

Right hemicolectomy does not confer a survival advantage in patients with mucinous carcinoma of the appendix and peritoneal seeding

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Background: Traditionally epithelial malignancies of the appendix with or without carcinomatosis have been treated by right hemicolectomy. Recent accumulation of a large number of patients with this disease has enabled a re-evaluation of this surgical judgement.

Methods: Clinical data on 501 patients with epithelial malignancy of the appendix were collected prospectively. All patients had peritoneal seeding at the time of referral and were treated by cytoreductive surgery and perioperative intraperitoneal chemotherapy. The main independent variable for statistical analysis was the surgical procedure used to resect the primary cancer (appendectomy alone *versus* right hemicolectomy). Nineteen other clinical and pathological variables were considered as control variables. The endpoint for all analyses was survival.

Results: Median follow-up after the initial diagnosis was 4 years. The rate of regional lymph node positivity was 5.0 per cent. When the incidence of lymph node metastasis was determined by histological type, it was statistically significantly higher in intestinal (66.7 per cent) than in mucinous (4.2 per cent) tumours ($P < 0.001$). The presence of lymph node metastases had no influence on prognosis ($P = 0.155$). The surgical procedure (appendectomy alone *versus* right hemicolectomy) had an influence on patient survival by univariate analysis ($P < 0.001$), but not by multivariate analysis ($P = 0.258$).

Conclusion: Right hemicolectomy does not confer a survival advantage in patients with mucinous appendiceal tumours with peritoneal seeding. These data suggest that right hemicolectomy should be avoided unless metastatic involvement of the appendiceal or distal ileocolic lymph nodes is documented by biopsy, or the resection margin is inadequate.

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Introduction

Primary epithelial tumours of the appendix are unusual. The reported incidence in appendectomy specimens ranges between 0.01 and 3.0 per cent, accounting for only 0.2–0.5 per cent of all tumours that arise in the gastrointestinal tract. Approximately 1 per cent of all colorectal cancers arise within the appendix^{1–4}.

Both adenomas and adenocarcinomas perforate the thin wall of the appendix and may disseminate to peritoneal surfaces in a characteristic manner early in their natural history⁵. As the disease progresses a large volume of mucinous tumour may result in intestinal obstruction, fistula formation and terminal starvation. Despite the

bland histopathological appearance of a large proportion of epithelial tumours, appendiceal adenoma with peritoneal seeding in the absence of specialized treatment is eventually fatal⁶. However, this outcome may not be readily apparent because of the indolent nature of the disease^{7,8}.

General surgeons are usually first confronted with a primary appendiceal tumour in the operating room. A preoperative diagnosis of appendiceal malignancy is seldom suspected. Surgical intervention is usually prompted by an expanding abdominal girth, an acute abdomen, an ovarian mass or a new hernia⁹. Well established guidelines for the surgical management of appendiceal carcinoid tumours exist and seem to function adequately^{1,10}. In contrast, recommendations regarding the management of epithelial

tumours of the appendix are based on heterogeneous and relatively small series from single institutions^{3,4,11–25}. Hesketh² suggested that patients treated by a right hemicolectomy had a survival advantage over those who had appendicectomy alone, and this view has been accepted by most surgeons as being correct. However, the authors' extensive experience of this disease treated by a standardized plan of management has allowed critical re-evaluation of this recommendation. The aim of the present study was to determine whether right hemicolectomy confers a survival advantage over appendicectomy alone in the surgical treatment of epithelial tumours of the appendix.

Patients and methods

Five hundred and one consecutive patients with a histologically confirmed diagnosis of appendiceal epithelial neoplasm were managed surgically by the senior author (P.H.S.) between December 1983 and December 2000. The mean age of the patients at the time of initial clinical presentation was 47.7 (median 47.0) years. There were 224 men (44.7 per cent) and 277 women (55.3 per cent).

