

Does Interval CRS stand better than Primary CRS in Advanced Carcinoma Ovary: A Comparative Study with Technical Description

Mukurdipi Ray^{1*}, TSHV Surya², Premanand N²

¹Department of Surgical Oncology, Dr BR Ambedkar Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India

²Senior Resident, Surgical Oncology, IRHH, AIIMS, New Delhi

Corresponding Author*

Mukurdipi Ray

Department of Surgical Oncology,

Dr BR Ambedkar Institute Rotary Cancer Hospital,

All India Institute of Medical Sciences, New Delhi, India.

Telephone: 011-29575259

E-mail: drmajormdrayaiimsdelhi@aiims.edu

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Abstract

Background: Neo-adjuvant chemotherapy is used in the patients of advanced ovarian cancer, not amenable for upfront surgery. Desmoplastic response to chemotherapy poses difficulty to complete surgical resection apart from anesthetic implications secondary to chemotherapy. Interval cyto-reductive surgery requires expertise and intensive perioperative care to minimize the complications and better surgical outcomes. Present study describes the technique, as practiced by the author emphasizing the importance of surgical skill and technique in interval setting and the author raised the question 'Does NACT really ease the burden?' Author explained it with his experiences in a tertiary oncological referral centre.

Methods: An audit of a prospectively maintained computerized ovarian cancer database in the department of surgical oncology was done. Intraoperative and immediate post-operative outcomes were analysed along with our surgical technique performed in 106 CRS after NACT and 95 upfront cases. We also compared between upfront and interval groups in terms of both perioperative and survival outcomes.

Results: In 516 cases of ovarian cancer operated from January 2014 to November 2020, but in this study, we included 201 patients who fulfilled the inclusion criteria. Post NACT cyto-reduction was performed in 106 patients and upfront cyto-reduction was performed in 95 cases. Nerve-sparing Hysterectomy and Nerve-sparing Retroperitoneal lymph node dissection were performed in 29.24% (31/106) cases. Nerve sparing surgery is less in interval group compare to upfront group 69.47% (66/95). Perioperative outcomes, in terms of less extensive surgical procedure, bowel resection rates, blood transfusions, readmission rate within 30 days of surgery, are better in post NACT group compared to upfront cyto-reduction. However, it is not statistically significant. Because the completeness of surgery is an issue and development of resistant clone to chemotherapy causing more relapse thereby compromised survival which is reflected in our study in the interval group (median DFS 44 months versus 38 months).

Conclusion: Interval cyto-reductive surgery seems easy but it is truly a surgical challenge with almost always an issue for optimal CRS. In true sense, it does not ease the burden as our results reflected it in terms of DFS. Thereby, NACT should not be used as an armamentarium to compensate for poor or inexperienced surgical skill.

Keywords: Tumor biology • Chemotherapy • Radiotherapy • Measurement of tumor

Introduction

Carcinoma Ovary is the most lethal Gynecological malignancy

worldwide [1]. Cyto-reductive surgery, followed by systemic chemotherapy, is the standard of care to date [2]. In India >80% of ovarian cancer patients present in advanced stages [3]; Upfront surgery with optimal cyto-reduction may not be feasible in some cases (40%-60%) [4]. Cyto-reduction in heavy disease burden can be complex and taxing to the patient as well as surgeons no doubts. Platinum and taxane-based neo-adjuvant chemotherapy, for 3-6 cycles is used in such cases to downgrade the disease where surgery is not feasible [5], but the surgeon's experience and skill that matters a lot. Interval cyto-reduction, after neo-adjuvant therapy, is a true challenge for the surgeon especially after six cycles. It seems easy but the desmoplastic reaction to chemotherapy fuses tissue planes and can make dissection difficult and unsatisfactory. Constant oozing from fragile capillaries spoil the field of dissection constantly thereby adds more challenge in terms of vital structures injury. Exposure to chemotherapy has multi-systemic implications due to its toxicity to healthy tissues leading to complications during anesthesia [6]. Chance of recurrence is also more because of two reasons (i) Malignant tissue may be left behind inadvertently because of indistinct desmoplastic plane between malignant and normal tissues, (ii) Development of clone of resistance cells to chemotherapy and as a result chance of relapse is more, (iii) Nerve sparing hysterectomy hardly possible thereby compromising quality of life.

