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STAGING LAPAROTOMY AND SURVIVAL IN CARCINOMA OF THE UTERINE CERVIX

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Several authors have recently recommended staging laparotomy in cervical carcinoma (AVERETTE et coll. 1972, 1975, BUCHSBAUM 1972, GUTHRIE et coll. 1974, LEPANTO et coll. 1975, NELSON et coll. 1974, PIVER et coll. 1974, UCMAKLI et coll. 1972, VAN NAGELL et coll. 1971, VONGTAMA et coll. 1974). Because surgical staging detects disease sometimes not apparent clinically, it has been hypothesized that treatment can be modified with the information made available surgically. As a result of this additional information, the treatment might be changed or individualiresult of this additional information, the treatment might be changed or individualized, and consequently survival rates might improve. However, sufficient evidence available in the literature indicates that the information gained in surgical staging of carcinoma of the uterine cervix will not improve survival. The purpose of this report is to determine by an analysis of sites of treatment failure previously reported in large series (1) if surgical staging can increase survival in this disease and (2) if morbidity from therapy will increase significantly.

The reasons for surgical staging are as follows: (1) The accuracy of clinical staging is less than that of surgical staging. (2) Surgical staging provides a more accurate assessment of the extent of disease. (3) Doses of radiation to areas routinely irradiated (the pelvis) can be modified depending on discrepancies in clinical or surgical evaluation. (4) Areas such as the periaortic nodes which are not routinely irradiated can be treated if disease is found in those areas. (5) Palliation will be more effective if those

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patients who are found to have incurable disease do not have to undergo either radical surgery or radical irradiation, thus minimizing their risks of complication from high dose irradiation.

Discrepancies in clinical and surgical staging

There should be no dispute that there are inaccuracies in clinical staging, but this alone cannot be used as a justification for staging laparotomy. It must be demonstrated that the information made available by surgery will affect treatment and increase survival before such an approach is deemed worthwhile.

In 1968, BRUNSCHWIG reported on the surgical treatment of early carcinoma of the cervix. Only 179 (64 %) of the 279 clinical Stage I patients were found to have that stage of disease surgically and pathologically. Also, among the 312 clinical Stage II patients, only 220 (68 %) were found to have surgical and pathologic Stage II disease. Since BRUNSCHWIG'S report there have been numerous reports confirming the relative inaccuracy of clinical versus surgical staging (AVERETTE et coll. 1972, 1975, BUCHSBAUM, GUTHRIE et coll., LEPANTO et coll., NELSON et coll., PIVER et coll., UCMAKLI et coll., VAN NAGELL et coll., VONGTAMA et coll.). Unlike the earlier report from BRUNSCHWIG, patients with all stages are included in these reports. The overall accuracy of clinical staging in these smaller series is 60 to 70 per cent, confirming the BRUNSCHWIG findings in Stages I and II and also showing the inaccuracy of clinical staging in Stages III and IV.

Individualization of treatment

A review of the general principles in the treatment of this disease should be made before describing how other authors propose individualizing treatment of carcinoma of the cervix. There is variation within the radiation therapy community regarding the treatment of cervical carcimona in its various stages; however, all variations are of a basic theme. The pelvis is treated with external megavoltage irradiation and central disease is boosted by intracavitary techniques. External therapy is emphasized in more advanced disease whereas intracavitary treatment is emphasized in earlier stages.

With the exception of Stage I disease in which 2 intracavitary insertions might be used, cervical carcinoma is basically treated with a single intracavitary irradiation to boost central disease, combined with external irradiation to the entire pelvis with fields usually measuring 15 cm × 15 cm. The therapy is individualized but the major influencing factor determining the therapy is the tolerance of the normal pelvis tissues. For example, if a mobile 2 cm parametrial nodule detected clinically is instead found surgically to be 4 cm and fixed to the lateral pelvic wall, the treatment will not be altered greatly. Generally the lymph nodes along the lateral pelvic walls are treated to approximately 55 to 60 Gy in Stages I–IV, not because the radiation

therapists can individualize dose, but because the normal pelvic tissues are irradiated to tolerance. If the principle that normal tissue tolerance is the limiting factor in pelvic treatment, it becomes apparent that surgical staging will not provide information that can significantly modify pelvic therapy since optimum permissible doses are usually given in all stages. There may be variation between the stages as to how that dose is given, i.e., emphasis is placed on intracavitary irradiation in Stage I, but maximum doses are given in all stages.

