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Resection of Liver Metastases—When Is It Worthwhile?

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Most of what has been learned about resection of hepatic metastases comes from the study of colorectal cancer because such lesions are so common. One-fourth or more of patients who have liver metastases from such lesions have hepatic tumors that can be removed, but only about 25% of these patients will live 5 years or more after such tumors have been removed. When resection so often fails to improve survival, there is a need to know when metastatic lesions should be removed. Study of determinants of prognosis, patterns of failure, and the natural history of the disease have shown that surgical failure is determined by the presence of extrahepatic metastases (even when removed) and limited resective margins. The patient's gender and the locoregional stage of the primary resected lesions influence survival, but not so much as to withhold resective treatment from these less favored groups. Studies of size, site, and number of hepatic metastases removed show therapeutic limitations associated with extremes, but these determinants of prognosis after resection must be studied in better ways. Although, at times, palliation is a reasonable goal, this aspect of resective treatment has not been studied well. When there are no good therapeutic alternatives to resection of hepatic metastases and when risk is low, such palliative operations may be justified. Only with further study will absolute contraindications to surgical therapy be well defined. There is an obvious need for biologic control of cancer.

As more surgeons are now able to remove large portions of the liver with little risk, it is time to ask not *how* such surgery can be done safely, but *when* it should be done—or when is it worthwhile? Some patients benefit by removal of hepatic metastases, but more are not helped at all. We must, therefore, analyze our failures to identify some guidelines for success as we look critically at the "progress" that has been made.

I learned about the risk, limitations, and benefits of resection of hepatic metastases from my mentor, John M. Waugh, nearly 30 years ago—and these things have changed little since that time. A study of his personal experience with resection of metastases from a variety of visceral cancers was published in 1963 [1], a year after his untimely death: the operative mortality rate was 4% and 20% of his 25 treated patients lived 5 years or more. Since then, many surgeons have been able to do what he did so well. Despite a general lowering of operative mortality, however, the death rate from cancer observed in surgically treated survivors has not really changed. Technical success has only italicized the limitations of our art, because biological rather than anatomical factors predominate.

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Evidence for "biological predeterminism in human cancer" offered by Ian MacDonald in 1951 [2] had to do with the *lack* of direct correlations between the "elapsed time since onset of neoplasia" or the size of primary lesion and the presence of surgically controllable metastases. There is now even more evidence to show that the fate of most patients who have cancer is determined by the natural history of each disease. Nevertheless, "capriciousness of cancer" [3] does not justify surgical therapeutic nihilism. Surgical aggressiveness based on blind fervor cannot be justified, particularly when operative risk is great; but there is still good reason to take a growing tumor out when operative risk is low, when therapeutic alternatives are not at hand, when palliation might result, or when hope may be given to the patient treated in this way. Despite the wide disparity of behavior of malignant disease, the diverse biological patterns, and the major role of the biological potential of most tumors [2], most often there is a reasonable surgical choice which lies somewhere between undue surgical reluctance and unjustified aggressiveness involving great risk.

Experience with resection of hepatic metastases from primary lesions other than colorectal cancers is too limited for determinant analysis [4, 5]. Most of what has been learned, however, about metastases from colorectal cancers can be applied clinically to the management of other visceral cancers that are well differentiated, originate where primary and regional growth can be controlled, and can spread to the liver by portal venous flow.

Hepatic Metastases from Colorectal Cancer

Most of what has been learned clinically about the resective treatment of hepatic metastases has had to do with colorectal cancers because these primary lesions are so common, usually can be removed widely along with regional lymphatic spread, and so often give rise to resectable hepatic metastases that *appear* to be the only residual sites of growth. What is known about the effect of removing hepatic metastases from such lesions is surprising when the capacity for primary tumors to shed into the bloodstream and to seed at distant sites precedes detectability of primary lesions by months or even years. Despite this fact, about one-fourth of patients who have had hepatic metastases from colorectal cancer removed survive 5 years or more.

Unfortunately, this evidence of some surgical success is better evidence of our blindness to what is really taking place, because patients die not from clinically evident metastases that have been removed, but from other small metastases that could not be seen. Better diagnostic tools and radiologists practiced in the use of computed tomography, magnetic resonance imaging, angiography, and ultrasound now let us see more metastases than could be seen before; but there remains great disparity between *appearance* and *reality* in the clinical assessment of each cancer's true extent.

Burdened by lack of knowledge of the range of spread and growth of each tumor, but having achieved an overall 5-year survival rate of about 25% for patients who have had colorectal liver metastases removed, it is reasonable to look for clinically evident determinants of prognosis which might serve as guides to choice of therapy—clinical indicators that might predict therapeutic failure or success. Fortunately, many good studies of this sort have been done in recent years. Unfortunately, the design of these studies is complicated by: (a) the lack of justification for randomization of resection, (b) the multiplicity of factors that can determine each patient's fate, and (c) the unseen presence of biological factors that prevail. Moreover, the results of such studies are interesting, but are less useful clinically than one would hope, because only a few obvious factors can be seen as absolute predictors of therapeutic failure, and most determinants are only qualifiers which may limit but not preclude some surgical success.

Results of surgical therapy have been studied in 2 other ways: analysis of patterns of recurrence which can be correlated with what was done, and studies of the natural history of untreated metastases which have some use for the evaluation of results of resective treatment.

