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CARCINOMA OF THE OVARY IN STAGE III

Effects of postoperative chemotherapy, radiation therapy and repeat laparotomy

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Ovarian carcinoma has the highest mortality rate of the malignant tumours of the female genital tract. The signs and symptoms of the disease are non-specific and the diagnosis is most often made at surgery, when most of the patients are at an advanced stage of the disease. Surgery together with chemotherapy or irradiation, or both in combination, is the main form of treatment in late as well as in early stages of the disease (BUSH & DEMBO 1980). In patients with stage III ovarian epithelial tumours the following points were evaluated: (1) The prognosis of extensively operated patients after postoperative treatment with radiation therapy alone or combined with chemotherapy. (2) The operability of primarily inoperable patients after preoperative treatment with radiation therapy alone or combined with chemotherapy. (3) The prognosis of patients with minimal residual disease after primary surgery or after repeat laparotomy.

Material and Methods

During the years 1975 through 1978, 391 patients with malignant epithelial ovarian tumours were treated at this Department of Oncology. According to the classification of FIGO (BARR 1980) 189 (48%) patients were stage III; 153 of these were included in a randomized prospective trial for comparing the results of irradiation (XRT) with those obtained from combined treatment with Melphalan and irradiation (M+XRT). Of the remaining 36 patients 27 (4 primarily extensively operated upon) were postoperatively treated with Melphalan alone due to their poor general condition or to certain technical problems. Nine patients were given other forms of therapy (3 of these had been primarily extensively operated upon). In the present report, mainly the patients in the randomized trial are discussed.

Primary operation. Most of the patients had been operated upon at other hospitals and then been referred to this department of oncology in the postoperative period. The intention with the primary operation was to perform bilateral salpingo-oophorectomy (SOEB) with or without total hysterectomy (HIT) and infracolic omentectomy (OME). This extensive surgery was performed in 58 patients.

The tumour was considered inoperable in 95 patients. Exploratory laparotomy had been performed in 72 of these patients, without an attempt to reduce the tumour volume. The remaining 23 patients were not submitted to primary surgery.

The patients in these two groups were included in a prospective randomized trial and were grouped according to two different treatment modalities (XRT versus M+XRT) according to odd or even date of birth. Faulty allocation occurred in both groups, 7 per cent in those extensively operated upon and 17 per cent in the other group. Alternative

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analysis following the recommendations of WHO (1979) has been done and resulted in essentially the same conclusions (Tables 1, 2).

Irradiation (XRT): External irradiation was given with 5 fractions to a dorsal field and 3 weeks later 6 or 7 fractions to an abdominal field, using one fraction a day and 5 fractions a week. Radiation parameters: 180 kV, HVL 1 mm Cu; SSD 70 to 80 cm, 600 cm^2 with a total of 20 Gy to the dorsal and 20 Gy to the abdominal field. The midpoint absorbed dose in the center of the field varied between 10 and 15 Gy, depending on the thickness of the patient. The cranial-caudal variation of the midway dose along the treated area causes another uncertainty in the dose figures. Supplementary intracavitary treatment was given once or twice with a rod-shaped applicator in the uterus or a flat applicator in the upper part of the vagina, diameter 7 mm×72 mm, containing 5.6 GBq Ra; 5 mm×44 mm×44 mm, containing 4.2 GBq Ra, 6 to 12 or 13 to 14 hours, respectively.

Chemotherapy and irradiation (M+XRT): Melphalan was infused intravenously during 6 to 8 h (1 mg/kg body weight to a maximum of 60 mg, given in 1000 ml invertose or sodium chloride solution). Three infusions were given at intervals of 4 weeks, starting the first day after the primary operation. Irradiation began 6 weeks after the third Melphalan infusion.

Reoperation was performed 6 weeks after the conclusion of irradiation. Only patients primarily considered inoperable were selected for reoperation. Patients with tumour progress or general poor physical condition were not reoperated (60% of the original 95 patients intended for reoperation). The intention with the reoperation was the same as for the primary operation (SOEB±HIT±OME).

