Original Article

A Review: Progress Against the Treatment of Ovarian Cancers

NehaTabassum[*1], Mythri.G[2], Zeba Raheem[3], Dr. Azeez. S.A[4]

[1,3]Deccan school of Pharmacy Hyderabad A.P India
[2]Department of Pharmaceutics Deccan school of Pharmacy Hyderabad A.P India
[4]Department of Pharmaceutics Deccan school of Pharmacy Hyderabad A.P India

Address for Correspondence

Deccan school of Pharmacy
Hyderabad
A.P India
E-mail:
sneha.tabassum@gmail.com

ABSTRACT

The American cancer society estimates the in 2013, 15,500 women will die of ovarian cancer in the United States. Women with ovarian cancers are living longer lives and have a betterquality of life as a result of advances in treatment and an improvedunderstanding of the disease. While chemotherapy once had an extremelymodest effect on ovarian cancer, today's treatments are much moreeffective at shrinking tumors and driving the disease intoremission, for all stages of the disease. Recent studies have shown thatovarian cancer is not one disease, but a spectrum of related diseaseswith unique genetic characteristics which may influence response totreatment. With these discoveries there is new potential to developpersonalized treatment regimens that are most effective and result infewer side effects. Most ovarian cancers respond well to initialchemotherapy, but the disease frequently reoccurs and more effectivedrugs are urgently needed to prevent and fight these recurrent tumors.New research offers reason for optimism. Cytoreductive surgery withHIPEC Hyperthermic Intra Peritoneal Chemotherapy is the latestintervention in the treatment of ovarian cancers. The goal of this surgery is to remove all the visible tumors, however, sometimes very small tumors and microscopic cancer cells are left behind and to prevent these cells from growing larger tumors in the abdomen the surgery is followed with HIPEC.

Keywords: ovarian cancer, HIPEC, cytoreductive surgery, tumors.

INTRODUCTION

Progress Against Ovarian Cancers

Pre 1970s

Early ovarian cancers were treated with alkylating agents, involving a family of chemotherapy drugs such as Melphanlan, Chlorambucil and Cyclophosphamide.

1978

First effective combination chemotherapy regimen for ovarian cancer

Researchers led by Robert Young develop a combination chemotherapy regimen for advanced ovarian cancer, known as HEXACEF. However, this new combination regimen causes significantly more side effects. Later research leads to the development of new and more effective combination chemotherapy regimen that uses Cisplatinsuch as Cyclophosphamide plus Cisplatin and a regimen called CHAP.

1981

Oral contraceptives found to cut ovarian cancer risk

Studies first begin suggesting that oral contraceptives use lowers the risk of developing ovarian cancers. Evidence continues to accumulate over the coming years, in 2008, a review of 45 published studies concludes the pill lowers ovarian cancer risk by 20%

Mid 1980s

Scientist discover "Biomarker" tied to Ovarian cancer –CA 125

Researchers determine that levels of the specific protein in blood, CA 125, are linked to ovarian cancer. , however,efforts to use CA-125 testing for early detection or to screen for ovarian cancer in healthy women have proven difficulty, because CA-125 levels can rise for reasons unrelated to ovarian cancer.

1989

FDA approves Carboplatin for ovarian cancer

The chemotherapy drug carboplatin becomes available as a second line of therapy for ovarian cancer, after being shows that it promotes tumor shrinkage.

1992-1994

Taxanes emerge as vital chemotherapy option for ovarian,breast cancer

A new family of treatment debuts with the FDA approval of paclitaxel for advanced ovarian cancer.this approach is later replaced by a regimen involving Paclitaxel and another chemotherapy drug, called Carboplatin which results in fewer side effects

1996

New chemotherapy drug for advanced ovarian cancer

Topotecan is approved to treat advanced ovarian cancer after other treatments have failed based on studies showing the drug increases survival. It interferes with DNA replication to prompt cancer cell death.

Late 1990's

BRCA1 BRCA 2 gene mutation linked to increased ovarian cancer risk

Researchers discover that mutations in the BRCA 1 and BRCA 2 genes raise a woman's ovarian cancer risk as much as 80%.this discovery leads to intense research on ways to reduce breast and ovarian cancer risk,

1999

FDA approves liposomal Doxorubicin for advanced ovarian cancer

Liposomal Doxorubicin receives accelerated FDA approval to treat advanced ovarian cancer that has progressed after prior treatment. The drug is unique because the active chemotherapy agent is encased in a microscopic fat bubble that releases the drug at the tumor site, delivering more of the chemotherapy directly to the tumor and less to other parts of the body, thereby limiting side effects.

