grade 3 or 4) were similar in the two groups (25% in the surgery group and 27% in the surgery-plus-HIPEC group, p=0.76). No differences were

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found between the two groups in health-related quality of life. The trial did not take into account certain factors such as BRCA status, FIGO tumor sub-stage III, response, or histological tumor type. The rates of progression-free survival and overall survival with HIPEC were similar to the rates among patients with interval debulking without HIPEC.

In patients with stage III epithelial ovarian cancer, HIPEC with interval cytoreductive surgery led to greater recurrence-free survival and overall survival compared with surgery alone, without increased incidence of side effects. The NCCN guidelines suggest that HIPEC can be considered during interval surgery on patients with stage III disease after neoadjuvant chemotherapy. However, at the ESGO-ESMO-ESP consensus conference, experts failed to reach a consensus, highlighting the current divergence of opinions.[26 27]

Lymph node

LION (2019)

LION[26] was a randomized controlled trial investigating systematic lymphadenectomy in patients with primary ovarian cancer (FIGO stage IIB through IV) who underwent complete macroscopic resection and had normal lymph nodes both before and during surgery. The primary outcome was overall survival.

Patients were randomized to either lymphadenectomy (pelvic and para-aortic) or no lymphadenectomy. A total of 627 patients were included, 323 in the lymphadenectomy group and 324 in the non-lymphadenectomy group. The median overall survival was 69.2 months in the no-lymphadenectomy group and 65.5 months in the lymphadenectomy group (HR for death in the lymphadenectomy group, 1.06 [95% CI 0.83 to 1.34; p=0.65]), and median progression-free survival was 25.5 months in both groups (HR for progression or death in the lymphadenectomy group, 1.11 [95% CI, 0.92 to 1.34] p=0.29). Postoperative complications occurred more frequently in the lymphadenectomy group. Repeat laparotomy was 12.4% in the lymphadenectomy group compared with 6.5% in the non-lymphadenectomy group (p=0.01), while mortality within 60 days was 3.1% vs 0.9% (p=0.049), respectively.

Some limitations of this study need to be considered: the low average number of patients per center, a selection bias as only patients with preserved performance status and radiologically negative lymph nodes were included and lack of information on prognostic factors in advanced ovarian cancer. Finally, the definition of a clinically negative lymph node was imprecise, as there may not always be a clear size difference between metastatic and non-metastatic nodes.

The authors concluded that in patients with macroscopically complete resection of advanced ovarian cancer and clinically negative lymph nodes, systematic pelvic and para-aortic lymphadenectomy is not associated with better outcomes compared with no lymphadenectomy and was associated with a higher incidence of postoperative complications.

Secondary cytoreduction

GOG-213 (2019)

GOG-213[28] was an open-label, phase 3, multicenter, international, randomized clinical trial designed to assess two clinically relevant hypotheses: that bevacizumab added to paclitaxel and carboplatin chemotherapy followed by maintenance bevacizumab improved overall survival (chemotherapy objective) and that secondary surgical cytoreduction in platinum-sensitive, surgically amenable patients improved overall survival (surgical objective).

The study included patients with recurrent ovarian cancer who had received one previous therapy, had a platinum-free interval of 6 months or more, had investigator-determined resectable disease to undergo secondary surgical cytoreduction, and then received platinum-based chemotherapy or received platinum-based chemotherapy alone. Adjuvant chemotherapy (paclitaxel-carboplatin or gemcitabine-carboplatin) and use of bevacizumab were at the discretion of the investigator.

A total of 485 patients were included. Of these, 240 patients were randomized to secondary cytoreduction before chemotherapy and 245 to chemotherapy alone. The median follow-up was 48.1 months. The median overall survival was 50.6 months for surgery and 64.7 months for no surgery (HR death for surgery vs no surgery was 1.29 [95% CI 0.97 to 1.72] p=0.08). Adjustments for platinum-free interval and chemotherapy choice did not alter the effect. The HR for disease progression or death (surgery vs no surgery) was 0.82 (95% CI, 0.66 to 1.01: median progression-free survival, 18.9 months and 16.2 months, respectively).