Continued chemotherapy. In patients primarily extensively operated upon (58 patients), the intention was to give chemotherapy in recurrent (progressive) or metastasizing disease. In the last years, however, the tendency to give chemotherapy as a part of the primary treatment has increased. Ten patients were treated with continued chemotherapy before any progress of the disease was noted.

In patients not primarily submitted to extensive surgery (95 patients) the intention was to give all patients (39 patients) chemotherapy after relaparotomy irrespective of type of operation and the extent of tumour growth. Thirty of the relaparotomized patients were thus treated with continued chemotherapy after the randomized treatment. In patients not relaparotomized (56 patients) chemotherapy was given as a rule only in progressive disease if the patient's general physical condition permitted it. Five patients were treated with continued chemotherapy before any progress of the disease was noted.

Table 1

Treatment allocation, primarily extensively operated patients

Patients primarily extensively operated	No. of cases	XRT	M+XRT	p-value
Patients entered	58	25	33	0.32
Patients treated regardless of allocation	58	27	31	0.23
Patients correctly allocated and treated	54	24	30	0.23

XRT=irradiation. M+XRT=chemotherapy and irradiation.

Table 2

Treatment allocation, primarily not extensively operated patients

Patients primarily not extensively operated	No. of cases	XRT	M+XRT	p-value
Patients entered	95	44	51	0.49
Patients treated regardless of allocation	95	50	45	0.69
Patients correctly allocated and treated	79	39	40	0.57

XRT=irradiation. M+XRT=chemotherapy and irradiation.

Table 3

The distribution of histopathologic type of tumour in patients extensively operated upon. Per cent in parentheses

Type	Total	Treatment	
		XRT	M+XRT
Serous	31 (53)	14 (52)	17 (55)
Mucinous	7 (12)	3 (11)	4 (13)
Endometroid	12 (21)	7 (26)	5 (16)
Mesonephroid	2 (3)	1 (4)	1 (3)
Anaplastic carcinoma	5 (9)	2 (7)	3 (10)
Unspecified adenocarcinoma	1 (2)		1 (3)
Total	58 (100)	27 (100)	31 (100)

XRT=irradiation. M+XRT=chemotherapy and irradiation.

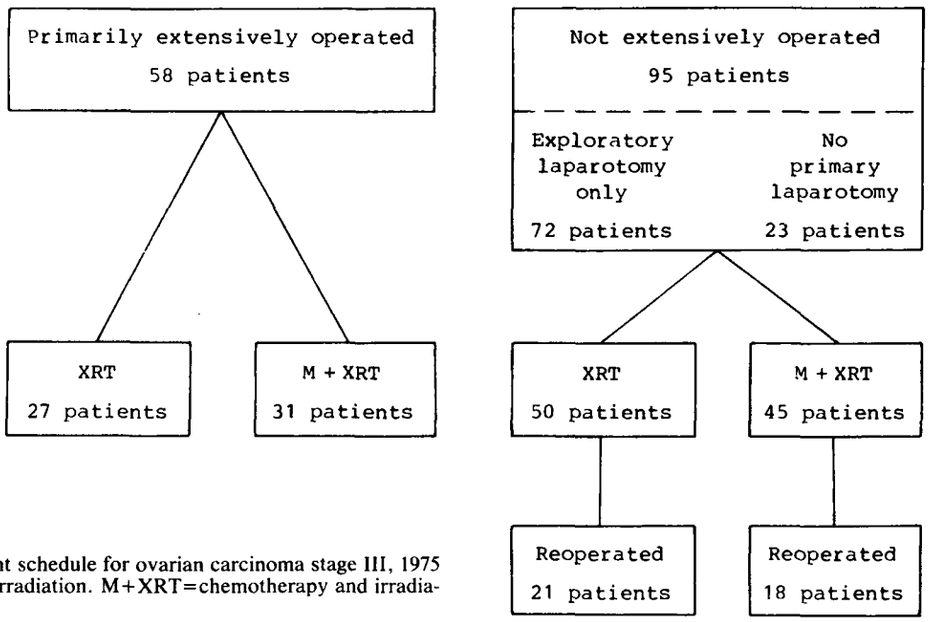

Fig. 1. Treatment schedule for ovarian carcinoma stage III, 1975 to 1978. XRT=irradiation. M+XRT=chemotherapy and irradiation.