Determinants of Prognosis—Institutional Experience

Our most recent institutional study [6] of determinants of prognosis involved 141 patients who had hepatic metastases from colorectal cancer removed between 1948 and 1982. The mean age of the patients was 56 years, and 60% were men. The size of metastatic lesions (mean, 4 cm) as well as site determined the extent of resection. More than half the lesions could be removed by simple wedge resection, but nearly one-third required removal of half or more of the liver. In three-fourths of the cases, solitary lesions were resected; in the rest, multiple lesions were removed from one or both lobes. More than half had Dukes' class C primary lesions, and 18% had extrahepatic metastases resected—extensions of tumor away from the primary and regional sites of growth [6]. Thirty-day mortality was 0 for 74 minor resections and 4% following 67 major resections.

Since the original group of 141 patients was treated, my colleagues and I have removed hepatic metastases from colorectal cancer from more than 120 other patients. The indications for resection were extended by our willingness to offer resection to more patients with multiple lesions, and by referral of more patients for whom choice of therapy involved difficult decisions regarding the risk-benefit proposition. Despite this trend, operative mortality has not increased. We have not yet studied long-term survival when statistical estimates of survival applied to patients observed for limited periods of time can be avoided by sensible delay.

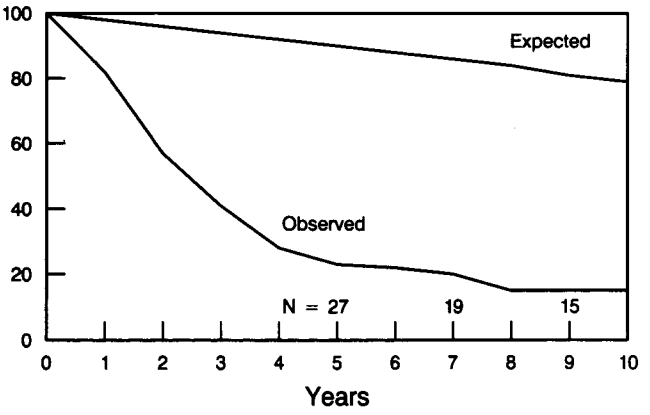

Fig. 1. Cumulative probability of survival (%) of 141 patients related to years of survival after resection of hepatic metastases from colorectal cancer. N = number of patients available for observation at 5, 7, and 9 years. After 5 years, observed survival parallels expected survival.

The 1983 study, involving univariate and multivariate analysis of 10 factors and 25 subgroups that might correlate with prognosis, was brought up to date in February, 1986, but publication has been delayed until now. These extended observations involve a total sample treated surgically 3 or more years ago with 89% and 56% of patients having resections done more than 5 and more than 10 years ago, respectively. Survival rates were correlated with: (a) the patient's age and gender, (b) the site, grade, and Dukes' stage of the primary lesion, (c) the size and number of hepatic metastases, and (d) the presence or absence of extrahepatic metastases, extent of resection, and the interval between resection of the primary cancer and the metastatic lesion(s). Survival rates (including operative mortality) were calculated by the life-table method of Kaplan-Meier, and statistical comparisons among subgroups were performed using the log-rank test.

This updated study confirms our earlier observation that 7 of 10 clinical and pathological determinants correlated poorly with survival rates observed. The overall survival rate of the 141 treated patients (23%) is shown in Fig. 1. As was evident in our previous univariate analysis, the presence of extrahepatic metastases (even when removed), and involvement of regional lymph nodes by the primary tumor were seen to be unfavorable determinants of prognosis (Figs. 2, 3). Having confirmed these 2 earlier observations, our extended analysis also showed gender to be a statistically significant determinant of prognosis (Fig. 4). Multivariate analysis of all factors (Cox proportional hazards model) also showed these 3 factors to have statistical significance: gender, $p < 0.02$; stage of primary lesion, $p < 0.01$; and extrahepatic metastases, $p < 0.03$.

These extended observations, which involved 79 patients treated 10–37 years ago, showed that observed survival rates of treated patients paralleled expected survival after 5 years—evidence that 5-year survival may be equivalent to cure.

Determinants of Prognosis—Observations of Other Authors

These determinants of prognosis have been identified by many other surgeons, and some recent analyses have shown other

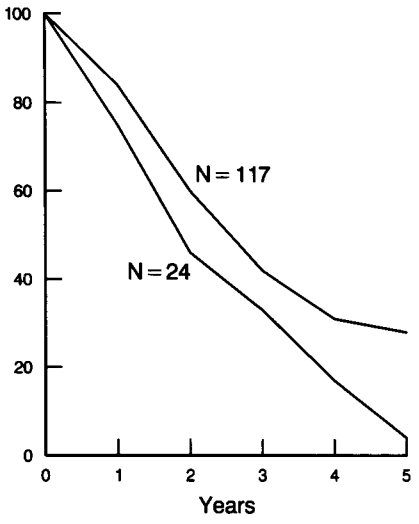

Fig. 2. Comparative survival rates after resection of hepatic metastases from patients who had no extrahepatic metastases (EHM) evident at the time of hepatic resection and patients who had extrahepatic metastases found and removed at the time of hepatic resection. Five-year survival rates without EHM (*top line*) = 28%, with EHM = 4%. $p < 0.01$ (log-rank test).