All patients had documented peritoneal surface spread of an appendiceal malignancy. Four hundred and eighteen patients (83.4 per cent) had peritoneal spread of the tumour at the time of initial diagnosis and in 83 patients (16.6 per cent) peritoneal dissemination was confirmed at reoperation. Two patients (0.4 per cent) had cytologically positive malignant pleural effusion at the time of diagnosis.

The clinical presentation was recorded in all but one patient. Patients were categorized by their initial signs and symptoms into one of three groups. The first group included patients who showed diffuse peritoneal tumour progression. These patients had increasing abdominal girth, ascites, palpable abdominal masses, chronic abdominal pain, weight loss, change in bowel habits, a mass identifiable by computed tomography, or a combination of these clinical features. The second group included patients with an acute abdomen or clinical suspicion of acute appendicitis. In the third group surgical intervention was indicated for a condition other than appendiceal pathology (herniorrhaphy, laparoscopy for infertility, elective abdominal surgery for gallstones or colonic pathology, hysterectomy for fibroids or menometrorrhagia).

Four hundred and forty-six patients (89.0 per cent) were managed initially at another institution and all had undergone at least one previous surgical procedure before referral (mean 1.4, median 1, range 1–6). In the case of 55 patients (11.0 per cent) referral to the authors' institution

occurred at the time of initial clinical presentation. For the patients managed elsewhere, the median time between the initial diagnosis and referral was 7 (range 0–308) months.

The extent of previous surgery before referral was assessed by a previous surgical score (PSS) with possible values between 0 and 3²⁶. Briefly, PSS-0 indicated biopsy only; PSS-1 indicated exploratory laparotomy with surgery in one or two abdominopelvic regions; PSS-2 indicated previous surgery involving between three and five abdominopelvic regions; and PSS-3 indicated that major cytoreduction had been carried out previously with dissection in more than five abdominopelvic regions. The abdominopelvic regions were identified by dividing the abdomen and pelvis by two sagittal planes intersected by two other transverse planes, one through both anterior superior iliac spines and the other through the most caudad point in the costal margins. A review of the operative reports from outside institutions determined the score for patients who had surgical treatment before referral.

Patients who had undergone right hemicolectomy at the referring hospital but who subsequently required excision of the ileocolic anastomosis with corresponding mesentery to clear recurrent tumour (referred to as redo right hemicolectomy) were included in the right hemicolectomy group. The appendicectomy-alone group also included patients who had a limited resection of the caecum to obtain clear margins around the primary tumour.

Previous use of chemotherapy was recorded as systemic alone, combined intraperitoneal and systemic, intraperitoneal alone, or none. The location of the primary tumour within the appendix was determined from the operative notes and pathology reports as involving the distal, middle third, base or all portions of the appendix.

On referral, all patients were treated by a strategy involving cytoreductive surgery with peritonectomy to eliminate all visible tumour in the abdomen and pelvis combined with perioperative intraperitoneal chemotherapy^{27,28}. Follow-up was performed at the patients' home-based institution. If recurrence isolated to the peritoneal cavity was demonstrated, the patient was retreated by the same strategy^{29,30}. None of these patients was treated with adjuvant or palliative radiation therapy. The extent of disease as assessed by a quantitative prognostic indicator, the peritoneal cancer index, has had no impact on survival in any previous report^{7,26,27,29}.

The size of the peritoneal tumour deposits remaining at the completion of cytoreductive surgery was determined by the completeness of cytoreduction (CC) score²⁶. The possible categories for this variable were no visible tumour deposits (CC-0), deposits less than 2.5 mm in greatest diameter (CC-1), deposits between 2.5 mm and 2.5 cm

(CC-2), and those greater than 2.5 cm in greatest diameter or a confluence of disease at any site (CC-3)²⁶.

The histological type was determined by the percentage of extracellular mucin found in the tumour; if it was 50 per cent or greater the tumour was considered to be mucinous type, and if it was less than 50 per cent the tumour was categorized as intestinal type. The presence or absence of a signet-ring cell type was also recorded; a signet-ring cell type was deemed present if seen in the primary appendiceal tumour or in peritoneal implants.