Table 4

Type of reoperation in patients primarily not extensively operated upon and the distribution between the treatment groups XRT (irradiation) and M+XRT (chemotherapy and irradiation). Per cent in parentheses

Type of reoperation	Preoperative treatment	
	XRT	M+XRT
None	29 (58)	27 (60)
Exploratory laparotomy	7 (14)	8 (18)
Salpingo-oophorectomy+ hysterectomy+omentectomy	14 (28)	10 (22)
Total	50 (100)	45 (100)

As a rule Melphalan was given at 6 to 8 weeks intervals up to a maximum dose of 800 mg or until progression of the disease was noted.

The treatment schedule is given in Fig. 1. The material was analysed with regard to histopathologic type and grading, age distribution and radicality of operation. The classification was made according to the WHO classification (FOX 1980). The grading was done according to the criteria established by Allan & Hertig (KENT & MCKAY 1960) and the tumours were classified as well, moderately and poorly differentiated. No borderline malignancy was included. The observation period was 2 to 6 years. Survival calculations were made using the life-table technique, the Lee-Desu test (LEE & DESU 1972) and the Cox proportional hazard model (KALBFLEISCH & PRENTICE 1980).

Results

Extensive surgery was performed in 58 patients (Fig. 1). The number of patients with no tumour or residual tumour ≤2 cm after the primary operation was 7 in the XRT group and 15 in the M+XRT group. The distribution by type is shown in Table 3. The distribution by grading was ~3 per cent well differentiated in both groups, 22 per cent moderately differentiated in the XRT group and 39 per cent in the M+XRT group, 74 per cent poorly differentiated in the XRT group and 58 per cent in the M+XRT group. The patients in the M+XRT group were younger ($p>0.05$) than those in the XRT group.

Less extensive surgery was carried out in 95 patients (Fig. 1, Table 4). The number of patients with no tumour or residual tumour ≤2 cm after reoperation was 5 in the XRT group and 7 in the M+XRT group. The distribution by type is given in Table 5. The distribution by grading was about the same in both groups. Moderately differentiated tumours were observed in 13 to 16 per cent, poorly differentiated in 76 to 78 per cent and ungraded tumours in 11 to 6 per cent, respectively. The age distribution was about the same in both groups.

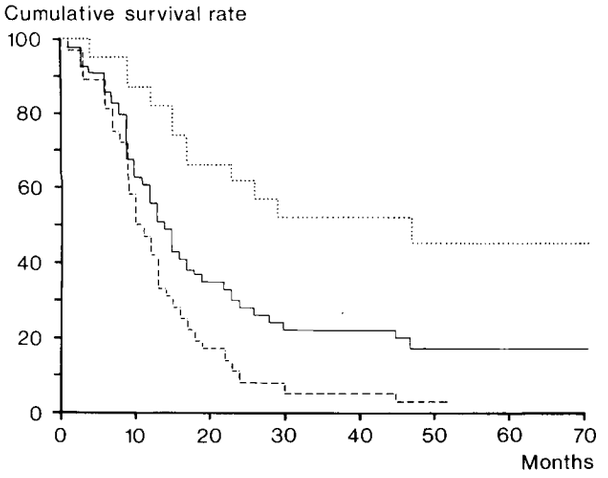

Fig. 2. Cumulative survival (in per cent) for extensively operated patients at the primary operation. All patients, n=58 (——). Residual tumour ≤2 cm, n=22 (· · · ·). Residual tumour >2 cm, n=36 (– – –).