As a whole, post-chemotherapy cyto-reductive surgery should be considered as a unique entity, mandating special surgical skill and experience. In this paper, we compared between interval with upfront cyto-reduction groups in terms of perioperative and survival outcomes. We described how to tackle this challenge by our step by step surgical technique based on our experience of 106 cases of Interval cyto-reduction. We firmly believe that if one could perform interval CRS perfectly, primary CRS would be looking easier.

Methods

Design

A clinical study comparative from a prospectively maintained electronic database in the Department of Surgical Oncology from Jan, 2014 to Dec, 2020. Description of meticulous surgical technique, Compared between Upfront and Interval Cyto-reduction groups in terms of Perioperative outcomes and median DFS.

An audit of computerized ovarian cancer database was performed. We included all the patients with advanced ovarian cancer FIGO stage III to IVA (American Joint Cancer Committee-TNM 8th edition) underwent cyto-reductive surgery and excluded the cases with incompletely entered data. Perioperative outcomes were analyzed between two groups along with median DFS.

Ethics approval

Institute ethics committee approval was taken as per institute protocol.

Objectives

Primary outcome was to determine overall survival in patients with BM after whole brain radiotherapy. Secondary outcome was to identify some predictive factors for survival, the level of concordance between CT and MRI brain and to identify predictive factors for development of brain metastasis in lung cancer patient's cohort.

Ethical considerations

This study is retrospective, all data were de-identified and most patients were expired by the time of analysis, for all those factors, this study was exempted from IBR approval.

Results and Discussion

In 516 cases of ovarian cancer patients operated from January 2014 to Dec 2020 but we included 201 patients in this study, Post chemotherapy

cyto-reduction was performed in 106 patients and upfront cyto-reduction was performed in 95 cases. Nerve-sparing Hysterectomy and Nerve-sparing Retroperitoneal lymph node dissection were performed in 29.24% (31/106) cases in interval group compared with 69.47% (66/95) in upfront group. Mean age of the patients was 48.9 years. Baseline characteristics were summarized in table 1. Majority of the patients undergoing upfront cyto-reduction has better performance status at baseline (ECOG 1 and optimized 2- 74.53% vs 25.47%). Duration of symptoms, histology, grade was not different among both the groups. Percentage of patients who are stage IVA at presentation was more in interval cyto-reduction group (34.90% vs 11.5%). Patients in the interval cyto-reduction group received a mean number of three cycles of Paclitaxel and Carboplatin.

We were able to achieve CC-0 in 71.5% patients in upfront group compared to 78.3% patients in the interval group. Upper abdominal surgical procedures including diaphragmatic peritonectomy, glissons capsulectomy, cholecystectomy, distal gastrectomy, splenectomy were required in 68.4% of upfront surgery group compared to 58.49% of patients in interval cyro-reduction group. Bowel resections were performed in 15.8% of patients undergoing upfront cyto-reduction compared to 10.37% of patients undergoing interval cyto-reduction. Intraoperative blood transfusions were needed in 38.9% patients in upfront surgery group compared to 18.86% in the interval group. There were more number of grade 3 and 4 (Clavien Dindo) complications in the postoperative period in the upfront group (15.8% vs 13.20%). Our postoperative mortality was 3 (3.1%) in upfront and 3 (2.83%) in interval group. Readmission rates within 30 days of surgery was also more in the upfront surgery group compared to interval cyto-reduction group (6.31% vs 2.83%). Peri-operative complications are summarized in table 2. The median follow-up time was 50 months. In primary group 14.7%(14) patients, Interval group 19.8% (20) patients had disease recurrence Overall, the median DFS was higher in primary (44 months) followed by interval groups (38 months).

Description of surgical technique for interval CRS

Preferred position: Low lithotomy position.

Anaesthesia: General anaesthesia with epidural block.

Catheterization: Foley catheter is attached loosely to the perineum, ensuring adequate length to facilitate the urinary bladder retraction during surgery.

