REPETITIVE DEBULKING SURGERY AS ADJUVANT TO CHEMOTHERAPY IN ADVANCED EPITHELIAL OVARIAN CANCER

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SUMMARY

The Auhtors refer their own experience on a planned prospective study of integrated chemosurgical treatment in advanced epithelial ovarian cancer.

Repetitive surgery interspersed with non cross resistant schedules of chemotherapy can achieve more than 60% of complete responses with an expected five years survival rate dependent on the residual disease after primary and expecially second operation. In particular residual neoplasia larger than five centimeters after the first laparotomy or larger than two centimeters left behind at second laparotomy constitutes the worst prognostic index.

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The surgical treatment of epithelial ovarian cancer is both the fundamental moment in a multidisciplinary strategy and an absolutely necessary step for correct primary staging and reevaluation of the disease ([1]).

Previous reports by our group underlined the possibility of performing repetitive (adjuvant) surgery interspersed with different non-cross resistant regimens of chemotherapy and of obtaining in this way over 60% complete pathological response ([2-8, 10-22]).

Our actual strategy, which started in 1978, is:

Primary surgery

Primary surgery (tab. 1) has always a double aim: diagnostic and therapeutic. Ovarian cancers are sensitive to a variety of chemotherapeutic agents and many studies have confirmed the importance of the extent of tumour masses after primary surgery in determining the results following chemotherapy.

First line chemotherapy

The first line chemotherapy (tab. 2) that we retain optimal is the association between Adryamycin and Cyclophosphamide according to Parker's protocol modified ([9]).

Second laparotomy is mandatory for the correct assessment in defining the responsiveness of the disease and for obtaining a further tumour reduction when needed. Our experience has pointed out the need of not stopping treatment after complete response is achieved but to continue chemotherapy with a non cross resistant schedule for consolidation.

Aims and modality of second laparotomy (tab. 3)

According to our philosophy second laparotomic look is not a merely "second look" but an integrated surgical proce-

Table 1. — *Advanced ovarian cancer.*

Primary surgery:
— xypho pubic laparotomy
— peritoneal citology
— hysterectomy + bilateral adnexectomy
— appendectomy
— omentectomy
— tumor debulking
— biopsies of any suspected areas
— biopsies of electives areas
diaphragm
retroperitoneal lymphnodes
pelvic peritoneum
— random biopsies

Table 2. — *Advanced ovarian cancer.*

1st line chemotherapy:

Adriamycine:	45-100 mg/mq i.v. day 1
Cyclophosphamide:	500-2000 mg/mq i.v. day 1

for patients in good conditions and with normal hepato-renal function: maximal dose every 21 days for five courses

Table 3. — *Advanced ovarian cancer.*

Role of second laparotomy:
— correct assessment of response of chemotherapy
— topographic assessment of residual disease
— radicalization of residual tumour masses with surgical converted complete remission
— surgical debulking with further tumour reduction
— pathological assessment of complete remission

dure with a precise "timing" and "modality". In our experience the second laparotomic look must be performed after four or five cycle of treatment.

This time allows a correct evaluation of the response to chemotherapy and the change, in cases of poor response, of chemotherapeutic regimen avoids progression of neoplasias.

In cases of complete response a consolidation second line chemotherapy is performed.

The second laparotomic look allows for remedying any surgical omissions of the first operation.

We don't believe that a non invasive instrumental technique is able to define certainly remission for patients clinically free of disease (t^0).

Second line chemotherapy

When pathological complete response is obtained the patient concludes treat-

Table 4. — *Advanced ovarian cancer.*

2nd line chemotherapy:
for patients with negative second look (no tumour found at second laparotomy)

CONSOLIDATION PROTOCOL

Polymelphalan: 80 mg/mq day 1 every 15 days for six courses

Table 5. — *Advanced ovarian cancer.*

2nd line chemotherapy:
for patients with surgical converted complete remission or with minimal surgical residual disease after second laparotomy:

"HD REGIMEN"

Exametilmelamine: 200 mg/mq days 8-21
Cis-Platinum: 50-80 mg/mq day 1 every 3 week

↓

THIRD LAPAROTOMY

Table 6. — *Advanced ovarian cancer.*

2nd line chemotherapy:
for patients with large residual disease after second laparotomy:
Cis-Platinum: 100 mg/mq day 7, every 21 days
5-FU: 500 mg/mq day 1-5 (for five courses)