2003

New chemotherapy regimen-docetaxel and paclitaxel- provides important treatment option. A large study finds that

combination chemotherapy with docetexal and carboplatin is as effective as the standard paclitaxel and carboplatin regimen for newly diagnosed, advanced ovarian cancer.

2005

Researchers work to decode the ovarian cancer genome

The national cancer institute launches the cancer genome atlas project, with an initial goal of mapping the genome of ovarian, brain and lung cancers.By mapping the complete genome of these cancers, scientists hope to identify many new genetic targets for future treatments.

2006

Researchers find some ovarian cancers begin in the Fallopian tubes

After assessing tissue from women with BRCA gene who had their ovarian and fallopian tubes surgically removed to reduce their cancer risk,researchers discover signs that some ovarian cancers may actually begin in the fallopian tubes and spread to the ovaries.These fallopian tube cancers,have different characteristics than cancers arising in the ovaries.This poses an additional challenge for cancer screening, since cancers that rise in the fallopian tubes are even harder to detect than ovarian cancers.

Researchers report that adding intraperitonealchemotherapy-delivering chemotherapy directly into the abdomen through a catheter – to intravenous chemotherapy following surgery extends survival by over a year for women with advanced ovarian cancer, compared to surgery and intravenous chemotherapy alone.

2009

Preventive surgery confirmed to reduce breast and ovarian cancer risk in women with BRCA gene mutations

A major review of previously published studies confirms that surgical removal of the ovaries and fallopian tubes in healthy pre menopausal women with BRCA gene mutations reduce the risk of breastcancer by 51% and the risk of ovarian and fallopian cancer by 79%

2010

Bevacizumab significantly delays progression of advanced ovarian cancer

A large study finds that adding the targeted drug Bevacizumab to initial chemotherapy treatment, and then using it as longer term “maintenance” therapy. Significantly slows the spread of the disease in women with cancer in their ovaries and surrounding tissue.Bevacizumab interferes with the growth of blood vessels needed to fuel a tumor’s growth-a process called angiogenesis.

“The cytoreductive surgery with HIPEC Hyperthermic Intra-Peritoneal Chemotherapy is the latest intervantion in the treatment of ovarian cancers**”**

CYTOREDUCTIVE SURGERY WITH HIPEC HYPERTHERMIC INTRA - PERITONEAL CHEMOTHERAPY

The goal of cytoreductive surgery is to remove all the visible tumours.However,sometimes very small tumour and microscopic cancer cells are left behind and to prevent these cells from growing larger tumours in the abdomen,the surgery is followed by hipec. The complete removal of all tumours is defined in medical terms as a complete cytoreduction. Completecytoreduction is the complete removal of all tumours leaving behind only tumour nodules that are less than 2.5 millimeter in size. Using intraperitoneal heated chemotherapy for these tumours is most effective.

HIPECis a chemotherapy solution heated to a temperature of 42 degree that is

used in conjunction with cytoreductive surgery. The heated chemotherapy batches the abdominal cavity to destroy non visible or microscopic tumour cells. Heat kills cancer cells and also enhances the effect of chemotherapy[6]. In this therapy following the cytoreductive surgery the patient is connected to a series of catheters or tubes and a pumping device that batches and entire abdominal cavity with heated chemotherapy solution and then back out for a constant flow. This melted allows the heated chemotherapy to reach all corners of the abdominal cavity and treat the cancer cells that couldpotentially form new cancerous tumor[1] Figure 1 & 2

Pharmacokinetic Advantage of Intraperitoneal Chemotherapy

Intraperitoneal delivery of cytotoxic drugs ,high regional concentration can be achieved while keeping systematic drug levels low that chemotherapy has a peritoneal plasma barrier , which maintains a continuous high concentration gradient of chemotherapeutic drug between the peritoneal cavity and plasma compartments[5].

Intraperitonealchemothearapy administration is that the blood drainage of the peritoneal surface occurs via the portal vein to the liver,providing a first pass effective detoxification and an increased exposure of potential hepatic micrometastasis to cytotoxic drugs

Hipec is effective in patients with peritoneal carcinomatosis originating from cancers of colon, rectum, stomach, appendix and ovaries aswell as mesothelioma, sarcomas and peritoneal cancers[2].