Total abdominal hysterectomy with salpingo-oophorectomy:

- Midline laparotomy with incision extending from xiphisternum to symphysis pubis for adequate exposure after initial assessment by diagnostic laparoscopy specially when CT PCI seems higher (>15).
- We prefer total parietal peritonectomy through extra pritoneal approach. We adopt parasuit technique and detached parietal peritoneum both the sides till the line of 'Toldt'. Apart from this, in interval pelvic peritoneum separated from pelvic sidewall and from the anterior vaginal wall Bilateral sub diaphragmatic peritoneum till subhepatic space right and peri splenic space in left.
- Abdomen opened through the parachute and disease burden

is assessed thoroughly, especially transmural small bowel infiltration, porta and SMA root

- Technique of THBSO, both round ligament ligated and divided first to increase uterine mobility.
- Both Uterosacral ligaments are divided to release the uterus from the posterior attachments, ensuring the intact hypogastric nerves between the ureter and uterosacral ligament.
- We prefer to perform Nerve-sparing Hysterectomy in all cases as a standard and but it is practically difficult in interval CRS cases. Though we consider, it should be the standard in all hysterectomy cases.
- The utero-vesical space is developed by dissecting the bladder from the cervix and anterior wall of upper vagina. The avascular dissection plane is maintained close to the cervical and vaginal walls to minimize inferior or hypogastric plexus and bladder injury.
- We developed para rectal space both sides with sponge holding forceps. We ligate the uterine artery and superficial uterine veins separately crossing in this space.
- The parametrial tunnel or ureteric tunnel appears in between two layers of the transverse cervical ligament. We retract ureters with vessel loops to safeguard and facilitate dissection at lower third near uterine vessels.
- The author described this area as the "Red Alert Zone" in his prior report [7]. The ureter and lateral part of deep uterine vein form its lateral, the side wall of cervix and upper vagina form the medial boundary, the superficial uterine vein and the uterine artery form the superior boundary, Base of the bladder forms the inferior boundary of this zone. Meticulous & careful dissection is required in this area to avoid injury of critical structures like the inferior hypogastric plexus, distal ureter, cervico-vesical vascular plexus, and base of urinary bladder.
- We face difficulty in post NACT cases where desmoplasia obscuring the tissue planes. In this region, we ligate inferior and middle vesical veins, before tying deep uterine vein to avoid constant bleeding specially after NACT, we ligate deep uterine vein medially in case of nerve sparing surgery. Careful dissection along the ureter, and vascular structures to prevent constant bleeding or gush of bleeding using clips, ligatures, compression to reduce nerve, ureteric and bladder injury. Specially para cervical and para colpos area dissection is very crucial.
- We perform colpotomy using 30 watt safeguarding the ureter both the side and thin bladder wall anteriorly.
- After specimen extraction, the vaginal vault is closed using an interlocking stitch with 1-0 polyglactin. Haemostasis is ensured in every step.

Pelvic lymph node dissection

The author follows the standard pelvic lymph node dissection

Table 1. Baseline Characteristics comparing patients undergoing upfront and interval cyto-reduction.

	Primary Cyto-reduction (N=95)	Interval Cyto-reduction (n=106)
Age, Years	48 (20-70)	50 (22-76)
Performance Status (ECOG)		
0-1	80 (84.2%)	272 (25.47%)
≥ 2	15 (15.8%)	79 (74.52%)
Duration of symptoms (months)	3.5 (1-16)	2.5 (0.5-12)
Histology		
Serous	77 (81%)	86 (81.13%)
Mucinous	8 (8.4%)	10 (9.43%)
Others	10 (11%)	10 (9.43%)
Grade		
Well differentiated	14 (14.8%)	18 (16.98%)
Moderately differentiated	52 (54.7%)	63 (59.43%)
Poorly differentiated	29 (30.5%)	25 (23.58%)
Stage		
III	84 (88.5%)	69 (65.09%)
IV	11 (11.5%)	37 (34.0%)

boundaries as 1 cm above the common iliac bifurcation superiorly, deep circumflex iliac vein inferiorly, genital branch of genitofemoral nerve laterally, Obturator nerve posteriorly and medially medial border of internal iliac vessel. We prefer to start dissection from lateral to medial by incising peritoneum over the psoas muscle near the genital branch of genitofemoral nerve. The peritoneal layer is reflected medially along with the lymph node chain, dissecting external iliac, internal iliac, obturator nodes separately.

For dissection, monopolar electro surgery is used with the generator in coagulation mode set to 20 w-25 w power. We carefully retract internal and external iliac veins using an eyelid retractor and ureter using a vessel loop to facilitate the dissection and avoid ureteric injury.