AVERETTE et coll. (1975) have described the largest series of patients with surgical staging. During a four and one-half year period ending in 1975, a total of 207 patients underwent surgical exploration. Seventy-five of the 207 patients explored had surgical stages which differed from the clinical staging, an overall discrepancy of 36 per cent. This discrepancy might seem to lead to the conclusion that significant changes might be made in therapy, but a critical review shows this to be unlikely.

In the series of AVERETTE et coll. 145 were clinically staged as having IB disease at the time of surgical exploration. However, 31 of the 38 patients with disease more extensive than IB still had disease only within the pelvis. The other 7 were found to have periaortic node metastases. If the basic principles of treatment outlined previously are followed, it will be noted that the treatment of the IB patients would be modified greatly only in the 7 patients with periaortic metastases—disease outside the usual pelvic portals. In these 7 patients it might be argued whether additional periaortic irradiation would be necessary. This is without question a different form of the therapy than would have been applied if the surgical findings had not been known. However, the question if periaortic treatment is highly effective and would result in overall increased survival results will be considered later and must be entertained before proceeding with exploratory surgery.

AVERETTE et coll. also found staging discrepancies in the 62 patients in Stages II–IV. However, only 11 patients were found to have disease outside the pelvic area. These patients had periaortic metastases and are the only ones who would have had significantly different treatment regimens based on laparotomy findings. The remaining 51 patients still were found to have disease only within the pelvis, a region that would be encompassed within the usual ports anyway.

Acceptance of the basic principles of treatment outlined previously makes it clear that the treatment of only those patients who were found to have periaortic node metastases would be significantly modified as a result of the surgical findings. But this could be justified if a highly effective treatment for the periaortic metastases were possible. The following analysis will show that this is not the case.

Improbability of improving survival in cervical carcinoma by staging laparotomy

An analysis of three large series of patients with cervical carcinoma previously reported in the literature will now be used to show that exploratory laparotomy will

Table 1

Analysis of site of treatment failure of 1 705 patients with carcinoma of the uterine cervix treated with megavoltage irradiation from September 1954 to December 1963 at M.D. Anderson Hospital (Paunier et coll.)

	Stage IB	Stage II	Stage III	Stage IV
Total treated	407	618	599	81
Causes of death				
Pelvic failure with or without distant failure	12	78	243	58
Distant failure alone	10	33	38	4
Complication death	5	7	25	1
Intercurrent death	14	29	27	1
No data	2	15	20	0
Total failures	27	118	306	63
Per cent distant failures	10/27 = 37	33/118 = 28	38/306 = 12	4/63 = 6
Per cent pelvic failures or complications	17/27 = 63	85/118 = 72	268/306 = 88	59/63 = 94
Per cent cure rate (5 years)	89	74	45	21

not result in improved survival. The cause of treatment failure from these series will be analyzed. The megavoltage experience from 1954 to 1963 as reported by PAUNIER et coll. (1967) will be reviewed. A total of 1 075 patients is included in this series. The experience of KOTTMEIER (1969) describing 3 063 cases and ROUSSEAU et coll. (1972) describing 1 212 cases will also be analyzed. These series were chosen because the treatment was primarily with radiation therapy and local control and distant failure data were available.

CHISM et coll. (1975) have analyzed a series of 532 patients and have concluded that only 3 per cent might have benefited from periaortic irradiation. In this present analysis similar assumptions as described by CHISM et coll. will be employed since the radiation therapy plan for an individual patient will change significantly only for those patients with laparotomy who are found to have periaortic metastases. It will be assumed that patients who were cured with conventional fields would not have needed extended field therapy (periaortic irradiation) and therefore would not have benefited from knowledge gained at exploratory laparotomy. A patient who relapsed with an active component in the pelvis also would not have benefited from exploratory surgery since the pelvic irradiation would not have been greatly altered by surgical findings. Additional periaortic treatment would not be of benefit if the patient were doomed to fail in the pelvis anyway. It will also be assumed that any patient developing distant metastases without any evidence of periaortic metastases at the time of failure would not benefit from exploratory surgery. Such metastases would likely be hematogenous and would not be detected at laparotomy.