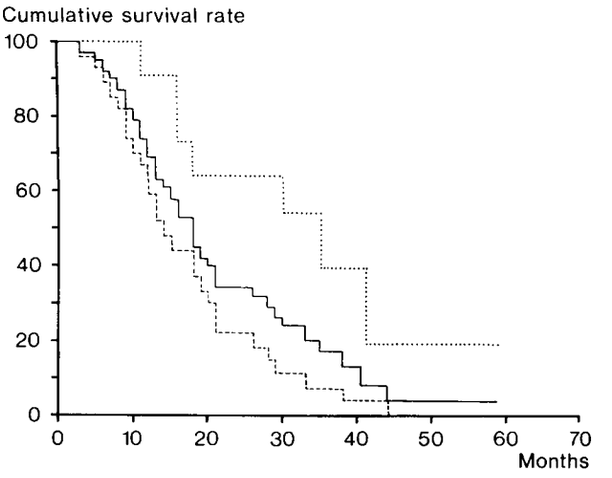

Fig. 3. Cumulative survival (in per cent) for patients reoperated in the group not extensively operated upon at the primary operation. Patients reoperated, n=39 (——). Residual tumour ≤2 cm, n=12 (· · · ·). Residual tumour >2 cm, n=27 (– – –).

Table 5

The distribution of histopathologic type of tumor in patients not extensively operated upon. Per cent in parentheses

Type	Total	Treatment	
		XRT	M+XRT
Serous	58 (61)	33 (66)	25 (56)
Mucinous	3 (3)	1 (2)	2 (4)
Endometroid	14 (15)	5 (10)	9 (20)
Mesonephroid	3 (3)	2 (4)	1 (2)
Anaplastic carcinoma	9 (10)	6 (12)	3 (7)
Unspecified adeno-carcinoma	8 (8)	3 (6)	5 (11)
Total	95 (100)	50 (100)	45 (100)

XRT=irradiation. M+XRT=chemotherapy and irradiation.

Thirty-four of the 153 patients included in the randomized trial were operated upon with no tumour (17 patients) and residual tumour ≤2 cm (17 patients). The distribution by type and grade was as follows: 21 serous, 5 mucinous, 5 endometroid, 1 mesonephroid and 2 anaplastic tumours; 22 poorly, 11 moderately and one well differentiated tumours.

Tables 6 and 7 give the median survival and 2- and 5-year survival for the patients in the two operation groups (extensive and not extensive primary operation) and the respective subgroups. The treatments were analysed within each group as shown in Tables 1 and 2 and no differences were observed between the two modes of therapy. The respective subgroups were analysed in the same way without any differences being observed.

The cumulative survival for patients primarily submitted to extensive surgery and for those reoperated after preoperative therapy appears in Figs 2 and 3. The patients with no or ≤2 cm residual tumour at surgery had longer survival than those operated upon with >2 cm residual tumour within each group ($p<0.005$ and $p<0.003$, respectively). The survival of patients with no or small residual tumour was not significantly lower in the group reoperated than in the group primarily operated ($p\geq0.3$; Fig 4).

The cumulative survival according to grade showed no difference in survival for patients with large postoperative tumours (>2 cm; $p>0.2$). Patients with no or small residual tumours and well or moderately differentiated tumours (12 patients) had, however, significantly longer survival than those with poorly differentiated tumours, 22 patients ($p=0.05$; Fig. 5).

No difference in survival was observed between patients operated with SOEB only and those operated with SOEB+HIT±OME within the group primarily extensively operated. These results were confirmed with the Cox analysis.

Discussion

The prognosis of patients with ovarian carcinoma is substantially improved if the tumour growth per-

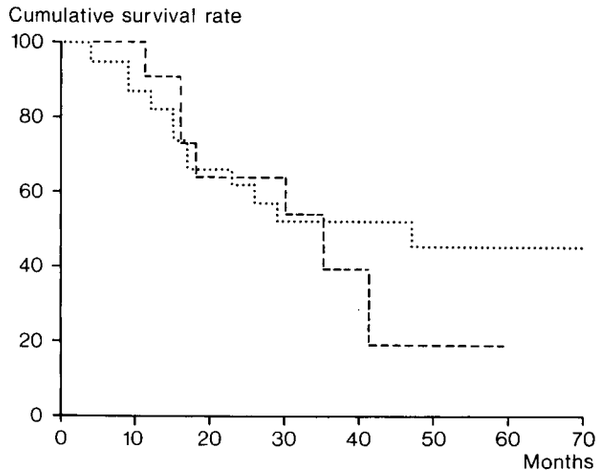

Fig. 4. Cumulative survival (in per cent) for patients primarily operated upon or reoperated with no or small residual tumours (≤2 cm). Primarily operated, n=22 (····). Reoperated, n=12 (– – –).

