Tropical Journal of Obstetrics & Gynaecology
ISSN-Print: 0189-5117
Online: 2543-148X
Official Publication of Society of Obstetrics & Gynaecology of Nigeria

Review Article

Challenges and Prospects of Neoadjuvant Chemotherapy for Gynaecologic Malignancies in Resource-Limited Settings: A Review Article

Oluwasola, Timothy A. Olusesan

Gynaecologic Oncology Unit, Department of Obstetrics and Gynaecology, University College Hospital, Ibadan; and College of Medicine, University of Ibadan

Correspondence Author
Dr Timothy A.O Oluwasola,
Department of Obstetrics & Gynaecology,
College of Medicine,
University of Ibadan,
Telephone - +2348033384064
E-MAIL:
taoluwasola@com.ui.edu.ng
; ta.oluwasola@ui.edu.ng

ABSTRACT

Administration of chemotherapeutic agents followed by interval debulking surgery has been reported to be non-inferior to primary debulking surgery (PDS) and adjuvant chemotherapy. Limitation of human and nonhuman facilities for optimal surgical intervention makes Neoadjuvant chemotherapy (NACT) a desirable alternative in resource-limited settings. NACT is gradually becoming an acceptable alternative in centers with limited facilities for comprehensive PDS. Moreover, some recent studies have described NACT as being non-inferior to the gold standard of PDS although it is important to note that strict patient selection remains an important criterion and serve as the hallmark for the success of NACT. This review aimed to explore the essence of NACT for gynecological malignancies, its challenges as well as prospects for resource–limited settings.

Keywords – Adjuvant, Adjunctive, Chemotherapy, Neoadjuvant, Resource-Limited Setting

INTRODUCTION

Neoadjuvant chemotherapy, (NACT), was first described in 1982 by Frei when it was found useful in the treatment of head and neck cancers especially when patients presented with inoperable tumors.[1] Among these patients, surgery tend to be inadequate, leaving large residual disease and limiting chances of survival in comparison with most early stage tumors in which surgery was the initial treatment of choice and complete resection was achievable with minimal morbidities.[2–5] Therefore, NACT has been described as chemical cytoreduction of chemo-sensitive tumors

which are done before any significant attempt is made at surgical reduction of such tumors.[6]

In most developing countries, late presentation remains a major challenge to successful management of most gynecologic malignancies as patients often present in the advanced stage of the disease and, at times, can only be offered symptomatic treatment.[7] Traditionally, post-surgical adjuvant therapies have included chemotherapy and/or radiotherapy depending on the tumor biology. The latter was best for large, unresectable but responsive tumors or resectable tumors with potential high surgical morbidities. [8–10] Moreover, the primary chemotherapy could be curative or palliative and may serve as radiosensitizer while also helping to significantly improve symptoms' control in chemo-sensitive tumors.[11] However, in resource-limited settings, the most appropriate option of care most often depends on available treatment options and expertise.[10]

Optimal Debulking Versus Neoadjuvant Treatment

The concept of maximal or optimal debulking has varied from that in which the largest residual tumor after surgery has diameter of less than 2cm to that of no residual tumor. This approach to cytoreduction which requires leaving no residual tumor in any form has been described as 'complete' or 'R0' surgery. [2,12–16] Factors contributing to the eventual outcome of optimum debulking surgery include surgical skills, training, experience, infrastructure, and tumor biology as well as disease burden in terms of stage, spread, size and site. [2,14]. NACT followed by surgery has helped to demonstrate improved perioperative outcomes in form of optimal cytoreduction, decreased blood loss, and reduced length of hospital stay.[6] On the other hand, pre-operative poor performance status of the patients resulting from poor nutritional and immunological status, anemia, hypoalbuminemia, late presentation, histopathology of the tumor, age as well as presence of co-morbid conditions such as obesity among others have contributed negatively to the overall outcome of the patients.[10,17]

In a comparative examination of the cost effectiveness of NACT and primary debulking surgery (PDS), a recent US economic–simulated study reported that, in the short term, NACT was associated with huge savings in cost and was associated with over a thousand fewer cancer-related deaths.[18] The authors also reported gain in the quality-adjusted life-years (QALY) for about 1715 simulated patients thereby making NACT an important treatment strategy for all outcomes with an overall conclusion, following sensitivity analysis, that NACT is cost-saving while offering improved outcomes.[18] This is in tandem with a similar reports by both Rowland et al and Forde et al in 2015.[19,20]

Currently, in most resource-limited settings, the management of gynecological cancers depends on the stage at presentation and extent of disease, available expertise, tumor biology including type and grade, presence or absence of co-morbidities and availability of funds. Available options of care include chemotherapy, surgery, radiotherapy, and immunotherapy depending on the tumor biology as most often, combination therapy involving two or more of these options are advocated although a multidisciplinary approach is highly recommended in current treatment strategies. However, the different forms of cancer management vis-à-vis surgery, systemic medications, radiation therapy or palliative care have always been expensive and inaccessible. [1,10,12,21–23]

NACT often involves the administration of three to four cycles of specific, tumor–sensitive chemotherapy followed by surgery – interval debulking surgery (IDS) midway and subsequent completion of the remaining cycles of chemotherapy after the surgery.[24] Operative morbidities are reduced with lower blood loss, less need for intensive care and/or prolonged post-operative hospital stay as well as reduction in post-operative infections – these are the attributes that make NACT an alternative of interest for resource–limited settings.