Table 2

Sites of treatment failure in carcinoma of the cervix (figures in parentheses represent percentages)

	Pelvic failure with or without distant failure	Distant (extrapelvic) failure alone
Radiumhemmet (1949–1957) 3 063 cases, 1 717 treatment failures (KOTTMEIER)		
Stage I	92/103 (89)	11/103 (11)
Stage II	756/853 (89)	97/853 (11)
Stage III	482/522 (92)	40/522 (8)
Stage IV	232/239 (97)	7/239 (3)
Overall	1 562/1 717 (91)	155/1 717 (9)
Fondation Curie (1956–1962) 1 212 cases, 554 failures (ROUSSEAU *et coll.*)		
Stage I	27/39 (69)	12/39 (31)
Stage II	228/237 (96)	9/237 (4)
Stage III	235/239 (98)	4/239 (2)
Stage IV	Nearly all Stage IV died with pelvic failure, exact figures not available	

The data available from PAUNIER et coll. will now be reviewed. In Stage I, 407 patients were treated from 1954–1963 (Table 1). Twenty-five patients failed therapy, 14 died of intercurrent disease, and 2 were lost to follow-up. There were 12 pelvic failures, 10 distant failures and 5 deaths from complication.

Ten of 27 (37 %) Stage I carcinoma failures died of distant disease alone, and 17 of 27 (63 %) of treatment failures were due to pelvic failure or complications. Unsurprisingly, as disease is more advanced the percentage of pelvic failures increases. The incidence of failures which are pelvic alone or combined with distant failure in Stages II, III, IV are 72, 88, and 94 per cent respectively. Similar local and distant failure rates have been reported by KOTTMEIER and ROUSSEAU et coll. (Table 2). A point which should become obvious is that failure to cure carcinoma of the cervix usually means failure to control pelvic disease in Stage I and almost always means failure to control pelvic disease in more advanced stages.

It was apparent from the series of PAUNIER et coll. regarding reasons for failure and location of distant metastases that staging laparotomy will probably not yield information which will result in increased survival rates (Table 3). If a hypothetical group of 100 patients with Stage IB disease is considered, only 11 might benefit from alterations in therapy since 89 are ultimately cured (PAUNIER et coll.). Of the 11 failures, 7 die of pelvic failure or complications, leaving only 4 patients who die with distant failure. But not all patients dying of distant failure die with disease in

Table 3

Hypothetical increase in survival from information gained by staging laparotomy as applied to data available from local control/distant failure cited in Table 1. A hypothetical group of 100 patients per stage is considered

	Stage 1 B	Stage II	Stage III	Stage IV
Patients per group	100	100	100	100
Subtract patients cured	−89	−74	−45	−21
Patients dying	11	26	55	79
Subtract patients dying with pelvic failure	− 7	−19	−48	−74
Patients with distant failure (all sites)	4	7	7	5
Subtract extra-periaortic distant failure	− 2	− 3.5	− 3.5	− 2.5
Maximum number of patients with periaortic failure alone	2	3.5	3.5	2.5
Subtract patients not salvaged by periaortic treatment (75 %)	− 1.5	− 2	− 2.0	− 2.0
Total patients salvaged	0.5	1.5	1.5	0.5
Subtract operative mortality 1 %	− 1.0	− 1.0	− 1.0	− 1.0
Overall salvage/patients per 100 treated	− 0.5	+ 0.5	+ 0.5	− 0.5

the periaortic nodes. As a reasonable estimate, it will be assumed that 50 per cent of patients who die of distant disease have metastases to the periaortic nodes, either in that site alone or in combination with distant disease elsewhere. This estimate is probably a liberal one. CARLSON et coll. (1952) showed that only 66 of 341 patients who failed distantly had evidence of periaortic nodal metastases alone or in combination with metastases elsewhere. This is an occurrence of 19, not 50 per cent, as will be assumed here. Since autopsy procedures were rare, it may be argued that many periaortic node metastases were microscopic and therefore undetected clinically. Consequently the incidence of periaortic metastases might be greater than the 19 per cent cited. However, a similar argument could be advanced in the analysis of the pelvic failure data. Undoubtedly the incidence of pelvic failures is higher than the figures listed in Table 1 since microscopic disease in the pelvis also escapes clinical detection. And consequently, if the incidence of pelvic failure is falsely low, the incidence of deaths from distant disease alone would be falsely high. Many of the patients who are thought to die of distant metastases alone might also be found to have microscopic pelvic disease at autopsy.

