

Quaternary cytoreductive surgery in ovarian cancer. A literature review

Nicolae Bacalbasa¹,
Irina Balescu²,
Alexandru Filipescu^{1,3}

1. UMF "Carol Davila",
Bucharest, Romania
2. Ponderas Hospital,
Bucharest, Romania
3. Elias Emergency Hospital,
Bucharest, Romania

Correspondence:
Dr. Nicolae Bacalbasa
e-mail: nicolaebacalbasa@gmail.com

Abstract

Ovarian cancer represents one of the most aggressive gynecologic malignancies, most women still being diagnosed in an advanced stage of the disease. Although primary maximal cytoreduction associated with adjuvant chemotherapy seems to be the most efficient way to achieve a good control of the disease most patients recur at a certain moment. In these cases secondary and tertiary cytoreduction appear to be associated with a significant survival benefit. Studies regarding the role of cytoreduction beyond tertiary surgery remain scarce but preliminary reports prove that in selected cases this might represent a reasonable option in order to prolong survival.

Keywords: ovarian cancer recurrence, quaternary cytoreduction, overall survival

Introduction

In 2008, ovarian cancer became the fifth cause of cancer related death, being responsible for 140.200 deaths in women worldwide⁽¹⁾. Most patients are diagnosed in an advanced stage of the disease, carrying a poor overall prognosis and a 5-year survival rate of 30-55%⁽²⁾.

The utility of cytoreductive surgery was first suggested by Meigs almost 100 years ago and demonstrated by Griffiths in 1970. Griffiths brought additional objective data and proved that there is a strong relation of inverse proportionality between the dimensions of the restant tissue at the end of cytoreduction and the overall survival^(3,4). The good response after cytoreduction can be explained through the Gompertzian' cell growth curve. The bulky tumoral masses associated with ovarian cancer which exist at the moment of the diagnosis are usually formed by old cells with low rate of growth and poor blood supply which are not susceptible to the chemotherapeutic agents. Once these bulky masses are resected only young cells with fast rate of growth remain and the response to chemotherapy significantly increases⁽⁵⁾.

Although a good control of the disease seems to be obtained after this association between primary complete cytoreduction and adjuvant platinum salts chemotherapy most women (70-90%) will develop multiple recurrences^(6,7,8). This aspect enables us to consider that ovarian cancer represents a chronic disease which presents in its natural course multiple episodes of relapse which can be managed through surgery and adjuvant chemotherapy. For this reason most recent studies are focused on searching if the same principles of cytoreductive surgery can be applied in ovarian cancer relapse and for how many times⁽⁹⁻¹²⁾. While a large number of studies have shown the benefits of cytoreductive surgery for secondary and even tertiary

relapse, things are still in debate when it comes about quaternary cytoreduction⁽⁹⁻¹¹⁾.

The role of quaternary cytoreduction in ovarian cancer

In their study developed at the Memorial Sloan Kettering Cancer Center Shih et al⁽¹⁰⁾ analyzed the influence of quaternary cytoreduction on overall survival on 15 patients with relapsed ovarian cancer. All of the 15 patients had undergone optimal primary, secondary and tertiary cytoreductive surgery, with residual disease varying from 0 to 1 cm. at the end of quaternary cytoreduction 10 patients had no gross residual disease, 2 patients had residual disease <0.5 cm, 1 patient had residual disease between 0.5 and 1 cm and 2 cases had residual disease >1 cm. Optimal residual disease was considered to be smaller than 1 cm. At univariate analysis residual disease at the moment of quaternary cytoreduction (<1 cm versus >1 cm) and the number of recurrent tumoral masses (single versus multiple) were identified to be the most significant prognostic factors (p=0.01 respectively p=0.008). The disease specific survival after quaternary cytoreduction was 34.8 months in patients with optimal resection (residual disease <1 cm) and only 10 months for patients with suboptimal resection. The patients with single recurrence had a median survival of 49.9 months while those with multiple recurrences had a median survival of only 19.5 months. This study was limited by the small number of patients (15 cases) and by the absence of a control group with the same characteristics of the tumor treated only by chemotherapy.