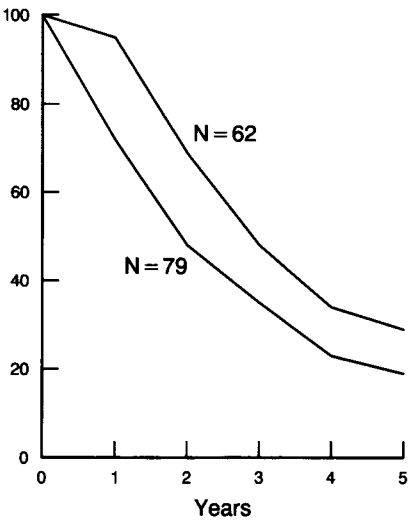

Fig. 3. Comparative survival rates after resection of hepatic metastases from patients who had Dukes' B and C (local/regional stage) primary lesions. Dukes' B (*top line*): 29% 5-year survival, Dukes' C (*bottom line*) 19% 5-year survival. $p < 0.05$ (log-rank test).

factors to have prognostic significance as well. The literature is vast, but only 6 reports [6–11] can be compared selectively here. Even the best studies reported in recent years are not easy to compare when clinical and statistical significance is difficult to find in analysis from small samples observed for a limited periods of time. I have tried to help the reader in this comparative analysis by constructing Table 1 which lists clinical and pathologic determinants vertically and the findings of 8 different groups of authors on horizontal lines. The readers' (and my) confusion may be reduced by considering one potential determinant of prognosis at a time.

Age of Patient

A patient's age may increase operative risk and decrease chance of long-term survival, however, experienced hepatic surgeons seem able to separate infirmity from age. Although some authors [7, 11] have found somewhat lower survival rates for patients older than age 70, no study has shown age alone to be a statistically significant determinant of operative mortality or of death from cancer following resection of hepatic metastases.

Gender of Patient

A patient's gender as it relates to survival after hepatic metasectomy has not been studied by most authors. Our early study [12] of a small number of treated patients showed all patients who lived 5 years or more after removal of hepatic metastases to be women. Subsequent analysis of a larger group (n = 141) [6] showed gender to have borderline statistical significance ($p = 0.054$); but extended observations of these same patients show gender to have statistical prognostic significance ($p < 0.02$) (Fig. 4). Cady and McDermott [9], in study of a smaller treated sample (n = 23; 14 women, 9 men) have

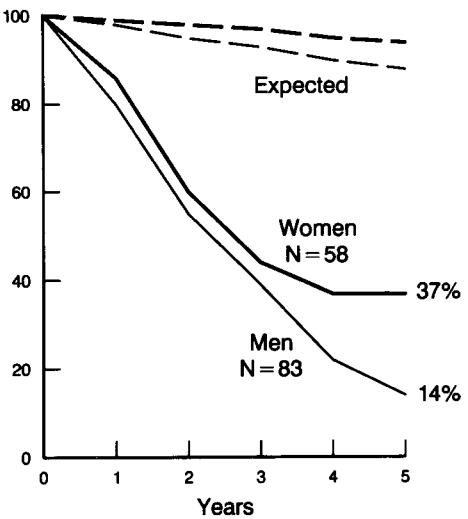

Fig. 4. Comparative survival rates of women and men after resection of hepatic metastases from colorectal cancer. $p < 0.04$ (log-rank test). Expected survival shown in broken lines.

reported a 67% 5-year survival rate for men as compared with a 36% survival rate for women following removal of hepatic metastases. This one easily identifiable, biological determinant should be studied more.

Site of the Primary Tumor

The site of the primary tumor (whether colonic or rectal) has not been found to have prognostic significance in relation to resection of hepatic metastases. The dual venous drainage of the rectum provides a pathway for both portal and systemic venous spread, and anatomical factors predispose to local recurrence of resected rectal lesions. Reports of results of hepatic metasectomy do not, however, involve total popula-

Table 1. Determinants of prognosis from 8 clinical studies.

	Foster [7] (1978)	Fortner [8] (1983)	Cady [9] (1985)	Ekberg [10] (1986)	Iwatsuki [11] (1986)	Hughes et al. (unpublished data) (1986)	Little (personal communication) (1986)	Adson (1986)
No. of patients	78	65	23	72	60	859[a]	26	141
Age	±		−		±	±		−
Sex			+				+	+
Primary lesion								
Site	−							−
Grade	±			−				−
Dukes' stage	−	+		−	+	+		+
Metastasis								
Size	+	±	−	+?	+	+[b]	+	−
Solitary versus multiple	+	−	?	+	−	+		−
No. of lesions			+	+	+	+	+	−
Resective margin			+	+		+	+	
Bilobar				−		−	+	
Extrahepatic metastases		+		+		+	+	+
Extent of resection	±			−	±	±[b]		−
Interval (1° to 2°)	−		−	−	−	+		−
5-year survival (%)	22	30	?	16	45	33	51	23
Operative mortality (%)	5	7	0	5.6	0		0	2.8[c]

[a] Hughes' multi-institutional study of the Registry of Hepatic Metastases (NCI/NIH) includes patients treated in other series listed here ([6–9, 11]). Statistical power has been derived from comprehensive study of these many patients.

[b] These observations of a metastatic lesion's size and the "size" of resection used are tentative when information about resective margins on all patients were not available.

[c] Actual survival rate observed from patients treated 3–37 years ago rather than estimates of survival derived from patients observed for unlisted periods of time. Early postoperative mortality is included.

+ = statistically significant, − = not statistically significant, ± = clinically apparent but not statistically significant, blank = not studied.

tions, but rather are studies of partial samples selected when metastases to lung or brain or bone have not been seen—and when primary and regional spread of tumor appears to have been controlled.