Forms of Chemotherapy

These include adjuvant, adjunctive and neoadjuvant forms of chemotherapy.[25] Adjuvant chemotherapy involves administration of cytotoxic drugs to patients after complete resection of the tumor to treat micrometastasis unlike adjunctive chemotherapy in which drugs are administered when there is incomplete tumor resection. However, in neoadjuvant chemotherapy, cytotoxic drugs are administered before surgery to shrink or downstage the tumor thus making resectability less difficult and less radical thereby improving local control and survival.

There are several documented advantages of NACT and reasons for its preference to PDS.[2,5,11–13,19,26–29,30–32] These include the fact that: (i) NACT

may decrease tumor bulk and extent of spread such that optimum cytoreduction becomes more feasible; (ii) NACT may improve patient's performance status and quality of life[3]; (iii) PDS often requires hospital admission while NACT can be administered in an outpatient setting without much delay; (iv) PDS may delay the commencement of adjuvant chemotherapy because of the potential of chemotherapy to interfere with wound healing although preoperative laparoscopic assessment has been reported to circumvent this where feasible[33]; and (v) when surgery is not curative, it is believed that residual cancer cells may multiply while the patient awaits recovery from surgery before the commencement of chemotherapy.[13] Although the last point is expected to be an advantage for chemo-sensitive tumors, it may end up being counterproductive in settings where patients have aversion for chemotherapy.

Approach to Neoadjuvant Chemotherapy

Strict patient selection is of great importance in adopting NACT and this should be adhered to in all cases to achieve optimal result. Prior to commencing NACT, the gold standard globally is to have core biopsy of the primary tumor or one of the metastatic sites to establish tissue diagnosis. However, in some cases like ovarian cancers, transvaginal ultrasound-guided biopsy or fine-needle aspirate for cytology in addition to serum CA-125/CEA ratio greater than 25 have been considered as acceptable alternatives – options of which are available in some resource-limited settings.[8,11,13,31,34] In settings with advanced radiological facilities and expertise, radiological staging is currently preferred to surgical staging in order to reduce tumor spread when taking biopsy.[35]

NACT followed by IDS will serve as an important alternative in centers with limited facilities for comprehensive PDS. Moreover, some recent studies have described NACT as being non-inferior to the gold standard of PDS.[5,8,13,27,31] It is important to re-emphasize that the success of NACT however begins with good patient selection.[15,26] In a recent Cochrane review, the authors reported no difference in overall survival, OS (1521 women; HR 1.06; 95% CI = 0.94 to 1.19) and progression-free survival, PFS (1631 women; HR 1.02; 95% CI 0.92 to 1.13) when patients with NACT followed by IDS were compared to those who had PDS followed by chemotherapy [13]. In the same review, it was reported that NACT may reduce the risk of serious adverse events, especially those around the time of surgery such as need for bowel resection and stoma formation.[13] Compared to PDS, available data from the same review by Coleridge et al[13] also suggested that NACT has the potential to lower the risk of: (i) additional need for blood transfusion (risk ratio (RR) 0.80; 95% CI 0.64 to 0.99; low certainty evidence); (ii) venous thromboembolism (RR 0.28; 95% CI 0.09 to 0.90; low-certainty evidence); (iii) infection (RR 0.30; 95% CI 0.16 to 0.56; moderate-certainty evidence); (iv) the need for stoma formation (RR 0.43, 95% CI 0.26 to 0.72; moderate-certainty evidence); and (v) bowel resection (RR 0.49, 95% CI 0.26 to 0.92).

Concerns About Using Neoadjuvant Chemotherapy

There have been several concerns about NACT, and these include (i) an apparent delay in the time taken before the removal of the tumor which may compromise the woman's survival and prognosis of the disease. This implies that in patients without any response to chemotherapy, administration of NACT risks delaying appropriate treatment[36]; (ii) risk of chemotherapy-induced fibrosis which may eventually lead to incomplete cytoreduction at surgery; (iii) the possibility of NACT to effectively shrink cancer deposits but leave microscopic diseases that will evade conventional surgical removal although laparoscopic and robotic surgeries have been adopted to reduce the impact of this concern in high income countries[37]; and (iv) the possibility of postoperative chemo-resistance if too many cycles of NACT are administered preoperatively although one meta-analysis has reported a negative association between overall survival and the number of NACT cycles administered;[30] and (v) unlike NACT, PDS tend to have the advantage of reducing the tumor bulk as well as the number of cancer cells, thereby enhancing the drugs' penetration of the tumor cells and reducing the risk of developing chemo-resistance.

Neoadjuvant Chemotherapy in Specific Gynecologic Cancers

Cervical Cancers:

One major motivation for applying NACT in the treatment of cervical cancer was to reduce tumor bulk so as to facilitate surgical resection.[38] Moreover, NACT has contributed significantly to tumor shrinkage and down-staging of initially inoperable cervical cancers to lower, operable stage.[38–41] Although some studies have failed to establish significant impact on survival following NACT compared to surgery alone especially among early stage cancers,[39,42,43] Iwata et al (2016) and Rydzewska et al (2012) among other studies have demonstrated some advantages of NACT, in carefully selected patients, such as reduction in risk factors for lymph node metastasis, vascular invasion, improvement in cure rate, safety and improvement in down-staging of tumors as well as suppression of remote metastasis.[10,25,38,44–47] Significant improvement on overall survival and disease free survival periods have also been documented.[43,48,49] Although there exists few areas of controversies in terms of patient selection, determination of cervical bulkiness and types/dosage of chemotherapy combination, both NACT and chemoradiotherapy methods have been described as reasonable treatment modalities for improving the quality of life (QoL) of patients with cervical cancer before surgery.[23,45,50–52] A recent systematic review and metaanalysis of 6 retrospective studies and one randomized controlled trial (RCT) favoured combined chemoradiotherapy over NACT followed by surgery but this is feasible where the required facilities are fully available.[53]