The morphology of the peritoneal tumour deposits was categorized according to the Ronnett criteria for mucinous tumours³¹. Briefly, disseminated peritoneal adenomucinosis (DPAM) was characterized by multifocal mucinous tumours adherent to but not invading into visceral and parietal peritoneal surfaces. The tumour cells were arranged in a single layer, showed minimal atypia and no mitoses. Mucinous adenocarcinoma (peritoneal mucinous carcinomatosis; PMCA) showed invasive peritoneal lesions composed of abundant epithelium with glandular or signet-ring morphology, architectural atypia and cytological atypia. The hybrid type predominantly demonstrated histological features of adenomucinosis, but foci (less than 5 per cent of the tumour cells) of well differentiated adenocarcinoma were identified within the peritoneal lesions.

Statistical analysis

The endpoint of the study was survival. The main independent variable considered was the surgical procedure (appendectomy alone *versus* right hemicolectomy) used to resect the primary tumour, regardless of the time in the clinical history when it was performed. Nineteen other clinical and pathological variables with a possible influence on patient survival were considered as control variables in the analysis. These included age, sex, initial clinical presentation, diagnosis of a second neoplasm, extent of surgical intervention before referral, previous surgical score, time between diagnosis and referral, chemotherapy before referral, tumour pathology (including histopathology of the primary tumour, signet-ring component, tumour perforation, tumour location within the appendix, morphology of the peritoneal implants), biological behaviour of the tumour (including peritoneal dissemination at the time of the initial diagnosis, peritoneal dissemination at the time of referral, metastases to distant organs, regional lymph node involvement), number of cytoreductive procedures performed by the authors and completeness of cytoreduction score. For patients who underwent right hemicolectomy, the timing of the procedure was analysed separately with

respect to its occurrence with or without cytoreductive surgery plus perioperative intraperitoneal chemotherapy.

Follow-up time was recorded from the time of initial diagnosis to the closing date of the study (May 2001), the death of the patient, or the date of the last available clinical information. Death caused by the disease was considered the terminal event for the survival analyses. Survival was estimated by the Kaplan–Meier method. Five-year survival, 10-year survival and median survival were assessed. Ninety-five per cent confidence intervals were calculated for each median survival estimate. Univariate analysis to evaluate the influence of the above-mentioned variables on survival was performed by the log rank test. The Cox proportional hazards regression model was used to estimate the effect of the surgical procedure (appendectomy alone *versus* right hemicolectomy) on survival, adjusted for other control variables. If control variables showed a statistically significant effect on survival by univariate analysis, or if they were considered clinically or theoretically relevant for the purpose of the study in light of the present state of knowledge regardless of the statistical significance, their effect on survival by multivariate analysis was determined. The likelihood ratio test was used to estimate the possible multivariate models, both by the forward inclusion and backward exclusion methods.

Comparison of categorical variables was done by the χ^2 test. Fisher's exact test was used where appropriate. $P \leq 0.050$ was considered statistically significant.

Results

Follow-up

No patient was lost to follow-up. Mean follow-up for the series was 5.4 years (median 4 (range 0–30) years). Current follow-up information was available for 96.8 per cent of the patients who were alive at the completion of data analysis (1 May 2001).

Overall survival

At the time of the last available follow-up 236 patients (47.1 per cent) had no evidence of disease, 77 (15.4 per cent) were alive with disease, 162 (32.3 per cent) had died from the disease and 26 (5.2 per cent) had died from causes not related to the disease. The overall median survival was 13 (95 per cent confidence interval (c.i.) 9 to 17) years. The overall 5- and 10-year survival rates were 71.9 and 54.5 per cent respectively.