Disadvantage of Intraperitoneal Chemotherapy

Tissue penetration-limited therapeutic tissue penetration unfortunately,for many agents it is difficult to accurately measure tissue penetration depth and concentration after intraperitonealadministration,there is a large inter individual variation.Length of the surgery can extend into the evening,the average surgery time is between 10-12 hrs[3].

Due to complexicity of the combined therapy of cytoreductive surgery and HIPEC,only handful of surgeons are approximately trained and experienced to offer this treatment method[7-13].

Hyperthermia

The clinical evidence indicate that malignant cells selectively destroyed by hyperthermia in the range of 42^0-43^0 degree centigrade.in malignant cells due to hypethermia ,an increased in number of lysosomes and lysoosmal cells enzyme activity results .these heat induced lysosomes are more labile in malignant cells and therefore result in increased structive capacity[4,14-16].

Choice of drug and drug dosage for HIPEC

The choice of the chemotherapeutic drug is very important and it is important to consider that the agent should lack severe direct local toxicity after intraperitonealadministration. Drugs should have a well established activity against the malignancy.Drugs that have to be metabolized systematically into their active form are appropriate for HIPEC[17].

HIPEC Drug Regimens

Different drugs regimens have been employed over years for HIPEC .Single drug and drug combination regimens are currently in use. Choosing of carrier solution is also important in the HIPECtreatment.Although different carrier solutions with varying chemical properties have been investigated, 1.5% dextrose isotonic peritoneal dialysis solution is the most widely employed. An important issue regarding toxicity of HIPEC has to do with dosaging. Both the drug dose and the carrier solution should be calculated

based on the body surface area so that toxicity can be predictable[18].

Preoperative intraperitoneal chemotherapy regimen that employ early post operativeintraperitoneal chemotherapy use moderate drug dose for HIPEC .while those do not employ epic use much higher dosage for HIPEC. In last few years, bidirectional HIPEC regimen have gained ground.

While in preoperative instillation chemotherapy the drug solution is usually left in the peritoneal cavity for 4 to more than 24 hrs.The duration of the HIPEC has been arbitory and versus from 30mints to 20hrs. Table-1

Occurrence Rates for Complications

Some studies into the complication rate for cytoreduction surgery and peritoneal chemotherapy state overall complication rates of approximately 40%. This percentage includes minor complications such as nausea, vomiting and diarrhea. Major complications Grade 3 or 4 are stated to be 20-25%. Complications that are severe enough to require a return to surgery are fewer, they are generally stated to be approximately 10%. Death rates vary from 2-4% in studies. Almost all complications, though, can be medically managed. Complication rates may also vary for different surgeons and facilities related to:

The experience of the surgeon.

- The particular technique used- i.e. open vs. closed technique for the peritoneal hyperthermic chemotherapy
- The use of peritoneal chemotherapy after surgery in addition to hyperthermic chemotherapy used during surgery some surgeons and facilities follow the initial surgery and
- Extent of surgery and time under anesthesia

Diabetics will be at higher risk for delayed wound healing and infection. A smoker or person with asthma or respiratory illness will be at greater risk for breathing related complications. It is best to attain the best health you are able to achieve prior to having this surgery[19-23].

Things you can do to help prevent complications

While not all complications can be anticipated or prevented, there are things a patient can do to prevent some of the potential complications.

- Preventing the formation of clots in the deep veins of the legs DVT-deep vein thrombosis helps prevent a second very serious and sometimes fatal complication, a pulmonary embolus. A pulmonary embolus is a clot usually a deep vein thrombosis that dislodges from the veins in the legs and then travels to the lungs.
- Pneumonia and Atelectasis- general anesthesia, prolonged bed rest and decreased movement, along with shallow breathing and underlying lung diseases are all risk factors for atelectasis, or a partial collapse of the lung. These same risk factors also prevent mucous and secretions from being expelled from the lungs and promote the development of pneumonia
- Ileus: Walk as much as you are able to tolerate. Not only will you expand your lungs and prevent deep vein thrombosis and pulmonary emboli, you will also help your bowels to become more active and to start moving sooner. The sooner your bowels and digestive tract start functioning, the sooner you will be able to be rid of the NG tube! Narcotics also can cause or aggravate an ileus, so as soon as you are able, decrease your use of narcotic pain medication.

Nausea and vomiting

Nausea and vomiting are very uncomfortable in any circumstance, but they are even more uncomfortable when you have

a very large incision in you abdomen. Talk to the staff until you are able to find a way to control nausea with medication.