Therefore, of the 4 patients with Stage I disease who die of distant disease alone, only 50 per cent, or 2, will have periaortic disease (Table 3). The other 2 will have distant disease in other sites—brain, bone, lung, etc. Thus, in Stage I, only 2 patients with periaortic disease might be saved if this region were irradiated initially. But the

success rate of curing patients with periaortic node metastases is probably much lower than the 25 per cent success rate which will be assumed here. SILBERSTEIN et coll. (1970) reported 2 patients who survived 5 years after treatment for periaortic metastases. VONGTAMA et coll. (1974) described only 4 per cent five-year survival in patients with periaortic metastases who were irradiated. FLETCHER & RUTLEDGE (1972) reported a 25 per cent survival without evidence of disease at 18 months in patients who had treatment of involved common iliac or periaortic lymph nodes. Confirmation of nodal disease in this series was made by surgery or lymphangiography. WHARTON et coll. (1975) updated the experiences of PAUNIER et coll. from 1967. Pretreatment exploratory laparotomy with selective pelvic and periaortic lymphadenectomy was performed in 121 patients. Of the 25 patients with malignant common iliac or periaortic nodes, only 4 were free of disease at last follow-up (all patients not at risk for 5 years).

All reports in the literature indicate that the salvage rate of patients with periaortic disease is less than the 25 per cent assumed here. But perhaps the most convincing evidence concerning the ineffectiveness of the treatment of periaortic nodal metastases can be found in the series reported by AVERETTE et coll. Only 4 of 18 patients with periaortic node metastases were alive at the time of that report. Three of 4 patients were clinically free of disease from 13 to 27 months (mean 16.2). All three patients had clinical Stage IB carcinoma. This is a survival of 19 per cent, again less than the 25 per cent which will be assumed here. If a liberal estimate of cure rate of 25 per cent in patients with periaortic metastases is assumed, the maximum number of Stage IB patients that might be salvaged by exploratory laparotomy is 25 per cent of 2 patients, or 0.5 patients per 100 (Table 2).

The added mortality and morbidity of the surgical staging procedure also must be considered. The approximate mortality rate is available in the report by AVERETTE et coll. (1975). Exploratory laparotomy was performed in 207 patients. One died postoperatively secondary to a myocardial infarction, and a second patient died on the fifteenth postoperative day secondary to uremia. This is an approximate operative mortality of one per cent. If this operative mortality rate is accepted, -0.5 patients having Stage IB disease per 100 treated would be cured with the knowledge gained by exploratory laparotomy (Table 3). Clearly this is no advantage.

Analysis of Stages II, III, IV also reveal no advantage and may even suggest a negative effect on overall survival in some stages. If a hypothetical group of 400 patients, 100 in each stage, is considered, the overall gain is zero. Data regarding cause of treatment failures given by KOTTMEIER and ROUSSEAU et coll. support the results of PAUNIER et coll. (Table 2). The vast majority of treatment failures are a result of failure to control disease within the pelvis. There can be little justification for searching for metastases to the periaortic nodes with an exploratory laparotomy if success or failure of therapy will be dependent on success or failure of treatment of pelvic disease. Data from three institutions make one point obvious. Success or failure in the treatment of carcinoma of the cervix depends on success or failure of

the treatment of the pelvic component of the disease. Nearly all patients with periaortic node metastases ultimately fail with disease in the pelvis anyway. By comparing the results from KOTTMEIER and from ROUSSEAU et coll. with those from PAUNIER et coll. it is evident that if pelvic failures constitute a higher percentage of total failures, the problem of periaortic metastases becomes even less important. As the percentage of pelvic failures increases, the importance of controlling disease outside the usual pelvic fields lessens.

Added morbidity from laparotomy

It is difficult to estimate the exact number of complications which will be incurred. WHARTON et coll. reported on a heterogeneously treated group. Exploratory laparotomy was performed in 121 patients. Selective node sampling was done in some patients and in others pelvic lymph node dissections. Postoperatively the patients were treated with radiation therapy, some under hyperbaric oxygen conditions. One patient died of a myocardial infarction at surgery and one died of a pulmonary embolism in the immediate postoperative period. Late complications following surgery and irradiation were numerous and devastating. Four patients developed gastric ulcers in the group that received periaortic irradiation. Two of these actually required partial gastrectomies. An additional 6 patients had small bowel perforations, and 5 of these patients died. Three patients developed ureteral obstruction from retroperitoneal fibrosis. Two required an ileal conduit and one underwent a ureteroileocystotomy.