The influence of the clinical and pathological features of appendiceal malignancy on patient survival, assessed by univariate analysis, is shown in *Table 1*. Eleven of the

Table 1 Survival evaluation of clinical and pathological features associated with appendiceal malignancy

Variable	d.f.	Univariate <i>P</i> (log rank)	Multivariate <i>P</i> * (Cox)
Sex	1	0.016 (female)	0.200
Initial clinical presentation (incidental <i>versus</i> acute abdomen <i>versus</i> signs of carcinomatosis)	2	0.003 (incidental)	0.330
Second neoplasm (present <i>versus</i> absent)	1	0.010 (present)	0.005 (present)
Previous surgical score (PSS-0, PSS-1, PSS-2, PSS-3)	3	0.046 (PSS-0)	0.227
Tumour location in appendix (tip, middle, base, all sites)	3	0.009 (tip)	0.241
Completeness of cytoreduction score (CC-0, CC-1, CC-2, CC-3)	3	< 0.001 (CC-0)	< 0.001 (CC-0)
Histological subtype (mucinous <i>versus</i> intestinal)	1	0.245	0.271
Cell type (signet-ring cells present <i>versus</i> absent)	1	< 0.001 (absent)	0.105
Tumour perforation (yes <i>versus</i> no)	1	0.009 (present)	0.326
Morphology of peritoneal lesion (DPAM, PMCA, hybrid, not classified, no tumour found, non-mucinous tumour)	5	< 0.001 (DPAM)	< 0.001 (DPAM)
Lymph node status (positive <i>versus</i> negative <i>versus</i> not assessed)	2	0.155	0.380
Distant metastases (present <i>versus</i> absent)	1	0.005 (absent)	0.248
Surgical procedure (appendicectomy alone <i>versus</i> right hemicolectomy <i>versus</i> none)	2	< 0.001 (appendicectomy alone)	0.258

Categories giving survival advantage are shown in parentheses. *Results were obtained by both the forward inclusion and backward exclusion methods. DPAM, disseminated peritoneal adenomucinosis; PMCA, peritoneal mucinous carcinomatosis.

20 clinical or pathological variables appeared to have an impact on survival in the univariate analysis; only three retained significance in the multivariate analysis.

Survival by initial clinical presentation

In the univariate analysis, patients who had an incidental diagnosis of an appendiceal malignancy prompted by studies unrelated to the appendiceal disorder had a survival advantage (median survival not reached) over those who presented with an acute abdomen (median survival 13 (95 per cent c.i. 9 to 17) years) or clinical signs suggesting carcinomatosis (median survival 11 (95 per cent c.i. 6 to 16) years) ($P = 0.003$). This significance was lost in the multivariate analysis ($P = 0.330$).

Survival by histological subtype (mucinous *versus* intestinal)

Histological type (mucinous *versus* intestinal) was not a significant survival variable. Median survival for patients with intestinal tumours was 5 (95 per cent c.i. 0 to 10) years whereas for those with mucinous tumours it was 13 (95 per cent c.i. 9 to 17) years.

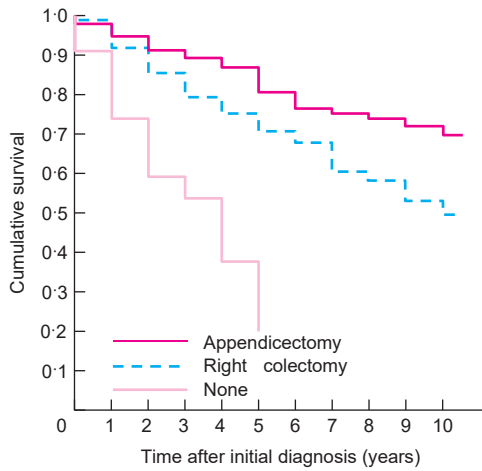
Survival by surgical procedure

Appendicectomy alone was performed in 198 patients (39.5 per cent); 280 (55.9 per cent) had a right hemicolectomy

at some time in the course of their disease, either at the first operation or as an interval procedure after appendicectomy. Twenty-three patients (4.6 per cent) had neither procedure. Forty-four (41.1 per cent) of 107 patients who underwent a right hemicolectomy at an outside institution subsequently had redo right hemicolectomy.