Grade or Degree of Undifferentiation of the Primary Tumor

The grade or degree of undifferentiation of the primary tumor must be a major deterrent to successful hepatic metasectomy when anaplasia usually can be seen as evidence of a cancer's biologic vitality. This factor cannot be studied well, however, when only 20% of patients who have colorectal cancer have undifferentiated lesions and when other obvious extensions related to such tumors so often preclude consideration of hepatic resection.

Locoregional Stage of Primary Lesion

The locoregional stage of the primary lesion has been seen by several authors [6, 8, 11] as a major determinant of survival following hepatic metasectomy. Contradictory reports [7, 10] are derived from smaller samples of treated patients observed for short periods of time or by co-existence of unseen determinants that may operate beyond the statistician's reach.

Size of Hepatic Metastases

The size of hepatic metastases removed has been related to prognosis by different surgeons in different ways. These studies are not easy to compare when it is so difficult to separate the *biological* significance of size (as it relates to time) from the *anatomical* significance of a tumor's size (and site) with respect to the chance for its wide removal. In this regard, our own studies of the consequence of size have been simplistic, because we did not study well the technical limitations that might relate to large size and a tumor's incomplete removal. Having found the median size of our resected metastases to be 4 cm, we looked for statistical power (and convenience) in a comparison of groups of equal number. The comparative survival curves of patients who had tumors smaller and larger than 4 cm were seen to be almost identical, and size, seen in this way, had no statistical significance ($p = 0.69$). Even this over simplified view is questioned by Foster's [5, 7] analysis done in a similar way. He found that "patients with tumors less than 5 cm in maximum diameter fared better," but did not offer details of his analysis. Also, Hughes et al. (unpublished data) found a somewhat decreased 5-year survival following resection of lesions 8 cm or more in size, but the difference was not statistically significant.

Other surgeons have studied the therapeutic limitations of very large size in a more specific way. Ekberg et al. [10] considered size as the percent of total liver volume occupied by tumor (less than 25%, 25–49%, and 50–74%) and found each increment of tumor volume to affect 5-year survival rates adversely ($p = 0.01$). In a similar way, Little (personal communication) found that patients who had liver replacement less than 25% benefited more often than those with replacement of greater proportions of the liver ($p = 0.013$). Also, Iwatsuki and co-workers [11], who expressed size as the amount of liver that had to be removed, found that "the survival of patients whose hepatic metastases could be totally removed only by trisegmentectomy was significantly lower than that of patients whose hepatic lesions could be easily removed by lobectomy or smaller resections" ($p = 0.01$).

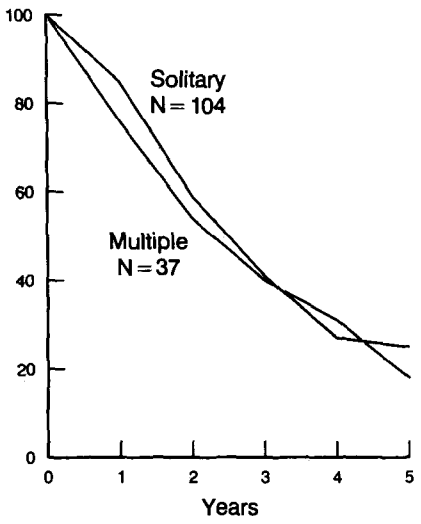

Fig. 5. Comparative survival rates of patients who had solitary and multiple hepatic metastases resected. Five-year survival: solitary = 25%, multiple = 18%. Only 9 patients had more than 3 lesions (p = 0.36).

There is a clue to our confusion here—the confusion that comes with incomplete analysis of the obvious relationships between site and size and the chance for resection of a tumor with margins uninvolved. Only Hughes et al. (unpublished data) have separated these 2 interrelated factors. They found that a lesion's size alone (> 8 cm) had no prognostic significance; but that narrow (≤ 1 cm) margins did ($p < 0.01$), and then found that "the 54 patients who had wedge resection of a solitary lesion greater than 4 cm in size had decreased survival, when compared to the 177 patients who had anatomic resection of a solitary lesion larger than 4 cm ($p < 0.02$)." This thoughtful report points up the need to study not just size alone, but also the *consequence* of size as it determines resective margins and the choice of resective operative procedures.

The extent to which some increase in size might have advantage—with respect to time involved for micrometastases to become apparent—cannot be studied well at this time.

Number of Hepatic Metastases

The number of hepatic metastases also has been seen by different authors in different ways, and my own view of multiplicity of resected lesions has been marked by change. Our first study [12] of 60 patients showed no 5-year survivors of 20 patients who had "multiple" lesions removed. Subsequent studies of a larger group (n = 141) [6] have shown comparative survival curves of patients who had solitary and multiple lesions removed to be almost identical (p = 0.36) (Fig. 5).

Reports of other authors have properly shown this analysis to be simplistic in our failure to consider exact numbers in a more specific way. Five [9–11] of the 8 authors sited in Table 1 have found survival to be limited after resection of more than 3 hepatic metastases; and some now consider such multiplicity to be an absolute contraindication to resective surgery. There is a need, however, to consider number in even more specific ways, when the *configuration* and *site* of origin of multiple metastases has not been studied well (see below).

The interrelationship between size and number of liver metastases should also be analyzed when larger treated samples can be studied. Size must be determined in part by time, and time should allow some micrometastases to become evident. Size might, therefore, have favorable prognostic significance when multiple metastases are removed. Small synchronous multiple metastases may be evident of widespread metastases, and large multiple metastases seen later might be evidence of more restricted spread. Our observations [6] and the studies by Ekberg et al. [10] confirm this view, but statistical significance has not been found.