The author's routine practice is to send different groups of pelvic nodes separately for histopathological examination with a target to dissect at least ten pelvic nodes on each side.

There could be a notable ooze from the dissected bed, mainly in post-chemotherapy cases, and this should be controlled using saline gauze compression for around three to five minutes. Then haemostasis is achieved using clips, sutures, and electro surgery in cases of a point source of bleeding or fibrin sealant/haemostat in diffuse ooze cases. Attempts to directly control the bleeding using artery forceps, blind suture ligation is discouraged to prevent nerve and ureteric injury.

Lymphatics leak to be taken care both by suturing and clips.

Retroperitoneal lymph node dissection

Post neo-adjuvant chemotherapy retro-peritoneal lymph node dissection is also a challenging. Significant desmoplastic reaction and increased vascular fragility in the retro peritoneum are seen in almost all patients specially who received six cycles NACT. The author follows the standard the retroperitoneal lymph node dissection template, which is defined as bilateral renal veins forming the superior, bilateral ureters as the lateral, and ureteric crossing over common iliac vessels as the inferior boundary in ovarian cancer cases. The author recommends adequate retroperitoneal exposure by kocherisation of the duodenum and colonic mobilization for beginners to perform a safe retro-peritoneal lymph node dissection, avoiding catastrophic bleeding. Successful nerve sparing retro-peritoneal lymph node dissection begets explicit anatomical knowledge of the course of hypogastric and mesenteric nerves, lumbar veins, gonadal vessels, and ureters throughout the retroperitoneal course.

Zone-wise retroperitoneal lymph node dissection

Author divide the retroperitoneal lymph node dissection template into six zones for ease of dissection (Figure 1). Two parallel imaginary lines divide the area into five zones. The first Imaginary Line (IL1) traverses at the level of the inferior mesenteric artery and another Imaginary Line (IL2) at the level of aortic bifurcation. Author published his design of retroperitoneal dissection as 'High Alert Zone' [8].

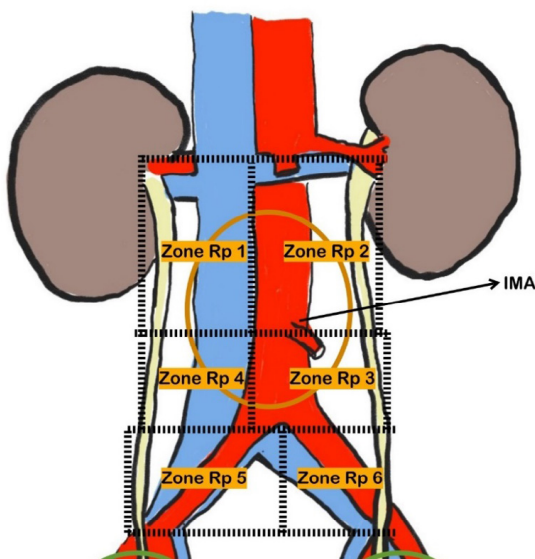


Figure 1. Picture of Retroperitoneal lymph node dissection describing five zones for ease of dissection.

Author's adopt the "Split and Roll technique" of retroperitoneal lymph node dissection, especially in post-chemotherapy cases. We prefer to start dissection from the right side as it is easier to save the right-sided hypogastric nerve with most of its fibers passing behind Inferior vena cava, and managing an injury if it occurs, is relatively more comfortable in the beginning stages of dissection. The right gonadal vein should be doubly ligated and divided at its draining site into Inferior vena cava and send as separate specimen. Pre and para caval dissection follows, keeping in mind the relatively fragile nature of Inferior vena cava compared to other vessels. The inferior vena cava is a low-pressure high-volume system. In an unfortunate instance of its branch avulsion or wall injury, we use vascular loop control or Cooley's clamps to gain proximal and distal control. The injured site is then repaired using a 4-0 polypropylene suture. We don't do retro-caval nodal dissection in carcinoma ovary cases. Three lumbar veins are encountered in this area, and their avulsion causes significant hemorrhage. We proceed then to the inter-aortocaval region, carefully retracting the Inferior vena cava sideways using an eyelid retractor. Three pairs of lumbar arteries encountered in this region are carefully preserved while dissecting off the nodal tissue. Para-aortic nodal dissection is done in two parts, first inferior to the Inferior mesenteric artery, and they subsequently superior to inferior mesenteric artery. The para-aortic nodal zone above inferior mesenteric artery is regarded as a "High Alert Zone"[8] for the following reasons:

1. It is the first zone where Retroperitoneal nodes metastasized and enlarged first.
2. High chance of lumbar vessel, left gonadal vessel, inferior mesenteric artery branches, Left renal vein, and ureteric injury.
3. Chance of injury to mesenteric nerves, superior lumbar vein crossing lateral to the aorta, while dissecting the infrarenal nodes.
4. Step by step approach with patience is required in this region to avoid inadvertent injuries. We perform both sharp and blunt dissection in this area using monopolar cautery and harmonic scalpel.
5. After completing retroperitoneal lymph node dissection, a glistening anterior spinal ligament is visible in the Retroperitoneal bed in all cases. In the final step, nodes around common iliac vessels and presacral region are dissected.
6. In our experience of post neo adjuvant chemotherapy retroperitoneal lymph node dissection, veins are usually very fragile with additional or neo vascularized fellow veins, which leads to increased vessel injury and bleeding. We lost one patient because of the uncontrolled hemorrhage in this area.
7. The author would like to highlight the importance of a clear and detailed visual appreciation of retroperitoneal anatomy in achieving safe surgical outcomes.
8. One may use a magnifying loupe (2.5x) if nerve-sparing retroperitoneal lymph node dissection is planned.
9. Use low power (20w-25w) electro-surgery settings.
10. Bleeders should be tackled immediately. If the bleeding is not controlled easily, reattempting after applying pressure with a sponge for five minutes can be helpful.
11. Judicious use of fibrin sealants and cellulose-based hemostats can help control the diffuse ooze encountered in the post-chemo situation.
12. Clipping the open lymphatic channels, especially in the renal hilum & Inter aortocaval area, can reduce lymphocele formations and lymphorrhoea.
13. Completion of Parietal Peritonectomy and Hyperthermic Intraperitoneal Chemotherapy:
14. We prefer an extraperitoneal approach to achieve total peritonectomy in post-chemotherapy cases. A total omentectomy is routinely performed. We perform Hyperthermic Intraperitoneal Chemotherapy in optimally cytoreduced patients with stable hemodynamics condition. The addition of Hyperthermic Intraperitoneal Chemotherapy in carefully selected cases

Table 2. Comparison of perioperative outcomes between upfront and interval cyto-reduction groups.

	Primary CRS (N=95)	Interval CRS (n=106)
Optimal cyto-reduction, n(%)	68 (71.5%)	83 (78.30%)
Upper abdominal surgical procedures, n(%)	65 (68.4%)	62 (58.49%)
Bowel Resection, n(%)	15 (15.8%)	11 (58.49%)
Intraoperative blood transfusions, n(%)	37 (38.9%)	20 (18.86%)
Postoperative complications, n(%)	15 (15.8%)	14 (13.20%)
Mean duration of hospital stay, days (range)	8 days	6.82 days
Readmission within 30 days of surgery, n(%)	6 (6.31%)	3 (2.83%)

does not add significant morbidity as per our experience of 204 cases. If the patient is hemodynamically unstable, the author prefers to wait 24 hours-48 hours to optimize the patient in the intensive care unit before performing a staged Hyperthermic Intraperitoneal Chemotherapy [9].

We routinely do retroperitoneal lymph node dissection in all cases as nodes act as a sanctum site and harbor microscopic disease which may give rise to late recurrences after HIPEC. There was substantial stage migration noted in stage IIIA (from 35 patients detected to have retroperitoneal nodes by CT were down staged to stage IIB or less in 12 patients.) This suggests the need for routine retroperitoneal lymph node dissection in this subset as it would help in accurate pathological staging and prognostication.

In a systematic review and meta-analysis by Benito et al included 29 studies and found that there was no difference in terms of OS and PFS between upfront and interval debulking surgery. However, surgical complexity and postoperative complications were reduced in the interval group [10].

Till date four randomized controlled trials comparing PDS versus IDS in advanced EOC. EORTC 55971 showed median OS 29 versus 30 months (not significant). Median PFS 12 versus 12 months. In CHORUS study showed median OS of 22.6 vs 24.1 months and PFS of 12 vs 10.7 months (both not significant). In JCOG 0602 study median OS 49 vs 43 months, PFS 15 vs 14 months (both not significant). In SCORPION trial median OS 41 vs 43 months and PFS 15 vs 14 months (both not significant). But all the studies showed higher surgical morbidity and mortality in PDS [11-13].