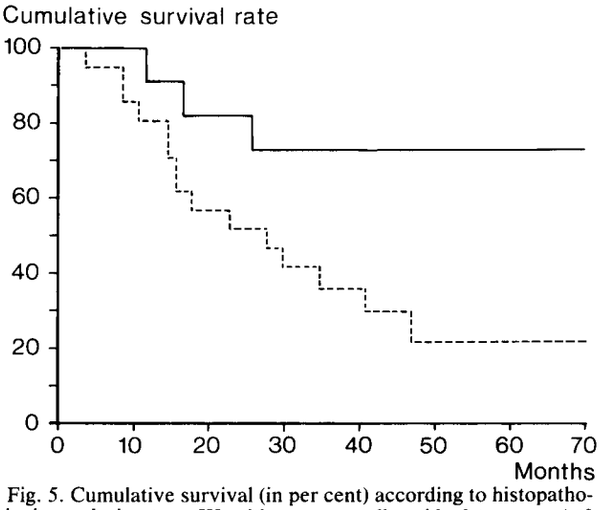

Fig. 5. Cumulative survival (in per cent) according to histopathologic grade in stage III with no or small residual tumours (≤2 cm). Well/moderately differentiated, n=12 (——). Poorly differentiated, n=22 (– – –).

mits a good tumour reduction (MUNNELL 1968, AURE et coll. 1971, SMITH & DAY 1979). The survival analysis in this material further validates this experience.

The standard operation technique in resectable tumours is bilateral salpingo-oophorectomy often combined with hysterectomy with or without omentectomy (W. G. SMITH 1979). The value of omentectomy is controversial. Some have reported better survival if omentectomy was included (MUNNELL

Table 6

Median survival and 2- and 5-year survival for patients primarily extensively operated upon

Patients primarily extensively operated	No. of cases	Median survival (months)	Two-year survival (per cent)	Five-year survival (per cent)
All patients	58	15	28	18
0–≤2 cm residual tumour	22	47	62	45
>2 cm residual tumour	36	11	8	0

Table 7

Median survival and 2- and 5-year survival for patients primarily not extensively operated upon

Patients primarily not extensively operated	No. of cases	Median survival (months)	Two-year survival (per cent)	Five-year survival (per cent)
All patients	95	9	19	2
Patients not reoperated	56	6	7	0
Patients reoperated	39	18	34	4
Reoperated with 0–≤2 cm residual tumour	12	35	64	19
Reoperated with >2 cm residual tumour	27	15	22	0

1968, 1969), while others have stated to the contrary (W. G. SMITH). However, hysterectomy is more commonly accepted, although there are reports that emphasize the opinion that hysterectomy did not improve the survival rate (DALLEY 1962, KOTTMEIER 1963).

In the present material hysterectomy was mainly performed if radical or minimal residual disease was thereby accomplished. In other cases the uterus was left for intrauterine irradiation. Omentectomy was mainly performed on the same indications if the omentum was affected by tumour growth. The patients operated primarily with SOEB only had not worse survival than patients operated with more extensive operation (SIGURDSSON et coll. 1982 b).

The treatment of large disseminated tumours differs. Some surgeons have tried to attain tumour reduction in these patients by using very extensive surgical measures, including extraperitoneal mobilization, often combined with intestinal resections and removal of para-aortic nodes (BARBER & BRUNSCHWIG 1965, HUDSON & CHIR 1973, GRIFFITHS et coll. 1979, W. G. SMITH, J. P. SMITH 1980, WIJNEN & ROSENSHEIN 1980). The complication rates were high at the beginning, but later lower complication rates were reported, which can be attributed to experience gained in selecting patients for surgery and to intensified postoperative care (GRIFFITHS et coll. 1979, J. P. SMITH 1980).