Margins of Uninvolved Liver

The margins of uninvolved liver removed beyond a resected metastasis has been shown to have prognostic significance. Cady et al. [9], Ekberg et al. [10], Hughes et al. (unpublished data), and Little (personal communication) have shown clearly that limited margins of resection are associated with limited survival. The relationship of this factor to the size and site of the tumor, and to the extent of resection used will be discussed below.

Presence of Extrahepatic Metastases

The presence of extrahepatic metastases (even when removed along with a metastatic liver lesion) has been shown to limit survival in a major way [6, 8, 10]. Hughes et al. (unpublished data) and Ekberg et al. [10] have studied extrahepatic spread in a more specific way. They believe that involvement of hilar, celiac, or choledochal lymph nodes that drain the liver (a form of tertiary metastasis) is a predictor of therapeutic failure.

Extent of Hepatic Resection

The extent of hepatic resection (whether a tumor is taken with an unanatomical wedge or by formal resection of one-fourth or one-half or more of the liver) is difficult to correlate with surgical results. One question is most important: Do extended operations give better results than limited operations do? The answer is no; but the question is wrong when it is asked without regard for the extent of lesions that have been removed. The fact that survival is better after small operations done for small lesions than after extended resections of large tumors [11, 13, 14] tells us more about the extremes of size (and margins) and about the true extent of metastases than about the choice of specific operations. Only when large operations are done for both large and small tumors will much be learned. Most surgeons are, however, disinclined to do studies in this way when, in most cases, extended operations can involve increased risk.

All published analyses [6–11] have involved a therapeutic variable already determined empirically or intuitively by each surgeon's reaction to the extent of lesions seen. When statistical hindsight is so taxed by surgical foresight, it is no wonder that little has been learned.

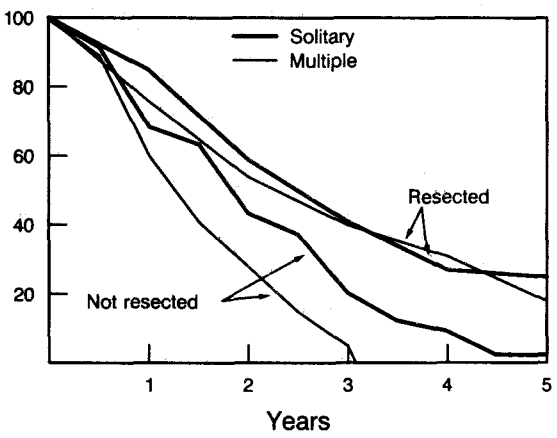

Fig. 6. The survival rates of patients treated by resection shown in Fig. 5 compared with survival rates of patients who had biopsy-proven solitary (n = 39) and multiple unilobar (n = 31) metastases that were not resected.

Time Between Resection and Removal of Metastasis

The interval between resection of the primary site of growth and removal of hepatic metastasis must have importance, when that interval so often involves a span of years. Statistical significance of this lapse of time has, however, been shown only by the careful study by Hughes et al. (unpublished data) of a large sample. It may be that the dormant state, which allows some patients to live for many years before their liver metastases are seen, is transitory.

Survival After Resection

Survival after resection has been reported variously in recent years, and survival rates reported by 2 authors [11, Little (personal communication)] are much better than the rest. I have not found the clue to their success when *all* determinants of prognosis ("theirs and ours") have not been studied well. Use of "estimates" of 5-year survival may play a role, as may unlisted selective factors. (One of our subgroups, patients who had major hepatic resection and no extrahepatic metastases, had a 5-year survival rate of 46%, including a 4% early postoperative mortality rate [5, 6].) When I first reviewed the survival rates reported by Starzl et al. [4], I attributed their success to more frequent use of extended hepatic resections. Now, having seen that such operations (keyed to management of larger tumors) have limited success [11], I do not know what is best to do.

Natural History Without Resection

The natural history of untreated cancer is the standard against which the effectiveness of any treatment should be measured, but is so seldom studied today when so little is left to nature. Untreated controls cannot be used in prospective studies when the value of resection has been seen. There has been a need, therefore, to study natural history retrospectively and imperfectly.

The survival curves of our patients who have had biopsy-proven solitary and multiple unilobar hepatic metastases that were not removed [14] are reproduced in Fig. 6. Comparison of survival rates of patients who had liver metastases resected [6] show that long-term survival rates are favorably affected by resection ($p < 0.0001$). Median survival rates (grouped by nature in the middle of these curves) give little evidence, however, of surgical failure or success. This comparison indicates that estimates of prognosis based on short periods of observation may be false. Also, as Little (personal communication) has suggested, the survival rates of subgroups of treated patients less favored by resection should be compared specifically with the survival rates of these untreated patients.

Incidence of Resectable Hepatic Metastases

The proportion of patients who have hepatic metastases that can be removed with hope of benefit has been estimated. The method of selection of patients for our study of natural history [14] offers some perspective in this regard. In the review of 466 patients who had biopsy-proven hepatic metastases from colorectal cancer from 1943 to 1976, we excluded patients who died soon after biopsy and those who had residual primary tumor or extrahepatic spread as well as patients who had jaundice, ascites, or other primary cancer.