CONCLUSION

- Women with ovarian cancer are living longer lives-and have a better quality of life–as result of advances in treatment and an improved understanding of the disease. For example:

The breakthrough discovery that specific gene mutations – in the BRCA 1 and BRCA 2 genes – increase a woman's risk for ovarian and breast cancer has led to important risk –reducing strategies. Women with these mutations can undergo frequent medical evaluations or even surgical removal of their ovaries and fallopian tubes a, which reduces their risk of ovarian cancers by as much as 80%

- While chemotherapy once has an extremely modest effect on ovarian cancer, today's treatments are much more effective at shrinkage tumors and driving the disease into remission, for all stages of the disease.
- Recent studies have shown that ovarian cancer is not one disease, but a spectrum of related disease with unique genetic characteristic which may influence response to treatment. With these discoveries there is new potential to develop personalized treatment regimen s that are more effective and result in fewer side effects.
- When detected early, ovarian cancer is one of the most curable forms of cancer – Five year survival rates are as high as 94% for early stage disease. But the absence of effective screening tools means that most women are diagnosed at a late stage, when cures are rare and long term survival rates are low.
- Most ovarian cancers respond well to initial chemotherapy, but the disease frequently reoccur and more effective drugs are urgently needed to prevent and fight these recurrent tumors.
- New research offers reason for optimism. Researchers' hope that an ongoing effort to map the ovarian cancer genome will provide new molecular targets that can be translated into more potent drug therapies for the disease , and may also lead to effective ways to prevent and screen for early stage disease.
- An evolution of principles by which gastrointestinal cancer is treated starting from the end of 1960's.early on, the major goal of cancer surgery was clearance of the primary cancer and achievement of an ro resection. Next , maximal containment during that resection was shown to be essential for containment , but also the knowledgeable use of CRS plus HIPEC, must be implemented as a third crucial requirement for the surgical management of selected patients with gastrointestinal cancer.

Finally as experience with this technology has increased, the associated morbidity and mortality have diminished making the treatment applicable to a large number of patients.Recent trends, as published by multiple institutions, suggest that, at experienced centers CRS and HIPEC are new standard of care for Appendiceal , Colorectal, Peritoneal mesothelioma.

REFERENCES

1. Arjen J. Witkamp, Eelco de Bree, Andres R. Van Goethem and Frans A. N. Zoetmulder.Rationale and techniques of intra-operative Hyperthermic Intraperitoneal Chemotherapy. CANCER TREATMENT REVIEWS 2001; 27: 365-374.
2. González-Moreno, Luis A González-Bayón, Gloria Ortega-Pérez. Hyperthermic Intraperitoneal Chemotherapy.*World J of Gastrointestinal Oncol* 2010;22: 68-75.