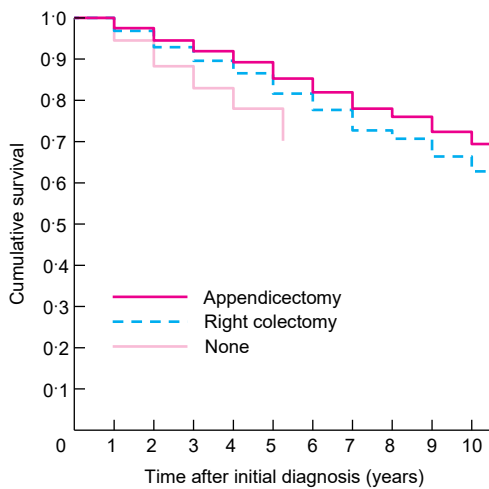
Univariate analysis revealed that the type of surgical procedure significantly affected patient survival ($P < 0.001$) (Fig. 1). A survival advantage was shown for patients treated by appendicectomy alone (median survival 18 (95 per cent c.i. 14 to 22) years) compared with those who underwent right hemicolectomy (median survival 10 (95 per cent c.i. 8 to 12) years). Whether the right hemicolectomy was performed at the time of appendicectomy or at a later time did not influence survival ($P = 0.276$). Patients who did not have either procedure as a result of an incomplete cytoreduction showed the least favourable survival (median survival 4 (95 per cent c.i. 2 to 6) years). However, when survival data were adjusted to control for other variables in the Cox proportional hazard regression model, the surgical procedure had no statistically significant impact on survival ($P = 0.258$) (Fig. 2).

It was hypothesized that patients more likely to be harmed by right hemicolectomy were those in whom tumour cell entrapment was possible within the right hemicolectomy site. To test this, the survival of two groups of patients was compared. In 107 patients right



No. at risk	0	1	2	3	4	5	6	7	8	9	10
Appendicectomy	198	190	184	155	132	112	88	72	64	53	40
Right colectomy	280	271	247	214	184	160	129	112	91	75	53
None	23	21	17	12	10	7					

Fig. 1 Analysis of survival by surgical procedure. $P < 0.001$ (log rank test)



No. at risk	0	1	2	3	4	5	6	7	8	9	10
Appendicectomy	198	190	184	155	132	112	88	72	64	53	40
Right colectomy	280	271	247	214	184	160	129	112	91	75	53
None	23	21	17	12	10	7					

Fig. 2 Adjusted analysis of survival by surgical procedure. $P = 0.258$ (Cox proportional hazards model)

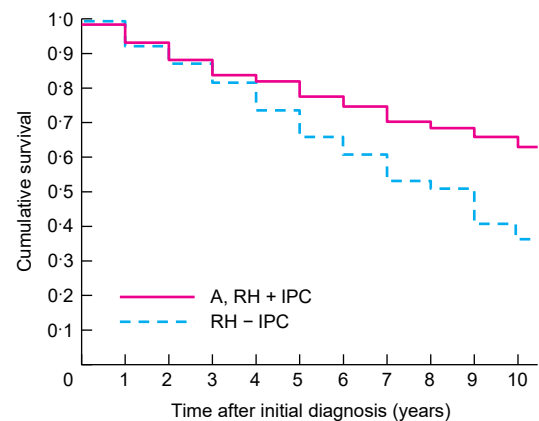
hemicolecotomy was performed at an outside institution with no prophylaxis for cancer implantation into the operative site. Median survival was 9 (95 per cent c.i. 7 to 11) years. In contrast, 198 patients had appendicectomy alone and 173 patients had right hemicolectomy with intraperitoneal chemotherapy protecting the resection site from tumour implantation. Median survival in these

patients was 16 (95 per cent c.i. 10 to 22) years. The difference was significant by univariate analysis ($P = 0.007$) (Fig. 3).