We found that 56 of the 466 patients had had metastases resected and then, with careful review of operative reports, found 70 patients with solitary (n = 39) or multi-unilateral (n = 31) liver metastases that likely could have been removed. Although this type of analysis must be faulty in some way, there is some evidence to show that 27% (56 plus 70 patients) of the 466 patients studied had hepatic metastases that could well have been removed. This good news is diminished, however, by our surgical limitations because it is likely that only 7–10% of the *total group* could have been helped by removal of their hepatic metastases. The need for biological control of cancer is emphasized by this broad view.

Patterns of Recurrence

Some of the limitations of resection of hepatic metastases can be identified in the patterns of failure seen after liver lesions have been removed [15–19]. Such studies are biased by variations in sensitivity of diagnostic tests at different sites, and may be flawed by the "cascade" phenomena, when one recurrent or residual growth may spread to another site. Nevertheless, such studies have demonstrated the general need for systemic rather than regional adjuvant therapy—because recurrence at multiple sites inside and outside the abdomen is most often seen.

Study of patterns of recurrence should answer another important question: How much of the liver must be resected to control all hepatic disease? This question is important because, for most surgeons, at some point the removal of larger portions of the liver involves increased risk. (Our own experience [6] involved no operative mortality for wedge and segmental resections, but a 4% rate of early postoperative death after removal of half or more of the liver, and only Starzl's group [11] has avoided surgical death in use of very major hepatic resections).

In a perfect study of patterns of recurrence, the occurrence of residual disease only in the liver should show that more liver should have been removed. Reports of the incidence of such "liver only" recurrence are, however, faulted by workings of

the metastatic process that cannot be seen clearly. A liver metastasis can arise from the primary tumor, from this "pioneer" metastasis (by intrahepatic spread) [20], or from residual metastasis outside the liver. When any of these events can occur at any time, the time of evident "recurrence" may have little to do with the time or site of its inception. Moreover, such seeding can happen in reverse when residual tumor in the liver can give rise to tertiary lymphatic, peritoneal, or distant hematogenous spread. Nevertheless, the incidence of hepatic tumor as the sole site of residual disease shows best the relationship between the optimal extent of resection and the true extent of hepatic metastases that were present when the obvious lesions were taken out.

The reported incidence of "recurrence" in the liver alone following resection of hepatic metastases varies from 5 to 28% [15–19]. Percentage incidence is expressed here as the proportion of all treated patients. Incidence calculated as a percent of patients having recurrences is, of course, higher, but does not affect conclusions that can be drawn here. Variations can be accounted for, however, by the different composition of treated groups. The major determinants of hepatic recurrence are involved or narrow resective margins, bilaterality of resected lesions [15, 16], and the number (≤ 4) of hepatic metastases removed [9, 16]. Two studies [15, 16] can be compared to show that the different incidence of these factors determines the different incidence of "liver only" recurrence in such reports. The occurrence of these 3 unfavorable factors was 2–6 times greater in the study by Ekberg et al. (liver only recurrences = 28%) than in that by Hughes et al. (16%).

When obvious determinants of hepatic recurrence [15, 16] (exposed or narrow margins and numerous or bilateral liver lesions) are discounted, the incidence of recurrence in the liver alone is seen to be less than 15% [11, 15, 17]. This low incidence of failure related to isolated hepatic residual disease indicates that survival is unlikely to be enhanced by extended hepatic resections—particularly when, after trisegmentectomy, there is no more liver that can be removed. Viewed conversely, the better survival seen after wedge resection of small lesions [11, 12] indicates that the extent of disease (even when seen so simplistically) has more importance than has the amount of liver that has been removed.

Discussion: One View of When Hepatic Metasectomy Should Be Done

When so much—and so little—is known, when should hepatic resection be offered, and when should it be withheld? This choice must be based chiefly on what has been learned from studies of determinants of prognosis, patterns of recurrence, and natural history of untreated disease; but even guidelines so derived must be qualified when retrospective studies have been done in so many different ways. A few factors can be largely ignored in decisions to offer or properly avoid resection of metastases: age (free of infirmity), the site or grade of the primary resected lesion (when local/regional residual or extrahepatic metastases cannot be seen), the interval between removal of the primary tumor and appearance of hepatic lesions and, to some extent, the number and size of metastatic liver lesions.

Even this short list must be qualified when age can be really old, when number of liver metastases must be considered in a different way (see below), and when large size has not been correlated well with tumor-free margins that can or cannot be gained. Nevertheless, it is possible to identify 2 groups of patients well: those likely to live long or be cured after removal of their liver lesions, and those whose survival is unaffected by what we do.

In the first group are patients whose primary colorectal lesions were well confined, who have 1–3 evident unilobar hepatic metastases that can likely be removed with wide margins, and who have no evidence of extrahepatic metastases. Hepatic resection is clearly indicated for them; and if extrahepatic metastases are not found at operation, their chance for extended life or cure is good (even when good involves a $\pm 50\%$ chance of therapeutic failure attributable to biologic phenomena that have no evident anatomical counterparts).