3. Eelco de Bree, Dimitris D. Tsiftsis and John Melissas,Hyperthermicintraperitoneal chemotherapy HIPEC in optiallycytoreduced peritoneal carcinomatosis of gynecology origin. Does it provide survival advantage?. Cytoreductive Surgery in Gynecologic Oncology: A Multidisciplinary Approach 2010; 73-99.
4. Amadori D., MD, Sansoni E., MD, Amadori A. Ovarian Cancer: Natural History and Metastatic Pattern. *Frontiers in Bioscience*1996; 56-59.
5. Spratt JS, Adcock RA, Sherrill W, Travathen S. Hyperthermic peritoneal perfusion system in canines. *Cancer Res* 1980; 40:253-255.
6. Storm FK. Clinical hyperthermia and chemotherapy, Radiol Clin N Am1989; 27: 621-627.
7. Robert F. Ozols. Intracavitary Chemotherapy in Ovarian Cancer—An Investigational Procedure. *West J Med*. 1985; 1423: 388–390.
8. El-Kareh AW, Secomb TW. A theoretical model for intraperitoneal delivery of cisplatin and the effect of hyperthermia on drug penetration distance. *Neoplasia*2004; 62: 117-127.
9. Los G, Verdegaal EM, Mutsaers PH, McVie JG. Penetration of carboplatin and cisplatin intorat peritoneal tumor nodules after intraperitoneal chemotherapy. *Cancer Chemother Pharmacol*1991;28 3: 159-165.
10. Fujimoto S, Takahashi M, Kobayashi K, Nagano K, Kure M, Mutoh T, Ohkubo H,Cytohistologic assessment of antitumor effects of intraperitonealhyperthermic perfusion with mitomycin C for patients with gastric cancer with peritoneal metastasis. *The Cancer J* 1992; 70: 2754-2760.
11. Panteix G, Guillaumont M, Cherpin L, Cuichard J, Gilly FN, Carry PY, Sayag A, Salle B, Brachet A, Bienvenu J. Study of the pharmacokinetics of mitomycin C in humans during intraperitonealchemohyperthermia with special mention of the concentration in local tissues,Oncology 1993;50: 366-370.
12. Vaart PJ, Vange N, Zoetmulder FA, Goethem AR, Tellingen O, BokkelHuinink WW, Beijnen JH, Bartelink H, Begg AC. Intraperitonealcisplatin with regional hyperthermia in advanced ovarian cancer: pharmacokinetics and cisplatin-DNA adduct formation in patients and ovarian cancer cell lines, *Eur Jof Cancer* 1998;341: 148-154.
13. Cavaliere R, Ciocatto EC, Giovanella BC, Heidelberger C, Johnson RO, Margottini M, Mondovi B, Moricca G, Rossi-Fanelli A. Selective heat sensitivity of cancer cells. Biochemical and clinical studies. *The Cancer J* 1967;20 9: 1351-1381.
14. Overgaard J, Effect of hyperthermia on malignant cells *in vivo*- A review and a hypothesis. *The Cancer J* 1977; 39: 2637-2646.
15. Sticca RP, Dach BW. Rationale for hyperthermia with intraoperative intraperitoneal chemotherapy agents. *Surg Oncol Clin N Am J* 2003; 12: 689-701.
16. Dudar TE, Jain RK. Differential response of normal and tumor microcirculation to hyperthermia. *Cancer Res J* 1984; 44: 605-612.
17. De Bree E, Tsiftsis DD. Principles of perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis. *Cancer Res J* 2007; 169: 39-51.
18. Mohamed F, Sugarbaker PH. Intraperitonealtaxanes. *Surg Oncol Clin N Am J* 2003; 12: 825-833.
19. Koga S, Hamazoe R, Maeta M et al. Prophylactic therapy for peritoneal recurrence of gastric cancer by continuous hyperthermic peritoneal perfusion with mitomycin-C. *The Cancer J* 1988; 61: 232-237.
20. Tsiftis D, de Bree E, Romanos J et al. Peritoneal expansion by artificially produced ascites during perfusion chemotherapy.*Arch Surgery journal* 1999; 134: 545-549.
21. Jacquet P, Sugarbaker PH. Peritoneal-plasma barrier. *Cancer Treat Res J* 1996; 82: 53- 63.
22. Jacquet P, Stephens AD, Averbach AM, Chang D, Ettinghausen SE, Dalton RR, Steves MA, Sugarbaker PH. Analysis of morbidity and mortality in 60 patients with peritoneal carcinomatosis treated by cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy. *The Cancer J* 1996; 77: 2622-2629.
23. Witkamp AJ, de Bree E, Kaag MM et al. Extensive cytoreductive surgery followed by intra-operative hyperthermicintraperitoneal

chemotherapy with mitomycin-C in patients with peritoneal carcinomatosis from colorectal origin. *Eur J Cancer* 2001; 378:979-984.

Table 1. Commonly- used HIPEC regimens

HIPEC drugs and doses	HIPEC duration in mints	Concomitant intravenous chemotherapy	EPIC	Indication
Mitomycin C, 15 mg/m2 Doxorubicin, 15 mg/m2	90	5-FU, 400 mg/m2 LV, 20 mg/m2	5-FU 4 d	Appendiceal, and colorectal carcinomatosis
Cisplatin, 50 mg/m2 Doxorubicin, 15 mg/m2	90	5-FU, 400 mg/m2 LV, 20 mg/m2	Taxol 4 d	Gastric cancer, peritoneal mesothelioma, ovarian cancer
Oxaliplatin, 130 mg/m2	60	5-FU, 400 mg/m2 LV, 20 mg/m2	5-FU 4 d	Appendiceal, and colorectal carcinomatosis
Melphalan, 50-70 mg/m2	60	NO	NO	Carcinomatosis with incomplete cytoreduction
Oxaliplatin, 460 mg/m2	30	5-FU, 400 mg/m2 LV, 20 mg/m2	*NO*	Colorectal carcinomatosis
Mitomycin C, 35 mg/m2	90	NO	NO	Appendiceal, and colorectal carcinomatosis
Cisplatin, 43 mg/L Doxorubicin ,15.25 mg/L	90	NO	NO	Peritoneal mesothelioma, advanced ovarian cancer
Mitomycin C, 3.3mg/m2/L Cisplatin, 25 mg/m2/L	90	NO	NO	Appendiceal, and colorectal carcinomatosis; advanced ovarian cancer; peritoneal mesothelioma
Mitomycin C, 10 mg/mL of perfusate	90	NO	NO	Appendiceal, gastric and colorectal carcinomatosis
Mitomycin C, 0.5 mg/kg Cisplatin 0.7 mg/kg	90	NO	NO	Peritoneal mesothelioma
Cisplatin, 20 mg/m2/L	90	NO	NO	Recurrent and chemoresistant stage Ⅲ ovarian cancer