It is difficult to evaluate these very extensive operations. PEREZ & OLSON (1970) have reported that surgical trauma may reduce the radiation sensitivity of the residual tumour cells. LONG et coll. (1967) and KOTTMEIER (1962, 1971) have emphasized the risk of cross-sectioning and traumatizing tumour masses in inoperable or doubtfully operable cases. The operation can be converted into an 'exercise in tumour dissemination' (LONG et coll.).

However, the prognosis of patients with advanced ovarian carcinoma where the postoperative residual tumours are 0 to ≤2 cm, is significantly better than in patients with larger residual tumours (MUNNELL, GRIFFITHS et coll. 1972, 1979, EDMONSON et coll. 1979, W. G. SMITH 1979, HANSON et coll. 1980, SCHWARTZ & SMITH 1980, J. P. SMITH 1980). This is confirmed by the present results and also holds true for the patients operated upon after preoperative treatment. The prognosis for those reoperated with no tumour or residual tumour ≤2 cm was not significantly worse than for those primarily extensively operated upon with the same tumour reduction. Most of the reoperated patients were, however, treated with continued chemotherapy. The prognostic significance of the tumour grade is demonstrated only in patients with no or small residual tumours (SIGURDSSON et coll. 1982 a).

The primary operability in the whole material was 65/189 (34%) patients. Of these, 25/65 (~39%) patients had macroscopic radicality or residual tumour ≤2 cm. The corresponding figures for the patients in the randomized trial were 58/153 (38%) and 22/58 (~38%).

In order to improve the operability and prognosis of patients with primarily inoperable tumour (95 patients), reoperation was performed after preoperative treatment with irradiation or combined chemotherapy and irradiation. The intended relaparotomy could be performed in 39/95 (41%) patients. In 12/39 (~31%) patients this operation was radical or resulted in residual tumour ≤2 cm. This was accomplished in spite of the fact that the radiation technique used was not optimal. The fact that different surgeons and hospitals are involved in the primary operation and the relaparotomies is thought to be of minor importance when considering operability due to the fact that skilled surgeons have been involved in these operations. Other authors have reported good tumour regression and increased operability after preoperative irradiation (PARKS 1945, CORSCADEN 1962, LONG et coll., FRICK et coll.) and at repeat operations after preoperative chemotherapy (SMITH et coll. 1976, SCHWARTZ & SMITH). In the present material, 37 of the 189 patients in the entire material (20%) and 34 of the 153 patients in the randomized trial (22%) were operated with macroscopic radicality or residual tumour ≤2 cm. This corresponds with a statement made by BUSH & DEMBO, who reported that 20 per cent of patients treated with maximum reductive surgery without preoperative treatment resulted in radical operation or residual tumour ≤2 cm. The preoperative treatment followed by reoperation seems thus to be an alternative to extremely extensive primary surgery in large disseminated tumours.

Postoperative adjunctive irradiation has been reported to give varying degrees of improvement in survival in advanced ovarian carcinoma (WALTER et coll. 1941, MUNNELL et coll. 1957, KOTTMEIER 1961, FUKS 1975). This effect has mainly been dependent on tumour size, number of anoxic cells and normal tissue tolerance (DELCLOS & QUINLAN 1969, BUSH & DEMBO, PECKHAM et coll. 1980, VAN

DER SCHUEREN et coll. 1980). In the last few years improved survival has been reported in patients with minimum residual disease after treatment with high voltage irradiation using stationary field techniques or moving-strip technique (DELCLOS & QUINLAN, DEMBO et coll. 1979b, CHASSAGNE 1980). The Princess Margaret Hospital Study (DEMBO et coll. 1979a) reported such a high rate of 5-year survival as 81 per cent in 'asymptomatic' stage III patients. BUSH & DEMBO stated that abdomino-pelvic irradiation was the treatment to be preferred in minimum tumour disease. In the present series, all patients were given orthovoltage irradiation.