↓

THIRD LAPAROTOMY

Table 7. — *Advanced ovarian cancer.*

3rd line chemotherapy	
3rd look:	
Negative:	Polymelphalan (80 mg/mq i.v. day 1 every 15 days for six courses
Positive:	Polymelphalan or experimental schedules (treatment failures)

Table 8. — *Ovarian cancer: Paduan Cooperative Group: clinical series.*

Year	Cases treated	III - IV stage eligible for protocol
1978	17	13
1979	20	15
1980	37	33
1981	35	22
1982	39	26
1983 (Jun)	19	4 (13 are in treatment)
Total	177	113 (63%)

Table 9. — *Advanced ovarian cancer: type of primary surgery.*

Primary surgery	N (%)	Residual disease (cm)			
		absent	<2	2-5	>5
Radical	27 (24)	27	—	—	—
Reductive	66 (58)	—	17	25	24
Explorative	20 (18)	—	—	—	20
Total	113 (100)	27 (24)	17 (14)	25 (22)	44 (40)

ment with a consolidation regimen with Polymelphalan (tab. 4).

This consolidation treatment aims at assuring against neoplastic localization not detected at the second look for the site or dimension, but probably become resistant to the first line chemotherapy.

When tumour is found at second look, even if microscopic or completely surgically removed (surgical converted complete remission after partial response to chemotherapy) the treatment is based on the use of cisplatinum. This drug is associated with hexametilmelamine (tab. 5) in patients with minimal residual disease or with 5 FU in patients with large (major than 5 cm) residual disease after second operation (tab. 6).

Table 10. — *Advanced ovarian cancer: primary surgery* (Jan. 1978.-Jun. 1983; 113 cases).

	No. cases
Total hysterectomy with bilateral adnexectomy	61
Monolateral adnexectomy	10
Bilateral adnexectomy	10
Subtotal hysterectomy with b.a.	3
Omentectomy	57
Appendectomy	25
Intestinal loops resection	6
Explorative laparotomy	20

Table 11. — *Advanced ovarian cancer: repetitive surgery.*

Primary surgery	N (%)	Second look laparotomy reductive		explorative	
		with RD	without RD (*)	neg.	pos.
Radical	26 (27)	1	2	22	1
Reductive	54 (57)	18	8	14	14
Explorative	15 (16)	3	6	1	5
Total	95 (100)	22 (23)	16 (17)	37 (39)	20 (21)

RD = residual disease
(*) = converted complete remission

Third look

After second line chemotherapy patients found positive at second look are submitted to third laparotomy with the same aims and modality described for repetitive surgery.

Table 12. — *Advanced ovarian cancer.*

	No. cases
Type of surgery at second look (95 cases):	
Total hysterectomy with bilateral adnexectomy	20
Bilateral adnexectomy	12
Monolateral adnexectomy	5
Omentectomy	32
Appendectomy	15
Intestinal loops resection	4
Debulking	22
Random biopsy	33
Explorative	27

If the third look is negative the patient will receive Polymelphalan as consolidation. If the third look is positive the patients might receive an experimental protocol (tab. 7).

Clinical series

Our comprehensive series consists of 413 cases observed since 1963 ([11, 12, 13]) the cases observed in the last five years are 177.

We consider now only 113 consecutive patients of stage 3 and 4 (according to FIGO classification) treated with above mentioned protocol (tab. 8).

27 patients (24%) had initial optimal surgery (radical surgery with absence of any neoplastic visible localization) 66 patients (58%) had reductive surgery of the tumour.

20 cases (18%) had only explorative laparotomy with minimal debulking or multiple biopsy only (tab. 9).

Types of surgical procedure performed at primary surgery are described in table 10.