Ovarian, Fallopian Tube and Peritoneal Cancers:

The use of NACT is mostly studied among patients with ovarian malignancies as they often present with advanced-stage tumor when optimal cytoreduction is feasible in less than 40%.[2,3,8,12–15,28–32,54–56] Documented advantages of the NACT approach include a risk reduction of perioperative morbidity and a higher rate of optimal resection than PDS.[36] However, it is noted that the possibility of attaining complete cytoreduction depends on several factors like the spread of the disease, the molecular features of the tumor, its microenvironment and the skills of the gynecologic oncology surgeon.[12] Variables often associated with increased likelihood of NACT use included age above 50 years, presence of additional co-morbidities, advanced-stage of disease at presentation, and higher-grade epithelial ovarian cancer as available evidences suggested that these patients potentially have greater risk for adverse events but tend to do better when they receive NACT instead of PDS.[57,58] In justifying the importance of carefully selecting suitable patients, positron emission tomography, magnetic resonance imaging and/or computed tomography have been used, in additional to the outlined clinical criteria, for patients' selection and assessment of tumor resectability with satisfactory response in centers with such facilities.[33,35,59]

Meanwhile, the possibilities of chemo-resistance have remained the main concern [60] although results from a Cochrane review claimed NACT is non-inferior to PDS.[13] Additionally, NACT offers a potential for an improved QoL for the patient[13] although another recent but limited systematic review and metaanalysis of three RCTs and 2 observational studies reported no clinically important difference in the QoL of patients undergoing either PDS or NACT.[61] Moreover, clinical outcomes of patients with complete cytoreduction were reported to be significantly better for PDS group compared to the NACT followed by IDS group. This implied that surgical achievement of no gross residual disease has different prognostic relevance for the two types of treatment modalities and should be the target of the surgeons. [12,62–64]

Corpus Uterine Cancers:

Most patients with endometrial cancer present in early stage and are cured with surgical intervention alone. Chemotherapy is however offered as the main treatment modality in advanced disease stage which occurs in about 10–15% of all newly diagnosed cases.[36] Meanwhile, adjuvant treatment recommendations for uterine cancers remain controversial and complicated as there are relatively few treatment options for metastatic diseases. Trials in cancers which are associated with older age and with obesity, have been challenged by worsening co-morbidities and cytotoxicity.[65] Patients' selection is critical among this category of people because of the different types, classes and grades of uterine cancers which subsequently impact on response and survival. According to de Lange et al (2019), NACT followed by IDS is a suitable non-inferior treatment strategy for patients with advanced endometrial cancer who are considered unsuitable for PDS regardless of histopathologic subtype.[66] This buttressed an earlier report, by Vandenput et al (2009), that NACT

followed by interval cytoreductive surgery was a reasonable option for endometrial cancers with transperitoneal spread.[67]

Vulvar Cancers:

The location of these cancers as well as the mode and time of presentation makes primary surgical approach to be preferred. However, the treatment approach of locally advanced vulvar cancer has significantly changed in the last few decades sequel to the recent advances in new drugs and chemotherapy development. It has gone from a primarily surgical management, based on major procedures in the past, to a more individualized management aimed at a better control of the disease, reduced toxicity, and improved quality of life for patients.[68,69] The use NACT involving Paclitaxel and Cisplatin with or without ifosfamide followed by surgery has been documented to be a viable therapeutic option for locally advanced vulvar cancers and associated with improved QoL.[1,23,70]

The argument against PDS for vulvar cancers remains that the extent and site of resection often predispose the patients to worse morbidities,[36,71] hence the preference for NACT in order to achieve some degree of debulking and avoid the morbidity from such extensive surgery.[36] Moreover, NACT is useful for preservation of sexual function and the anal sphincters in younger patients.[72] In a report by Raspagliesi et al (2014), the presence of positive margins after NACT and surgery as well as local recurrences, even in patients with negative margins seem detrimental. They therefore posited that additional studies are necessary to help in establishing the categories of patients who will benefit more from either of NACT plus surgery or chemo-radiotherapy, while considering the patients' QoL and available surgical expertise in resource-limited settings.[70] Patients with unresectable tumors are expected to be managed with appropriate chemotherapy alone.[71]

Vaginal Cancers: There are very few studies on the management of these cancers probably due to their rarity or rather because patients tend to present earlier and the management is often definitive with surgical interventions.[73] In separate case series by Benedetti Panici et al (2008) and Diao et al, (2017), the authors concluded that NACT followed by radical surgery is a feasible therapeutic strategy with good short and long-term results.[74,75] Vaginal reconstruction with excellent outcome has been achieved in a young patient following NACT.[76]

Challenges of Adopting Neoadjuvant Chemotherapy in Low Resource Settings:

Generally, challenges of cancer care are myriad and multifaceted presenting as limited availability and accessibility of facilities for diagnosis and optimum management, limited number of competent health care practitioners, affordability of care as well as regulatory and cultural barriers.[7,21,77] Worse still, the challenges for adopting NACT in low resource settings are equally numerous but quite surmountable and they include the following:

i. *Biopsies for Tissue Diagnosis:* This is probably the most common challenge for the institution of NACT in resource-limited setting. However, as earlier discussed, FNAC, serum CA125/CEA ratio and ascitic fluid cytology can be reasonably employed in conjunction with radiological staging of inaccessible tumors especially if suspected to be ovarian in origin.
ii. *Consent:* Most patients would rather have immediate relief from their current complaints than add the side effects of chemotherapy to the challenges. Detailed counseling and strict criteria for patient selection are both key to solving this challenge. There are cultural beliefs that chemotherapy is meant to kill the patient faster rather than treat her disease condition thereby contributing to refusal of the patient and her relatives to give consent for chemotherapy. Incorporation of survivors and palliative care practitioners into the counselling team will have great impact in establishing the right and appropriate information for the patients' comprehension.
iii. *Funds:* Most patients in developing countries pay out of pocket for cancer care and this poses a limitation or restriction to optimal care as majority are unable to gather the total cost required for care at once. Unfortunately, they occasionally mislead the healthcare providers into commencing treatment before stating that funds have been exhausted thereby creating unnecessary gaps in timing either for administration of chemotherapeutic agent or in the surgical intervention. It is always good to have an estimated total cost of care and explain the essence to both the patient and her relatives

before commencing treatment. In settings where payment for care is taken off the patients, acceptance of chemotherapy were hinged on factors such as documented success rate and convenience of treatment, agreeing with the need for the treatment, trust in the physician's recommendation while factors that lead to refusal of cancer treatment included fear of side effects, concerns about the discomfort of the treatments and, occasionally, transportation difficulties.[78]

iv. *Multidisciplinary Tumor (MDT) Boards***:** The role of the radiologists, cytopathologists and histopathologists cannot be overemphasized in ensuring definitive diagnosis and in taking decisions for optimal care. So also, are the oncology nurses, medical oncologists, and other members of the cancer care team. These members are expected to meet regularly to review patients care and plan for further interventions based on available evidence from patients' response which can be adapted from using a reproducible validated tool – the chemotherapy response score. [78–83] Lack of MDT boards in many centers is primarily due to lack of trained personnel in the specific areas of need while the available few hands are overstretched.[84]

v. *Blood Transfusion Services:* The subsequent hematological needs of patients on chemotherapy warrant accessibility to functional hematologic and blood bank services. Prompt correction of hematologic derangements have significant role to play in the eventual outcome of the patient.

vi. *Facilities for Minimal Access Surgeries:* Lack of facilities as well as competent surgeons in the field of minimal access surgeries for gynecological cancers have contributed immensely to the limits/extent of tumor debulking. [33,85] However, with appropriate use of NACT for relevant, well-selected, chemo-sensitive cases, tumor bulk is reduced while surgical planes expectedly become better highlighted for a skilled surgeon to achieve much impact.

vii. *Newer drugs***:** Occasionally, newer drugs are introduced into the cancer care world with the expectation that it will be better in some ways than the current ones. Unfortunately, these are associated with 2 major problems which include cost [21] as well as non-inclusion of people in the resource-limited settings in the clinical trial validating such drugs.[86] It is hoped that documentation of experiences in all centers in the resource-limited settings will further support the agitation for inclusion in global clinical trials for newer drugs.

viii. *Follow up:* Follow up of patients is a major challenge especially when they have experienced some relief. Some patients often claim they are now well while some will claim lack of funds especially for follow up investigations. Detailed explanation of the disease state as well as the goal of treatment will help in motivating the patients to complete their treatment.

Prospects of Neoadjuvant Chemotherapy in Resource-Limited Settings:

Despite the several challenges, there are potential prospects for adopting NACT in resource-limited settings and these include:

1. ***Better outcome for patients with advanced disease****:* The overall survival and disease progression free period are marginally better in the local environment compared to PDS probably due to limitation of surgical skills among the practitioners. This is particularly important as there are more practitioners in the developing countries who primarily trained as gynecologists but practice gynecologic oncology simply out of interest compared to those practitioners who trained fully as Gynecologic oncologists.[84] However, availability of validated chemotherapy response scoring system makes it easy for the multidisciplinary team to review patients' progress and make appropriate evidence-based decision. [78–83,87]
2. ***Improved Quality of Life***: With reduction in tumor mass and ascites following NACT, there is a great improvement in the overall QoL for these patients. Post operatively, they tend to have less morbidity and can resume further chemotherapy within the shortest possible time.
3. ***Involvement in Clinical Trials*****:** The adoption of NACT can provide leverage for participation in organized clinical trials that further benefit both the patients and the society. It has become imperative for

pharmaceutical companies and global clinical trial researchers to consider the potential differential responses of people in developing countries to newer drugs and to accommodate them in subsequent research activities. [86]

4. ***International collaborations*:** Adoption of NACT will further enable international collaborations because of standardization of care and practice. In addition, it will help to reduce the bias often introduced by limited surgical facilities and put all patients on similar baseline for reporting, monitoring and for follow up. Increased collaboration between low income and high-income countries will significantly contribute to overcome most problems encountered in cancer care in the resource-limited settings as well as open new research frontiers, network and opportunities in the low-income countries which currently carry much of the global cancer burden.[77]

CONCLUSION:

The limitation of required surgical facilities particularly makes NACT a choice alternative for managing selected patients with gynecologic malignancies. The decision to institute NACT followed by surgery should be based upon clinical findings, radiologic findings, presence, or absence of co-morbidities as well as availability of expertise. All patients with gynecologic cancers should be managed by a multidisciplinary team as tumor board decisions are essential parts of comprehensive cancer care. In patients undergoing PDS, efforts should be made to leave no visible residual tumor and then followed by adjuvant treatment as appropriate. However, those patients who are planned for NACT, after careful selection, should receive three to four cycles of appropriate chemotherapy followed by IDS and later followed by additional cycles of chemotherapy to complete the required regimen.