In a study by Sarah et al. comparing upfront versus interval surgery including 1713 women with stage IIIC/IV ovarian cancer, there was little or no difference in primary survival outcomes. NACT reduced the risk of serious adverse events. In a study by SVS Deo et al, after NACT, complete response occurred in 17 patients (20.7%), 50 (61.0%) had partial response and no response was documented in 15 (18.3%) patients. Optimal surgical cyto-reduction could be achieved in 72% of the patients. NACT down staged the disease enabling optimal cyto-reduction. In previous study by the authors including 200 patients, 5-year overall survival was 53.7% in the upfront CRS group and 42.2% in the NACT group. There was no survival advantage noted with IDS [14-16].

Conclusion

Interval cyto-reductive surgery is always a surgical challenge though it seems to be easier than upfront surgery apparently. It apparently eases the burden to some extent, in terms of perioperative outcomes with standard

CRS technique. Author strongly oppose the random selection of stage IIIC onwards patients for NACT. As NACT cannot be the compensatory to poor surgical skill. Post NACT Interval CRS is inferior in terms of surgical satisfaction in surgery, recurrence, DFS and OS though immediate peri operative outcomes are lecuratine in interval CRS cases.

References

1. Bray, Freddie, et al. "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries." *CA: Cancer J Clin* 68.6 (2018): 394-424.
2. Van Driel, Willemien J., et al. "Hyperthermic intraperitoneal chemotherapy in ovarian cancer." *N Engl J Med* 378.3 (2018): 230-240.
3. Torre, Lindsey A., et al. "Ovarian cancer statistics, 2018." *CA: Cancer J Clin* 68.4 (2018): 284-296.
4. Deo, S. V. S., et al. "Neoadjuvant chemotherapy followed by surgical cytoreduction in advanced epithelial ovarian cancer." *Indian J Cancer* 43.3 (2006): 117.
5. Armstrong, Deborah K., et al. "NCCN guidelines insights: ovarian cancer, version 1.2019: featured updates to the NCCN guidelines." *J Natl Compr Cancer Netw* 17.8 (2019): 896-909.
6. Allan, Neil, Catherine Siller, and Andrew Breen. "Anaesthetic implications of chemotherapy." *Contin Educ Anaesth. Crit Care Pain* 12.2 (2012): 52-56.
7. Ray, Mukur Dipi, Navin Kumar, and Raghuram Kuppusamy. "The red alert zone in pelvis for radical hysterectomy: the precise anatomy and safe surgical technique." *J Gynecol Surg* 36.4 (2020): 194-197.
8. Ray, Mukur Dipi, and Navin Kumar. "High alert zones in nerve-sparing retroperitoneal lymph node dissection in gynecologic cancers: A precise anatomy and safe surgical technique." *J Gynecol Surg* 36.6 (2020): 331-336.
9. Ray, Mukur Dipi, et al. "Staged HIPEC may be feasible when it is not possible along with the same setting of CRS." *J Cancer Res Rev Rep* 138 (2021).
10. Chiofalo, Benito, et al. "Primary debulking surgery vs. interval debulking surgery for advanced ovarian cancer: review of the literature and meta-analysis." *Minerva med* 110.4 (2019): 330-340.
11. Vergote, Ignace, 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* 19.12 (2018): 1680-1687.
12. Onda, Takashi, 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 Group Study JCOG0602." *Eur j cancer* 64 (2016): 22-31.
13. Mandilaras, Victoria, et al. "TP53 mutations in high grade serous ovarian cancer and impact on clinical outcomes: a comparison of next generation sequencing and bioinformatics analyses." *Int J Gynecol Cancer* 29.2 (2019).
14. Coleridge, Sarah L., et al. "Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer." *Cochrane Database Syst Rev* 2 (2021).
15. Deo, S. V. S., et al. "Neoadjuvant chemotherapy followed by surgical cytoreduction in advanced epithelial ovarian cancer." *Indian J cancer* 43.3 (2006): 117.
16. Ray, Mukur Dipi, et al. "Upfront cytoreductive surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer in Indian patients." *Future Oncol* 17.27 (2021): 3607-3614.