 ISSN 2321 – 2748

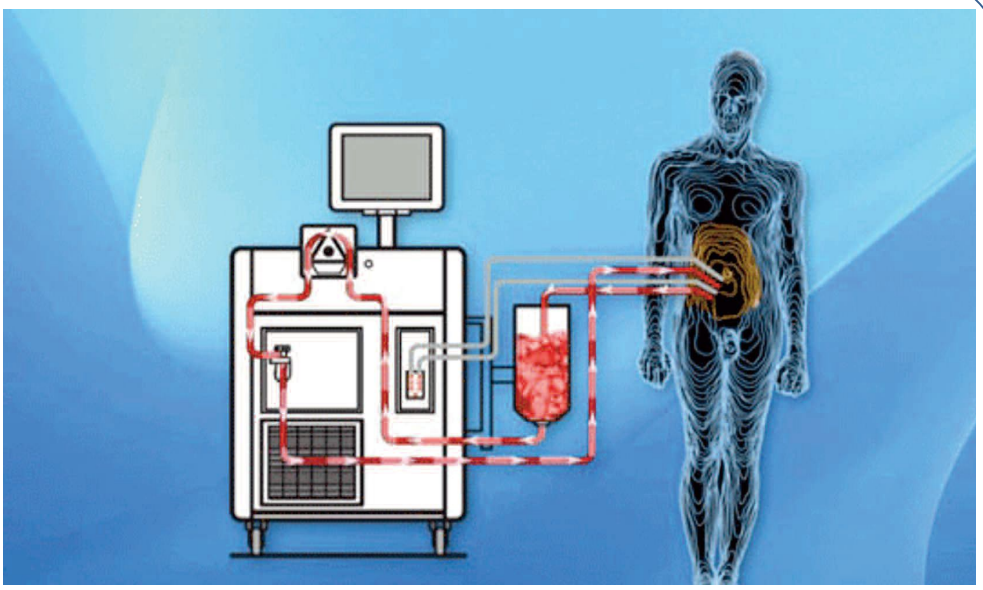

Figure.1. hyperthermic interperitoneal chemotherapy

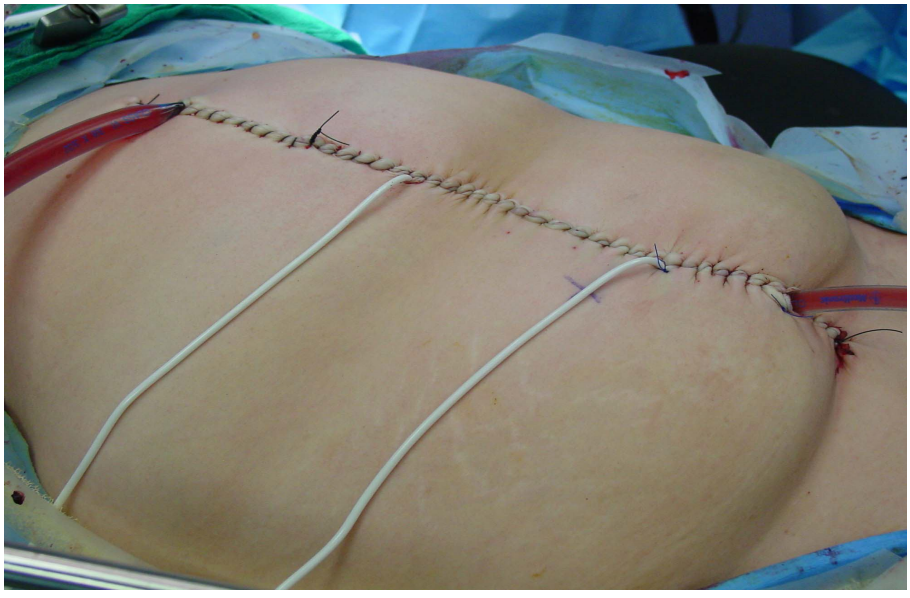

Figure.2. cytoreductive surgery