Adoption of NACT for management of gynecologic malignancies in resource-limited settings has the potential to positively influence the narratives of management outcomes for the patients. Further documentation of experiences from various centers in these settings will help in facilitating a properly conducted metaanalysis and thus contribute scientific evidence to current global practices.

REFERENCES

1. Restivo A, Gordinier M, Granai CO. New treatment concepts for gynecologic pelvic malignancies: Neoadjuvant therapies. Surg Oncol Clin N Am. 2005;14(2):239–47.
2. Yang L, Zhang B, Xing G, Du J, Yang B, Yuan Q, et al. Neoadjuvant chemotherapy versus primary debulking surgery in advanced epithelial ovarian cancer: A meta-analysis of peri-operative outcome. PLoS One. 2017;12(10):1–15.
3. Cowan R, Chi D, Kehoe S, Nankivell M, Leary A. Primary surgery or neoadjuvant chemotherapy in advanced ovarian cancer: The Debate Continues…. Am Soc Clin Oncol Educ B. 2016;36:153–62.
4. Lopresti ML, Bandera CA, Miner TJ. New approaches to improving survival after neoadjuvant chemotherapy: the role of intraperitoneal therapy and heated intraperitoneal chemotherapy in ovarian cancer. Am Soc Clin Oncol Educ B. 2019;(39):19–23.
5. Vergote I, Coens C, Nankivell M, Kristensen GB, Parmar MKB, Ehlen T, et al. Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials. Lancet Oncol. 2018;19(12):1680–7.
6. Singh JC, Tiersten A. Neoadjuvant chemotherapy in ovarian cancer. In: Bathe O, editor. Neoadjuvant Chemotherapy - Current

Applications in Clinical Practice. InTechOpen; www.intechopen.com; 2012. p. 73–80.
7. Oluwasola TAO, Oladewa AC. Challenges of gynaecological cancer care in Nigeria – a review article. African J Med Med Sci. 2018;47:227–37.
8. Van Meurs HS, Tajik P, Hof MHP, Vergote I, Kenter GG, Mol BWJ, et al. Which patients benefit most from primary surgery or neoadjuvant chemotherapy in stage IIIC or IV ovarian cancer? An exploratory analysis of the European Organisation for Research and Treatment of Cancer 55971 randomised trial. Eur J Cancer. 2013;49(15):3191–201.
9. Kristeleit RS, Miller RE, Kohn EC. Gynecologic Cancers: Emerging novel strategies for targeting DNA repair deficiency. Am Soc Clin Oncol Educ B. 2016;36:e259–68.
10. Kumar L, Pramanik R, Kumar S, Bhatla N, Malik S. Neoadjuvant chemotherapy in gynaecological cancers - Implications for staging. Best Pract Res Clin Obstet Gynaecol 2015;29(6):790–801.
11. Vergote I, Du Bois A, Amant F, Heitz F, Leunen K, Harter P. Neoadjuvant chemotherapy in advanced ovarian cancer: On what do we agree and disagree? Gynecol Oncol. 2013;128(1):6–11.
12. Kobal B, Noventa M, Cvjeticanin B, Barbic M, Meglic L, Herzog M, et al. Primary debulking surgery versus primary neoadjuvant chemotherapy for high grade advanced stage ovarian cancer: Comparison of survivals. Radiol Oncol. 2018;52(3):307–19.
13. Coleridge SL, Bryant A, Lyons TJ, Goodall RJ, Kehoe S, Morrison J. Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer. Cochrane Database Syst Rev. 2019;(10):Art. No.: CD005343.
14. Naito Y, Miura Y, Takano T. Neoadjuvant chemotherapy or primary surgery in advanced ovarian cancer. N Engl J Med. 2010;363(24):2371.
15. Park TW, Kuhn WC. Neoadjuvant chemotheraphy in ovarian cancer. Expert Rev Anticancer Ther. 2004;4(4):639–47.
16. Meyer LA, Cronin AM, Sun CC, Bixel K, Bookman MA, Cristea MC, et al. Use and effectiveness of neoadjuvant chemotherapy for treatment of ovarian cancer. J Clin Oncol. 2016;34(32):3854–63.
17. Schwartz PE. Contemporary considerations for neoadjuvant chemotherapy in primary ovarian cancer. Curr Oncol Rep. 2009;11(6):457–65.
18. Cole AL, Barber EL, Gogate A, Tran AQ, Wheeler SB. Economic analysis of neoadjuvant chemotherapy versus primary debulking surgery for advanced epithelial ovarian cancer using an aggressive surgical paradigm. Int J Gynecol Cancer. 2018;28(6):1077–84.
19. Forde GK, Chang J, Ziogas A, Tewari K, Bristow RE. Costs of treatment for elderly women with advanced ovarian cancer in a Medicare population. Gynecol Oncol. 2015;137(3):479–84.
20. Rowland MR, Lesnock JL, Farris C, Kelley JL, Krivak TC. Cost-utility Comparison of neoadjuvant chemotherapy versus primary debulking surgery for treatment of advanced-stage ovarian cancer in patients 65 years old or older. Am J Obstet Gynecol. 2015;212(6):763.e1-8.
21. Ruff P, Al-sukhun S, Blanchard C, Shulman LN. Access to cancer therapeutics in low- and middle-income countries. In: American Society of Clinical Oncology Educational Book. Chicago: ASCO Educational Books; 2016. p. 58–65.
22. Kosty MP, Pickard T, Viale P. Collaborative practice in an era of multidisciplinary care. Am Soc Clin Oncol Educ B. 2016;36:3–8.
23. Reed NS, Sadozye AH. Update on chemotherapy in gynaecological cancers. Obstet Gynaecol. 2016;18(3):182–8.
24. Vanderpuye VD, Scott PA, Ayettey-Anie H. Principles of Radiotherapy and Chemotherapy in Gynaecology Cancers. In: Kwawukume EY, Ekele BA, Danso KA, Emuveyan EE, editors. Comprehensive Gynaecology in the Tropics. Kwa. Accra: G-Pak Limited; 2017. p. 521–42.