Survival by lymph node status

The pathology reports specifically noted lymph node status in 111 (39.6 per cent) of the 280 patients who had right hemicolectomy. In addition, nine patients who underwent appendicectomy alone had periappendiceal or mesoappendiceal nodes submitted for histopathological examination. Thus, 120 patients had lymph node involvement assessed, of whom 25 had positive lymph nodes and 95 had negative lymph nodes. In 381 patients (76.0 per cent) no histological assessment of regional lymph nodes was recorded. One hundred and sixty-nine cytoreductive specimens at the time of right hemicolectomy had bulky peritoneal surface mucinous tumour and insufficient lymph node enlargement to prompt lymph node sampling by the pathologist. The 212 patients who did not undergo right hemicolectomy did not have regional lymph nodes of the appendix sampled.

Only 25 patients (5.0 per cent) had documented involvement of regional lymph nodes (periappendiceal, mesoappendiceal or ileocolic) at any time during the history of their disease, representing 20.8 per cent of the patients who had regional lymph nodes assessed histologically. Included among the patients with regional lymphatic involvement were three patients who were initially deemed



No. at risk	0	1	2	3	4	5	6	7	8	9	10
A, RH + IPC	371	359	337	285	241	210	174	152	129	109	82
RH - IPC	107	102	94	84	75	63	45	35	28	21	12

Fig. 3 Comparison of survival in patients who underwent appendicectomy alone or right colectomy and intraperitoneal chemotherapy (A, RH + IPC) with that of patients who had right colectomy in the absence of intraperitoneal chemotherapy (RH - IPC). $P = 0.007$ (log rank test)

node negative but who had lymph nodes found at redo right hemicolectomy.

The incidence of regional lymph node metastases was significantly greater in patients with intestinal-type tumours (66.7 per cent) than in those with mucinous tumours (4.2 per cent) ($P < 0.001$). Lymph node positivity was greater in patients with PMCA (10.7 per cent) than in patients with hybrid-type tumours (2.5 per cent) or DPAM (1.6 per cent) ($P < 0.001$). In contrast, signet-ring cell type tumours were not associated with a higher incidence of regional lymph node metastasis.

No statistically significant differences in survival were found between patients with documented positive regional lymph node metastases (median survival 7 (95 per cent c.i. 4 to 10) years), the group with a documented absence of regional lymph node involvement (median survival not reached) and the group that did not undergo pathological assessment of the regional lymph nodes (median survival 13 (95 per cent c.i. 9 to 17) years). This was found both by univariate ($P = 0.155$) and multivariate ($P = 0.380$) analysis (Fig. 4).

Survival by distant metastases

Thirty-two patients (6.4 per cent) had disease outside the abdomen or pelvis at some time during their disease process. Median survival of these patients was 6 (95 per cent

c.i. 3 to 9) years. In the 469 patients who did not develop distant metastases the median survival was 13 (95 per cent c.i. 9 to 17) years. The presence of distant metastases was significantly associated with survival on univariate ($P = 0.005$) but not multivariate ($P = 0.248$) analysis.

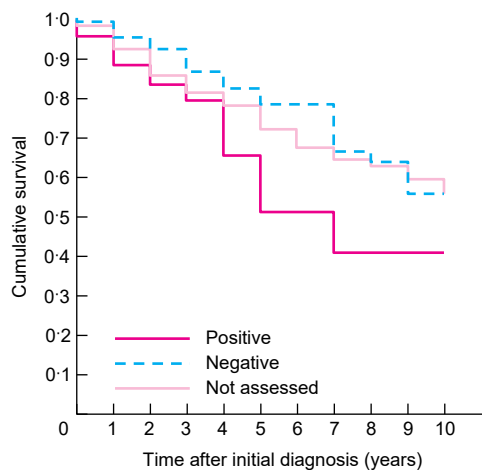
Survival by second neoplasm, morphology of peritoneal lesion and completeness of cytoreduction score

Univariate analysis of these data showed that the presence of a second neoplasm ($P = 0.010$), the morphology of peritoneal lesion ($P < 0.001$) and the completeness of cytoreduction ($P < 0.001$) were significant determinants of survival (Table 1).