The largest study of cytoreductive surgery beyond the third relapse comes from Fotopoulou et al; it was conducted in the Department of Gynecology at the Charite Campus Virchow Clinic between October 2000

Received:
January 11, 2014
Revised:
March 05, 2014
Accepted:
July 12, 2014

and January 2012 and included 49 patients⁽¹³⁾. This study included all surgical procedures performed after the fourth relapse, 4 patients being included for even the fifth relapse. Their results were in concordance with Shih's study, the most important prognostic factors being the residual disease at the end of the 4th cytoreduction and the number of recurrent tumoral masses. The patients with no residual disease at the end of the quaternary cytoreduction had an overall survival of 43 months while those with residual disease had only 13.4 months survival. More than that, Fotopoulou's study demonstrated that adjuvant chemotherapy after quaternary cytoreduction seems to improve the overall survival ($p=0,001$). In multivariate analysis the same study demonstrated that only the number of recurrences and adjuvant chemotherapy after the quaternary resection offer a significant protective impact on overall survival. The fact that the residual disease after quaternary cytoreduction did not have prognostic value in multivariate analysis can be due

to the relatively small number of patients included in this study. Although the high value of ascites volume, platinum resistance or the presence of extrapelvic disease were thought to be poor prognostic factors when evaluating the recurrent disease, they failed to demonstrate their statistical significance when it comes about quaternary cytoreductive surgery. This fact might be explained by the high selections process of the surgical candidates⁽¹³⁾.

Conclusions and Future Directions

The most important prognostic factors remain the number of recurrent tumors and dimensions of the residual disease after quaternary cytoreductive surgery.

Although quaternary cytoreductive surgery associated with adjuvant chemotherapy seems to be an efficient way of controlling ovarian cancer recurrence even further than the fourth relapse future larger prospectively and multicenter studies are needed to validate the present data. ■

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; 61 (2): 69-90
2. Randall L, Berman M. Management of Adnexal Masses. *ACOG Practice Bulletin- Clinical Management Guidelines for Obstetrician-Gynecologists* No. 83, 2007.
3. Meigs JV. *Tumors of the female pelvic organs*. New York: Macmillan, 1934.
4. Griffiths CT. Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. *Natl Cancer Inst Monogr* 1975, 42, 101-4.
5. Shih K, Chi D. Maximal cytoreductive effort in epithelial ovarian cancer surgery. *J Gynecol Oncol* 2010, 21, 2, 75-80.
6. Eisenkop SM, Friedman RL, Wang HJ. Complete cytoreductive surgery is feasible and maximizes survival in patients with advanced epithelial ovarian cancer: a prospective study. *Gynecol Oncol* 1998, 69, 103-8.
7. Muggia FM, Braly PS, Brady MF, et al. Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: a gynecologic oncology group study. *J Clin Oncol* 2000, 18, 106-15.
8. Ozols RF. Recurrent ovarian cancer: evidence-based treatment. *J Clin Oncol* 2002, 20, 1161-3.
9. Shih, K.K., Chi, D.S., Barakat, R.R., Leitao M.M., Tertiary cytoreduction in patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer: An updated series, *Gynecologic Oncology* 117, 2010, 330-5.
10. Shih KK, Chi DS, Barakat RR, Leitao MM. Beyond tertiary cytoreduction in patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, *Gynecologic Oncology* 116, 2010, 364-9.
11. Gultekin M, Velipas M, Lu A, Aksan G, Dursun P, Dogan U, Yuce K, Ayhan A. A Third Evaluation of Tertiary Cytoreduction, *Journal of Surgical Oncology* 2008;98:530-534
12. Leitao JrM, Kardos S, Barakat R, Chi D. Tertiary cytoreduction in patients with recurrent ovarian carcinoma, *Gynecologic Oncology* 95, 2004, 181-8.
13. Fotopoulou C, Savvatis K, Kosian P, Braicu I, Papanikolaou G, Pietzner K, Schmidt S, Sehouli J. Quaternary cytoreductive surgery in ovarian cancer: does surgical effort still matter? *British Journal of Cancer* 2013, 108, 32-8.