The second group of patients, whose poor prospects can be seen so well, have either extrahepatic metastases, numerous hepatic metastases involving more than half of the liver, large lesions that encroach on major hepatic veins or contralateral hilar ducts or veins, or lesions so sited as to preclude resection with free margins. Few of these patients will live beyond 3 years, even when all visible tumor has been removed. The presence of even one of these unfavorable factors is, therefore, seen by some surgeons [10] as an absolute contraindication to hepatic resection. (The additive effect of more than one predictor of poor prognosis may have absolue significance [15], but the significance of combinations of determinants of prognosis must be studied more.) I am not sure that such a conclusion is warranted when the studies have not involved palliation as a reasonable goal. One-half of our patients who had liver metastases so large as to require removal of one-half or more of the liver had symptoms caused by their hepatic growth [3]. Results of resection of such tumors cannot be measured in terms of longevity alone when many months or a few years of a patient's comfort and lack of fear may be a proper goal. Decisions about this group of patients are complicated by discovery of adverse determinants only after committment to surgical evaluation (the finding of extrahepatic metastases), or after resection is well along (poor margins found too late). At this point, surgical momentum (a proper blend of both the surgeon's and the patient's expectations) may properly prevail—when risk is low and when nothing better can be done.

Unfortunately, there is a third group of patients seen more often (and less clearly) than the other 2: patients with indicators of prognosis that may predict limited survival but cannot be seen as absolute. Men and patients whose primary lesions extend to regional nodes are less often helped than are their opposites, but not enough less to deny them resective surgery. Size and number of hepatic metastases will also remain imperfect predictors of prognosis until they are studied in more specific and better ways. Size, per se, has less real importance than have resected margins that relate to a tumor's site near congeries of hepatic veins and the vena cava or the hepatic hilar trinity; and the number of metastases should not be viewed in simple terms when multiple liver lesions can arise and be arranged in different ways.

The surgeon should, therefore, look beyond size alone to make judgments about free margins that might be gained, and number of metastases (≥ 4) should be accepted as an absolute

contraindication to resection only after the *configuration* of lesions has been studied in more specific ways. Multiple metastases may come from the primary tumor or may develop as secondary satellites arising from and adjacent to such "primary" metastatic growths. In fact, Willis [20] concluded that "the majority of hepatic growths are probable local intrahepatic descendents, generations removed from the pioneer metastasis."

Although 5 surgeons [9–11, Hughes, Little] have found the resection of more than 3 metastases to be followed by very poor survival, this finding should not yet be considered law. Langer [21] has found that "patients whose metastatic tumor consists of 1 large lesion with surrounding satellite nodules had expected survival resembling that of true solitary metastases." And recently, I have reached a similar conclusion, having finally reviewed our own material in a more specific way to find that 9 of our 141 patients had 4 or more metastases removed. Four of these 9 patients lived more than 4 years and 2 are still living 10 years following resection. Both of these long-surviving patients had multiple satellites surrounding a large "pioneer" metastases. These findings along with Lander's observations are contradicted by Ekberg et al. [10] who found satellite spread to portend limited prognosis. The predominance of narrow resective margins (60%) beyond tumors taken out may, however, account for these opposite conclusions.

These difficult decisions must not always be made when patients are first seen and, at times, observation can be justified. It is unreasonable to wait for a resectable hepatic metastasis to become unresectable, but small lesions that can be removed safely after doubling in size may be watched for 3 months or more to see if other lesions do appear. This guessing game involves risk of metastases from metsatases, but on balance, is a reasonable game to play—when we know so little, it is reasonable to consider size, site, and multiplicity in this way.

Guidance for treatment of individuals must come from study of groups, but studies of loose data are not a source of gospel. There are times when decisions must be based on observation of individuals, as unscientific as this may seem to some surgeons.

Epilogue

Today, in our search for truth, there is a need for statistical analyses to show when half-truths may lead us clinically astray. Direct observation of each patient may also show some truths that statisticians have not been asked to see. "The admitted accuracy of mathematics [may be] prematurely applied to biological problems" [22, 23] when so few biological phenomena can be seen.[1] A phenomena must be defined before it can be numbered [24]; and when size and multiplicity of metastatic lesions have not been well defined, they cannot be numbered well.

[1] Carcinoembryonic antigen levels can be measured and, therefore, can be seen; however, correlations of preoperative levels of this biological marker with postoperative survival rates have not been shown [8]. Also, Tsushima et al. (unpublished data) have correlated nuclear DNA ploidy measurements with survival rates of our surgically treated patients [6] to find only that the best predictors of long-term survival (aneuploid-high DNA index > 2.6) were found in only 4% of our surgically treated patients.

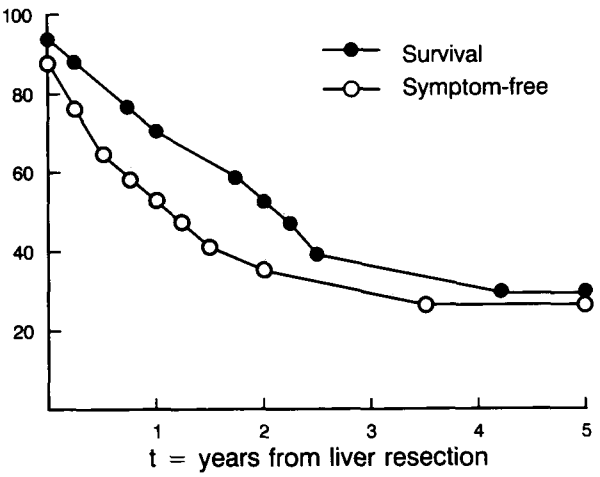

Fig. 7. The relationship between length of survival and length of life free of symptoms relates to recurrent cancer following 67 major hepatic resections done for metastatic colorectal cancer.

Therapeutic success cannot be measured by length of life alone when comfort may be an equal goal. The quality of life is difficult to measure, but that is not a good reason for surgeons to ignore the human spirit. For most patients, the hope for life and quality of each day and night of life is more real than a crude prediction of longevity. Many surgical decisions can be made comfortably and "scientifically" today by resorting to statistical analyses, but too often we are only guessing. It is then that we must think more of the patient's comfort than of our own, and must admit that our science and our humanism may be far apart. "Modern certainties" [25] born of a shallow science may become a burden when humanism is our real goal.