The use of chemotherapy before irradiation has been proposed for diminishing tumour volume and rule out micrometastases. However, the Gynecologic Oncology Group (LEWIS & BLESSING 1977) could not find any improvement by using Melphalan before irradiation in patients with residual tumour ≤3 cm. These results were difficult to evaluate due to certain errors in the protocol. SMITH et coll. (1972) found no improvement in survival for patients treated with supplementary irradiation after Melphalan treatment with good tumour response, but they stated that the irradiation was poorly tolerated. JOHNSON et coll. (1972) reported no improvement in survival using irradiation in conjunction with alkylating agents. In the present series, Melphalan, given before irradiation did not increase the operability in primarily inoperable patients, neither was any improvement observed among extensively operated patients. The radiation therapy was well tolerated by all patients.

Improved survival after postoperative chemotherapy has been reported in advanced ovarian carcinoma (TOBIAS & GRIFFITHS 1976, YOUNG et coll. 1978, TROPÉ 1981). The effect depends on the amount of residual tumour and the number of chemotherapy courses given (GRIFFITHS et coll. 1979, W. G. SMITH 1979, SCHWARTZ & SMITH). GRIFFITHS et coll. (1972) have reported that single drug alkylating agents enhanced the effects of irradiation. SMITH et coll. (1975) reported better results in patients treated postoperatively with Melphalan (12 courses) than in patients treated with moving-strip irradiation to the whole abdomen followed by additional pelvic boost. According to BUSH et coll. (1977), it is difficult to evaluate these results due to the fact that the material was not stratified by histopathologic grade and stage, and most of the favourable patients were included in the Melphalan group. SMITH & DAY later reported contradictory results in another series where patients irradiated postoperatively fared better than those treated by chemotherapy. Combination chemotherapy seems to be more effective than single drug chemotherapy (BARLOW & PIVER 1977, YOUNG et coll., HOLLAND et coll. 1980, TROPÉ), especially when used in patients with minimum residual disease (YOUNG et coll., GRIFFITHS et coll. 1979), or after completed irradiation (LEWIS & BLESSING). In the present series, the effects of continued chemotherapy given after the randomized treatment is not evaluable because of patient selection, but adjustment for continued chemotherapy within each treatment group did not alter the results (KALBFLEISCH & PRENTICE). Different opinions thus exist about the optimum adjunctive treatment in patients with postoperative minimum residual disease, but the prognosis is improved, irrespective of whether irradiation alone or chemotherapy alone is used postoperatively (GRIFFITHS et coll. 1979, W. G. SMITH 1979, BUSH & DEMBO).

In widespread postoperative disease, chemotherapy seems to be the treatment most preferred (YOUNG et coll., BUSH & DEMBO, HOLLAND et coll., TROPÉ). Chemotherapy given before postoperative irradiation as in the present series did not, however, give any advantages.

Conclusion

(1) In extensively operated patients, postoperative irradiation alone has the same effect on survival as the combined use of chemotherapy and irradiation.

(2) In primarily inoperable patients, preoperative irradiation alone has the same effect on operability as the combined use of chemotherapy and irradiation.

(3) Patients with no tumour or residual tumour ≤2 cm postoperatively have significantly longer survival than patients with residual tumour >2 cm.

(4) The tumour grade has only significance in patients with no or small residual tumours (≤2 cm) postoperatively.

(5) In primarily inoperable patients, relaparotomies after preoperative treatment resulted in the same operative radicality and approximately the same survival as in patients primarily submitted to extensive surgery.

SUMMARY

A prospective randomized trial was carried out in 153 patients with stage III malignant epithelial tumours for comparing the effects of irradiation or combination of chemotherapy and irradiation on prognosis and operability. No significant differences between these two treatment modalities were found. Of the patients primarily considered inoperable were 41 per cent operated upon after preoperative treatment. Minimum residual disease (0 *to ≤2 cm) occurred in 38 per cent of the primarily operated* and in 31 per cent of those operated upon after preoperative treatment. Preoperative irradiation in primarily inoperable patients enabled more effective surgical measures at relaparotomy. The size of the residual tumour after surgery and the tumour grade influenced the survival.

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