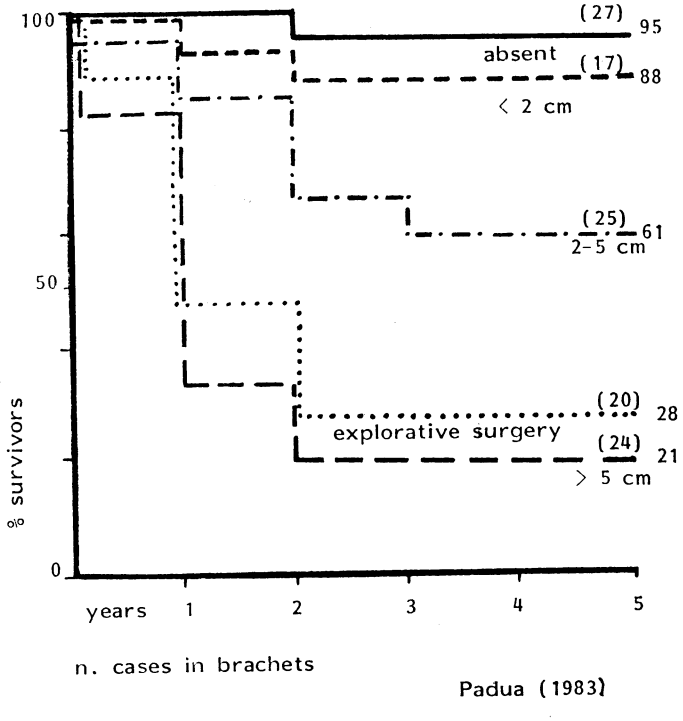

Fig. 1. — Advanced ovarian cancer: percent survival according to residual disease after primary surgery (113 cases).

In 95 of these cases we performed second laparotomic look which resulted negative in 37 (39%) patients.

In 16 (17%) cases laparotomic look was positive but the contemporary surgical debulking removed all visible tumour with a consequent complete remission.

obtain a complete surgical remission after second line chemotherapy for masses not resecable at second intervention.

CONCLUSIONS

– Repetitive surgery is possible without mortality or gross morbidity.

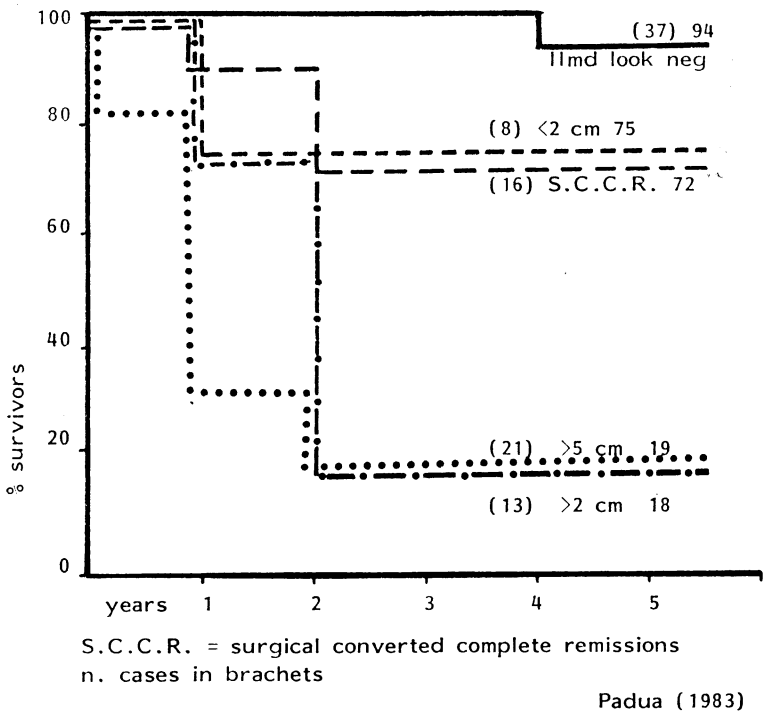

Fig. 2. — Advanced ovarian cancer: percent survival according to residual disease after second laparotomy (95 cases).

Only in 20 patients (21%) the second look revealed a tumour extension or localization susceptible of major debulking (tab. 11).

The type of operation performed at second laparotomy is described in table 12.

In 25 cases with residual disease after second look or with complete remission achieved after surgery we performed a third laparotomic look.

In 10 cases (40%) the exploration was negative; in 3 cases it was possible to

– Integration of repetitive surgery and non cross resistant chemotherapies can give over 60% of complete remission.

– Most reliable bad prognosis indexes are the residues larger than 5 cm left behind in first (fig. 1) and especially second operation (fig. 2).

– Only in cases presenting residual neoplasia after primary surgery which has shown no significant responsiveness to firstline chemotherapy may laparotomy not be indicated for the second look.

Metastases which cannot be removed by the first intervention and do not show at least objective remission after chemotherapy contra-indicate repeated surgery.

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