It should be noted that the study had no defined patient eligibility criteria for surgery, there was a lack of data on the extent of residual disease after primary debulking surgery and it remains unclear how many patients from the non-surgical group crossed over and received surgery later.

The authors concluded that secondary cytoreductive surgery followed by chemotherapy in patients with platinum-sensitive, recurrent ovarian cancer did not result in longer overall survival than chemotherapy alone.

SOC-1 (2021)

SOC-1[29] was a multicentre, open-label, randomized, controlled, phase 3 trial to assess the efficacy of secondary cytoreduction plus chemotherapy vs chemotherapy alone in patients with platinum-sensitive relapsed ovarian cancer. The primary endpoints were progression-free survival and overall survival. Patients aged 18 years and older with a platinum-free interval of at least 6 months and potentially resectable disease according to the international model (iMODEL) score and PET-CT imaging were eligible. An iMODEL score of 4.7 or lower predicted a potentially complete resection. In total, 357 patients were recruited and randomly assigned to the surgery group (182) or the no-surgery group (175). The median follow-up was 36.0 months.

Median progression-free survival was 17.4 months (95% CI 15.0 to 19.8) in the surgery group and 11.9 months (10.0–13.8) in the no-surgery group (HR 0.58 [95% CI 0.45 to 0.74] p<0.0001). A prespecified interim overall survival analysis showed no statistically significant difference between both groups. Median overall survival was 58.1 months (95% CI not estimable) in the surgery group and 53.9 months (42.2–65.5) in the no-surgery group (HR 0.82 [95% CI 0.57 to 1.19]). It is important to mention that only 1% of patients received bevacizumab and 37% of patients in the no-surgery group crossed over to surgery at subsequent relapse.

Secondary cytoreduction followed by chemotherapy improved progression-free survival with acceptable morbidity compared with chemotherapy alone for patients with platinum-sensitive, relapsed ovarian cancer selected using iMODEL scores and PET-CT imaging.

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DESKTOP III (2021)

Desktop III[30] was a multicenter prospectively randomized trial to assess the role of secondary cytoreductive surgery in patients with recurrent ovarian cancer. The primary outcome was overall survival. The inclusion criteria were patients with relapsed histologically diagnosed, clinically defined as a lesion that is palpable or visible on ultrasonographic imaging, or relapsed disease radiologically diagnosed at least 6 months after the previous course of initial platinum-based chemotherapy (platinum-sensitive disease) and a positive Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) score.

In total, 407 participants were randomly assigned to either chemotherapy alone (n=201) or cytoreductive surgery and chemotherapy (n=206). Of those who underwent surgery, 75.5% achieved a complete resection. Median overall survival was 53.7 months for the surgery group and 46.0 months for the no-surgery group (HR for death, 0.75 [95% CI, 0.59 to 0.96] p=0.02). However, among the patients assigned to the surgery group, those who achieved a complete resection had a median overall survival of 61.9 months. Quality of life measures through 1 year of follow-up did not differ between the two groups. Among the study limitations only 23.1% of patients received bevacizumab, there were different distributions of histological subtypes in both arms, the percentage of complete cytoreduction was higher than that published in other studies and the survival benefit was only observed in those patients in whom R0 was achieved.

The authors concluded that in patients with recurrent ovarian cancer, secondary cytoreductive surgery followed by chemotherapy resulted in longer overall survival than chemotherapy, especially in those patients in whom complete resection surgery was achieved.

CONCLUSION

Over the past 10 years we have witnessed significant advances in the treatment of vulvar, cervical, endometrial, and ovarian tumors. The emergence of techniques such as sentinel lymph node sampling, the decreased emphasis on radicality in the treatment of cervical cancer, and the incorporation of neoadjuvant therapy for ovarian cancer are evidence of this shift. Our ultimate objective remains to offer patients the best possible outcomes in terms of survival and disease-free survival with the lowest possible morbidity. Our field is moving toward less radical procedures with improved perioperative outcomes. Similarly, it is essential for future prospects, that treatments are tailored to patients' characteristics, fertility preferences and resources. Future advances in imaging technologies, including 3D models and artificial intelligence, will likely expand our capabilities toward more targeted surgical options.

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