25. Klufio CA, Konney TO. Epithelial Ovarian Cancer. In: Kwawukume EY, Ekele BA, Danso KA, Emuveyan EE, editors. Comprehensive Gynaecology in the Tropics. 2nd ed. Accra: G-Pak Limited; 2017. p. 605–34.
26. Mahner S, Trillsch F, Chi D, Harter P, Pfisterer J, Hilpert F, et al. Neoadjuvant chemotherapy in ovarian cancer revisited. Ann Oncol. 2016;27(Supplement 1):i30–2.
27. Onda T, Satoh T, Saito T, Kasamatsu T, Nakanishi T, Nakamura K, et al. Comparison of treatment invasiveness between upfront debulking surgery versus interval debulking surgery following neoadjuvant chemotherapy for stage III/IV ovarian, tubal, and peritoneal cancers in a phase III randomised trial: Japan Clinical Oncology Gr. Eur J Cancer. 2016;64(April):22–31.
28. Duska LR, Tew WP, Moore KN. Epithelial ovarian cancer in older women: Defining the best management approach. Am Soc Clin Oncol Educ B. 2015;35:e311–21.
29. Fagotti A, Ferrandina G, Vizzielli G, Fanfani F, Gallotta V, Chiantera V, et al. Phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): Final analysis of peri-operative outcome. Eur J Cancer [Internet]. 2016;59:22–33.
30. Bristow RE, Chi DS. Platinum-based neoadjuvant chemotherapy and interval surgical cytoreduction for advanced ovarian cancer: A meta-analysis. Gynecol Oncol. 2006;103(3):1070–6.
31. Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): An open-label, randomised, controlled, non-inferiority trial. Lancet. 2015;386(9990):249–57.
32. Yoneoka Y, Ishikawa M, Uehara T, Shimizu H, Uno M, Murakami T, et al. Treatment strategies for patients with advanced ovarian cancer undergoing neoadjuvant chemotherapy: interval debulking surgery or additional chemotherapy? J Gynecol Oncol. 2019;30(5):e81.
33. Bland AE, Everett EN, Pastore LM, Andersen WA, Taylor PT. Predictors of suboptimal surgical cytoreduction in women with advanced epithelial ovarian cancer treated with initial chemotherapy. Int J Gynecol Cancer. 2008;18(4):629–36.
34. Kong TW, Chang SJ, Paek J, Cho H, Lee Y, Lee EJ, et al. Transvaginal Sonography-guided core biopsy of adnexal masses as a useful diagnostic alternative replacing cytologic examination or laparoscopy in advanced ovarian cancer patients. Int J Gynecol Cancer. 2016;26(6):1041–7.
35. Roze JF, Hoogendam JP, van de Wetering F t, Spijker R, Verleye L, Vlayen J, et al. Positron emission tomography (PET) and magnetic resonance imaging (MRI) for assessing tumour resectability in advanced epithelial ovarian/fallopian tube/primary peritoneal cancer. Cochrane Database Syst Rev. 2018;(10):Art No CD012567.
36. Suprasert P. Neoadjuvant Chemotherapy in Gynecologic Cancers. In: Oliver Bathe, editor. Neoadjuvant Chemotherapy – Current Applications in Clinical Practice. InTechOpen; www.intechopen.com; 2012. p. 59–72.
37. Van De Vrie R, Rutten MJ, Asseler JD, Leeflang MM, Kenter GG, Mol BWJ, et al. Laparoscopy for diagnosing resectability of disease in women with advanced ovarian cancer. Cochrane Database Syst Rev. 2019;(3):Art. No.: CD009786.
38. Eiriksson L, Miroshnichenko G, Covens A. Neoadjuvant chemotherapy in treatment of cervical cancer. In: Bathe O, editor. Neoadjuvant Chemotherapy – Current Applications in Clinical Practice. InTechOpen; www.intechopen.com; 2012. p. 81–108.
39. Zhao H, He Y, Yang SL, Zhao Q, Wu YM. Neoadjuvant chemotherapy with radical surgery vs radical surgery alone for cervical cancer: A systematic review and meta-analysis. Onco Targets Ther. 2019;12:1881–91.