Discussion

The standard operation currently used for patients with an appendiceal epithelial malignancy is right hemicolectomy with lymph node dissection and an ileocolic anastomosis. In the present study an aggressive treatment strategy involving cytoreductive surgery and perioperative intraperitoneal chemotherapy showed no benefit in the group of patients who had right hemicolectomy compared with appendicectomy alone. It is the authors' opinion that a change in the treatment recommendation for this group of patients should be considered.

The present data do not, however, suggest that right hemicolectomy should never be performed as some patients with positive lymph nodes survived long term and it must be assumed that resection of these lymph nodes was of benefit. However, patients who had right hemicolectomy in the absence of intraperitoneal chemotherapy had a survival disadvantage. Taking these data together the following recommendations are proposed for limited use of right hemicolectomy in patients with appendiceal cancer and peritoneal seeding. Right hemicolectomy should be performed (1) if it is necessary to clear the primary tumour or achieve complete cytoreduction; (2) if lymph node involvement is demonstrated by histopathological examination of the appendiceal or ileocolic lymph nodes; and (3) if a non-mucinous histological type is identified by histopathological examination. This opinion leads the authors to suggest a new approach to the intraoperative management of patients with peritoneal seeding from a perforated epithelial appendiceal malignancy. The appendicectomy should be performed and a clear margin of resection achieved. The mesoappendix with its lymph nodes should be removed *en bloc* with the appendix, and subjected to both gross and histopathological assessment.



No. at risk	0	1	2	3	4	5	6	7	8	9	10
Positive	25	24	22	19	18	14	7	6	4	4	4
Negative	95	90	85	76	63	54	41	35	28	24	14
Not assessed	381	368	341	286	245	212	174	145	125	104	78

Fig. 4 Analysis of survival according to regional lymph node status. The data suggest that 40 per cent had long-term benefit from right colectomy with lymphadenectomy. $P = 0.155$ (log rank test)

If gross examination suggests cancerous involvement, a frozen-section examination should be carried out. If positive, a radical right hemicolectomy with lymph node dissection should be performed. However, if a clear margin can be obtained and no lymph nodes are shown to be involved by malignancy, right hemicolectomy should not be performed.

The authors' hypothesis that the peritoneum constitutes a first line of defence against carcinomatosis is not unique. Pestieau and Sugarbaker³² showed that the concomitant treatment of colonic cancer with peritoneal seeding by hemicolectomy, peritonectomy and perioperative intraperitoneal chemotherapy was associated with a significant survival advantage compared with colonic resection and treatment of carcinomatosis at a later time. Furthermore, Sugarbaker and Chang³³ showed that the extent of previous surgery was a significant determinant of survival in patients with appendiceal malignancy. Look *et al.*³⁴ noted a statistically significant survival difference in patients who had minimal *versus* extensive previous surgery for ovarian cancer when an attempt at salvage by cytoreductive surgery plus intraperitoneal chemotherapy was made. Both these reports suggested that the greater the extent of the previous dissection the more problematic was a complete cytoreduction. Ortega-Perez and Sugarbaker³⁵ studied four patients with invasion of paracaval tissues by an appendiceal mucinous tumour that had been removed by right hemicolectomy. They hypothesized that open tissue planes at the site of right hemicolectomy resulted in deep invasion of a tumour that is usually minimally aggressive.

The present data support a change in the standard of care for patients with mucinous carcinoma of the appendix. Routine right hemicolectomy should no longer be recommended if cytoreductive surgery plus perioperative intraperitoneal chemotherapy is used. Right hemicolectomy is reserved for patients with positive appendiceal or distal ileocolic lymph nodes documented by biopsy, or an inadequate margin of resection.

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