Complications would not be expected to be this severe with routine exploratory laparotomies since many of the patients had routine pelvic lymphadenectomies, more extensive surgery than selective node sampling. It might be justified to assume that the complications would be less than those reported by WHARTON et coll., but how much less is uncertain.

Exploratory laparotomy, preliminary results

The previous theoretical analysis indicates that exploratory laparotomy will not increase cure rates in cervical carcinoma. Preliminary results as yet show no reason to believe otherwise. AVERETTE et coll. (1975) have reported the largest series, 207 patients undergoing staging laparotomy. As previously noted only 4 of 18 patients with periaortic disease are still alive, with a mean follow-up of 16.2 months. It is not surprising that so few patients with periaortic metastases survived since relatively low doses (40–45 Gy) have been employed because of a reluctance to exceed tolerance of normal tissues in the treatment volume. Two patients died postoperatively. This is a net gain of 1 patient. Three patients with periaortic metastases are surviving and 2 patients have died from surgery. Again follow-up time is minimal. The investigation was initiated in 1971, and the majority of the patients have not had five-year follow-up.

No detailed survival or complication data are related in that report. Doubtfulness must arise when a new type of treatment approach is advocated without presenting preliminary survival results or complication rates.

The other large series of staging laparotomies in cervical carcimona was reported by NELSON et coll. (1974). Ninety-four patients with squamous cell carcinoma of the cervix underwent a staging laparotomy and discrepancies were found between clinical and surgical stages. Patients have been followed for a maximum of 3 years. The Stage II-B patients who had an exploratory laparotomy had a survival of 64.5 per cent whereas patients with Stage II-B disease treated during the same period and with no exploratory laparotomy had a survival of 92.8 per cent. The survival in patients with Stage III disease was 57 per cent in those explored and 60 per cent in those unexplored. The authors conclude that the data on survival are meaningless and only suggest that patients with Stage II-B carcinoma were adversely affected by laparotomy.

Conclusions

(1) Surgical staging is more accurate than clinical staging in squamous cell carcinoma of the uterine cervix.

(2) Conventional radiation therapy of cervical carcinoma routinely demands pelvic doses which are limited by normal tissue tolerance.

(3) The only information gained by exploratory laparotomy which might alter therapy significantly is the discovery of periaortic nodal metastases.

(4) Because pelvic failures account for the overwhelming majority of treatment failures, control of periaortic disease, if possible, will not increase cure rates since failure will likely occur in the pelvis anyway.

(5) Chances of controlling periaortic metastases are small, and combined surgical exploration and irradiation will increase complications.

(6) Analysis of large series of cervical carcinoma previously reported indicates little benefit and perhaps even a detrimental effect from exploratory laparotomy.

(7) Preliminary reports of patients undergoing exploratory laparotomy show no increase in cure rates.

(8) Routine use of exploratory laparotomy in carcinoma of the uterine cervix is not justified based on data about the disease which are already available.

SUMMARY

Pretreatment staging laparotomy in carcinoma of the uterine cervix has been advocated because surgical staging may detect disease not apparent clinically. An analysis of survival and local control data from previously reported large series of patients with carcinoma of the uterine cervix shows that surgical staging does not increase survival rates. It is likely that surgical staging may also increase morbidity from therapy.

ZUSAMMENFASSUNG

Die Laparotomie vor einer Behandlung eines Karzinoms der Cervix uteri ist befürwortet worden, weil bei der chirurgischen Stadieneinteilung eine nicht klinisch manifeste Erkrankung festgestellt werden kann. Eine Analyse der Überlebens- und lokalen Kontrolldaten für rapportierte grosse Serien von Patienten mit einen Karzinom der Cervix uteri zeigt, dass die chirurgische Stadieneinteilung nicht die Überlebensrate verbessert. Es ist wahrscheinlich, dass die chirurgische Stadieneinteilung die Morbidität durch die Therapie ansteigen lässt.

RÉSUMÉ

Certains auteurs ont proposé, dans le cancer du col de l'utérus, une laparotomie destinée à déterminer le stade avant le traitement, pensant que la détermination chirurgicale du stade peut déceler une extension qui n'est pas apparente cliniquement. L'analyse des taux de survie et les données du contrôle local provenant de grandes séries publiées de malades atteintes du cancer du col de l'utérus montrent que la détermination chirurgicale du stade n'augmente pas les taux de survie. Il est vraisemblable que la détermination chirurgicale du stade accroît la morbidité due au traitement.

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