40. Zhao H, He Y, Zhu LR, Wang JL, Guo HY, Xu T, et al. Effect of neoadjuvant chemotherapy followed by radical surgery for FIGO stage IB2/IIA2 cervical cancer: A multi-center retrospective clinical study. Medicine (Baltimore). 2019;98(21):e15604.
41. Akl FM, Akl MF, Befky B, Gaballah K, Gadelhak B. Neoadjuvant Chemotherapy Followed by Radical Surgery. Clin Oncol. 2018;3:1523.
42. Yan W, Si L, Ding Y, Qiu S, Zhang Q, Liu L. Neoadjuvant chemotherapy does not improve the prognosis and lymph node metastasis rate of locally advanced cervical squamous cell carcinoma: A retrospective cohort study in China. Medicine 2019;98(39):e17234.
43. Gong L, Zhang JW, Yin RT, Wang P, Liu H, Zheng Y, et al. Safety and efficacy of neoadjuvant chemotherapy followed by radical surgery versus radical surgery alone in locally advanced cervical cancer patients. Int J Gynecol Cancer. 2016;26(4):722–8.
44. Iwata T, Miyauchi A, Suga Y, Nishio H, Nakamura M, Ohno A, et al. Neoadjuvant chemotherapy for locally advanced cervical cancer. Chinese J Cancer Res. 2016;28(2):235–40.
45. Lapresa M, Parma G, Portuesi R, Colombo N. Neoadjuvant chemotherapy in cervical cancer: An update. Expert Rev Anticancer Ther. 2015;15(10):1171–81.
46. Chuang LT, Temin S, Camacho R, Feldman S, Gultekin M, Gupta V, et al. Management and Care of Women With Invasive Cervical Cancer : American Society of Clinical Oncology Resource-Stratified Clinical Practice Guideline. J Glob Oncol. 2016;2(5):311–40.
47. Rydzewska L, Tierney J, Vale CL, Symonds PR. Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer. Cochrane Database Syst Rev. 2012;(12):Art. No.: CD007406.
48. Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med. 1999;340(15):1154–61.
49. De Azevedo CRAS, Thuler LCS, De Mello MJG, Ferreira CG. Neoadjuvant chemotherapy followed by chemoradiation in cervical carcinoma: A review. Int J Gynecol Cancer. 2016;26(4):729–36.
50. Gupta S, Maheshwari A, Parab P, Mahantshetty U, Hawaldar R, Sastri S, et al. Neoadjuvant chemotherapy followed by radical surgery versus concomitant chemotherapy and radiotherapy in patients with stage IB2, IIA, or IIB squamous cervical cancer: a randomized controlled trial. J Clin Oncol. 2018;36(16):1548–55.
51. Mandić A. Neoadjuvant chemotherapy in treatment of cervical cancer - Controversies. Arch Oncol. 2005;13(2):89–90.
52. Shirali E, Yarandi F, Behtash N, Hemmatian O. Neoadjuvant chemotherapy in cervical cancer: a review article. J Obstet Gynecol Cancer Res. 2018;3(2):87–91.
53. Zou W, Han Y, Zhang Y, Hu C, Feng Y, Zhang H, et al. Neoadjuvant chemotherapy plus surgery versus concurrent chemoradiotherapy in stage IB2-IIB cervical cancer: A systematic review and meta-analysis. PLoS One. 2019;14(11):1–13.
54. Fujiwara K, McAlpine JN, Lheureux S, Matsumura N, Oza AM. Paradigm Shift in the Management Strategy for Epithelial Ovarian Cancer. Am Soc Clin Oncol Educ B. 2016;36:e247–57.
55. Vergote IB, Van Nieuwenhuysen E, Vanderstichele A. How to select neoadjuvant chemotherapy or primary debulking surgery in patients with stage IIIC or IV ovarian carcinoma. J Clin Oncol. 2016;34(32):3827–8.
56. Wright AA, Bohlke K, Armstrong DK, Bookman MA, Cliby WA, Coleman RL, et al. Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. Gynecol Oncol. 2016;143(1):3–15.

57. Leiserowitz GS, Lin JF, Tergas AI, Cliby WA, Bristow RE. Factors predicting use of neoadjuvant chemotherapy compared with primary debulking surgery in advanced stage ovarian cancer - A national cancer database study. Int J Gynecol Cancer. 2017;27(4):675–83.
58. Markauskas A, Mogensen O, Christensen RDP, Jensen PT. Primary surgery or interval debulking for advanced epithelial ovarian cancer: Does it matter? Int J Gynecol Cancer. 2014;24(8):1420–8.
59. Risum S, Loft A, Engelholm SA, Høgdall E, Berthelsen AK, Nedergaard L, et al. Positron emission tomography/computed tomography predictors of overall survival in stage IIIC/IV ovarian cancer. Int J Gynecol Cancer. 2012;22(7):1163–9.
60. Luo Y, Lee M, Kim HS, Chung HH, Song YS. Effect of neoadjuvant chemotherapy on platinum resistance in stage IIIC and IV epithelial ovarian cancer. Medicine 2016;95(36):e4797.
61. Kumar S, Long J, Kehoe S, Sundar S, Cummins C. Quality of life outcomes following surgery for advanced ovarian cancer: A systematic review and meta-analysis. Int J Gynecol Cancer. 2019;29(8):1285–91.
62. Gadducci A, Cosio S, Zizioli V, Notaro S, Tana R, Panattoni A, et al. Patterns of recurrence and clinical outcome of patients with stage IIIC to Stage IV Epithelial Ovarian Cancer in complete response after primary debulking surgery plus chemotherapy or neoadjuvant chemotherapy followed by interval debulking surgery: An Ita. Int J Gynecol Cancer. 2017;27(1):28–36.
63. Gao Y, Li Y, Zhang C, Han J, Liang H, Zhang K, et al. Evaluating the benefits of neoadjuvant chemotherapy for advanced epithelial ovarian cancer: a retrospective study. J Ovarian Res. 2019;12(1):85.
64. May T, Comeau R, Sun P, Kotsopoulos J, Narod SA, Rosen B, et al. A Comparison of survival outcomes in advanced serous ovarian cancer patients treated with primary debulking surgery versus neoadjuvant chemotherapy. Int J Gynecol Cancer. 2017;27(4):668–74.
65. Brooks RA, Fleming GF, Lastra RR, Lee NK, Moroney JW, Son CH, et al. Current recommendations and recent progress in endometrial cancer. CA Cancer J Clin. 2019;258–79.
66. de Lange NM, Ezendam NPM, Kwon JS, Vandenput I, Mirchandani D, Amant F, et al. Neoadjuvant chemotherapy followed by surgery for advanced-stage endometrial cancer. Curr Oncol. 2019;26(2):e226–32.
67. Vandenput I, Van Calster B, Capoen A, Leunen K, Berteloot P, Neven P, et al. Neoadjuvant chemotherapy followed by interval debulking surgery in patients with serous endometrial cancer with transperitoneal spread (stage IV): A new preferred treatment. Br J Cancer. 2009;101(2):244–9.
68. Martinez-Castro P, Poveda A, Guinot JL, Minig L. Treatment of Inoperable Vulvar Cancer: Where We Come from and Where Are We Going. Int J Gynecol Cancer. 2016;26(9):1694–8.
69. Aragona AM, Cuneo N, Soderini AH, Alcoba E, Greco A, Reyes C, et al. Tailoring the treatment of locally advanced squamous cell carcinoma of the vulva: Neoadjuvant chemotherapy followed by radical surgery: Results from a multicenter study. Int J Gynecol Cancer. 2012;22(7):1258–63.
70. Raspagliesi F, Zanaboni F, Martinelli F, Scasso S, Laufer J, Ditto A. Role of paclitaxel and cisplatin as the neoadjuvant treatment for locally advanced squamous cell carcinoma of the vulva. J Gynecol Oncol. 2014;25(1):22–9.
71. Natesan D, Susko M, Havrilesky L, Chino J. Definitive Chemoradiotherapy for Vulvar Cancer. Int J Gynecol Cancer. 2016;26(9):1699–705.
72. Geisler JP, Manahan KJ, Buller RE. Neoadjuvant chemotherapy in vulvar cancer: Avoiding primary exenteration. Gynecol Oncol. 2006;100(1):53–7.
73. Jain V, Sekhon R, Giri S, Bora RR, Batra K, Bajracharya A, et al. Role of Radical Surgery