I do not claim that our newly formed science should be ignored, but rather suggest that we must take a better look at palliation of existing or imminent discomforts and the spiritual comfort of the patients whom we are asked to see. Little has said that "the lack of method for quantifying palliation has led to much sterile argument about optimum treatment" (unpublished data), but that is no reason to dodge that issue. Although no surgeon cited in this article has studied palliation statistically, it must be considered here. The median size of metastatic lesions that I have removed by major hepatic resections is 13 cm. One-third had discomfort from that mass, and another third or more of them were likely to have given into these hepatic metastases before they were troubled by other sites of spread. I have studied the time of reappearance of symptoms related to recurrence at any site [3] and consider their palliation to have been a reasonable goal—even when the time and discomfort involved in major surgery is subtracted from what was gained. Collier, who studied our 67 patients who had major hepatic resections done, found that length of life without symptoms closely paralleled length of life (Fig. 7). So it seems that patients were not made to live longer in order to suffer for a longer time.

The aggressive treatment of asymptomatic patients who have liver metastases is quite another thing that brings to mind Hoerr's observation which he "modestly named—'Hoerr's Law'": "it is difficult to make the asymptomatic patient feel better" [26]. He does qualify this obvious truth to say that "this is not to say that the patient with an asymptomatic cancer will

not be helped" and suggests that we should be guided by the fact that "we operate on patients, not on diseases" [26]. These observations may be considered along with Foster's [7] disapproval of treatment that "may rob the patient of comfortable days at home."

This blend of science and humanism is not easy to achieve. We cannot always act so that hope might triumph over judgment, but we must not ignore the patient's need for hope when operative risk and morbidity are low, when there are no therapeutic alternatives, and when, at times, palliative efforts may give rise to cure. We should hope to blend our science and our humanity into an art that our patients can perceive as grace.

Résumé

La majorité des faits que nous avons appris à propos de la résection des métastases hépatiques est la conséquence de l'étude du cancer colo-rectal qui est particulièrement fréquent. Un quart (ou plus) des malades qui présentent des métastases hépatiques secondaires à un cancer colo-rectal peut subir leur exérèses mais seulement 25% des opérés survivent 5 ans ou plus. Devant des faits aussi peu favorables il est nécessaire de déterminer avec précision les lésions susceptibles d'être traitées. L'étude des facteurs de pronostic, des modalités de l'échec, et de l'histoire naturelle de la maladie a montré que la faillite de la chirurgie est imputable à la présence de métastases extra-hépatiques (même si elles sont extirpées) et aux marges limitées de la résection. Le genre du malade et le stade évolutif de la lésion primitive réséquée ont une influence sur la survie mais pas au point de rejeter la résection chez les groupes moins favorisés. Les études de la taille, du siège et du nombre de métastases hépatiques extirpées montrent les limites de la thérapeutique dans les cas extrêmes mais en fait ces facteurs de pronostic après résection doivent être mieux étudiés. Bien que parfois le traitement palliatif constitute un but raisonnable, cet aspect de l'exérèse n'a pas fait l'objet d'une étude sérieuse. Quand il n'y a pas d'alternative thérapeutique meilleure que l'éxérèse des métastases hépatiques cette intervention palliative paraît justifiée dès lors que les risques paraissent faibles. Ce sont des études plus approfondies qui permettront de définir les contre-indications du traitement chirurgical. A la lumière de ces considérations, il apparait indispensable de découvrir le traitement biologique du cancer.

Resumen

Casi todo lo apprendido sobre resección de metástasis hepáticas proviene del estudio del cáncer colorrectal, entidad en la cual tales lesiones son comunes. Una cuarta parte o más de los pacientes con metástasis hepáticas de esta neoplasia poseen tumores hepáticos que pueden ser resecados, pero sólo el 25% de tales pacientes sobrevive 5 o más años después de la resección. Cuando la resección falla en forma tan protuberante en cuanto a mejorar la supervivencia, se hace necesario determinar cuándo deben ser resecadas las lesiones metastáticas. Estudios sobre los factores determinantes del pronóstico, patrones de falla, y la historia natural de la enfermedad, han demostrado que las fallas quirúrgicas son el resultado de la presencia de metástasis extrahepáticas (aún cuando son removidas) y márgenes de resección limitados. El sexo del paciente y el estado locorregional de las lesiones primarias sometidas a resección influyen sobre la supervivencia pero no tanto como para dejar de brindar tratamiento operatorio a subgrupos menos favorables de pacientes. Los estudios del tamaño, ubicación, y número de las metástasis hepáticas resecadas señalan las limitaciones terapéuticas asociadas con los casos extremos, pero estos factores determinantes de pronóstico después de resección merecen ser estudiados mediante mejores métodos. Aunque en algunas ocasiones la paliación aparece como un objetivo razonable, este aspecto de la terapia con resección no ha sido bien estudiado. Cuando no existen buenas alternativas terapéuticas frente a la resección de las metástasis hepáticas y cuando el riesgo es bajo, tales operaciones paliativas pueden ser justificadas. Sólo a través de mayor y más profundo estudio podrán definirse las contraindicaciones absolutas de la terapia quirúrgica. Aparece obvia la necesidad del control biológico del cáncer.

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