in Early Stages of Vaginal Cancer-Our Experience. Int J Gynecol Cancer. 2016;26(6):1176–81.

74. Benedetti Panici P, Bellati F, Plotti F, Di Donato V, Antonilli M, Perniola G, et al. Neoadjuvant chemotherapy followed by radical surgery in patients affected by vaginal carcinoma. Gynecol Oncol. 2008;111(2):307–11.
75. Diao Y, Jiao J, Song K, Wang L, Lv T, Dai S, et al. Effects of neoadjuvant chemotherapy on patients with primary vaginal squamous cell carcinoma. Mol Clin Oncol. 2017;7(3):395–8.
76. Lv L, Sun Y, Liu H, Lou J, Peng Z. Neoadjuvant chemotherapy followed by radical surgery and reconstruction of the vagina in a patient with stage II primary vaginal squamous carcinoma. J Obstet Gynaecol Res. 2010;36(6):1245–8.
77. Basile S, Angioli R, Manci N, Palaia I, Plotti F, Benedetti Panici P. Gynecological cancers in developing countries: The challenge of chemotherapy in low-resources setting. Int J Gynecol Cancer. 2006;16(4):1491–7.
78. Ivantsov AO. Pathological response of ovarian cancer to neoadjuvant chemotherapy. Chinese Clin Oncol. 2018;7(6):59–66.
79. Cohen PA, Powell A, Böhm S, Gilks CB, Stewart CJR, Meniawy TM, et al. Pathological chemotherapy response score is prognostic in tubo-ovarian high-grade serous carcinoma: A systematic review and meta-analysis of individual patient data. Gynecol Oncol. 2019;154(2):441–8.
80. Singh P, Kaushal V, Rai B, Rajwanshi A, Gupta N, Dey P, et al. The chemotherapy response score is a useful histological predictor of prognosis in high-grade serous carcinoma. Histopahtology. 2018;72(4):619–25.
81. Said I, Böhm S, Beasley J, Ellery P, Faruqi AZ, Ganesan R, et al. The chemotherapy response score (CRS): Interobserver reproducibility in a simple and prognostically relevant system for reporting the histologic response to neoadjuvant chemotherapy in Tuboovarian High-grade Serous Carcinoma. Int J Gynecol Pathol. 2017;36(2):172–9.
82. Lee JY, Chung YS, Na K, Kim HM, Park CK, Nam EJ, et al. External validation of chemotherapy response score system for histopathological assessment of tumor regression after neoadjuvant chemotherapy in tubo-ovarian high-grade serous carcinoma. J Gynecol Oncol. 2017;28(6):1–9.
83. Williams AT, Ganesan R. Role of the pathologist in assessing response to treatment of ovarian and endometrial cancers. Histopathology. 2020;76(1):93–101.
84. Wu ES, Jeronimo J, Feldman S. Barriers and Challenges to Treatment Alternatives for Early-Stage Cervical Cancer in Lower-Resource Settings. J Glob Oncol. 2017;3(5):572–82.
85. Corrado G, Mancini E, Cutillo G, Baiocco E, Vici P, Sergi D, et al. Laparoscopic debulking surgery in the management of advanced ovarian cancer after neoadjuvant chemotherapy. Int J Gynecol Cancer. 2015;25(7):1253–7.
86. Grover S, Xu M, Jhingran A, Mahantshetty U, Chuang L, Small W, et al. Clinical trials in low and middle-income countries — Successes and challenges. Gynecol Oncol Reports. 2017;19:5–9.
87. Böhm S, Faruqi A, Said I, Lockley M, Brockbank E, Jeyarajah A, et al. Chemotherapy response score: Development and validation of a system to quantify histopathologic response to neoadjuvant chemotherapy in tubo-ovarian high- grade serous carcinoma. J Clin Oncol. 2015;33(22):2457–63.