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History and present status of pulmonary metastasectomy in colorectal cancer

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Abstract

Clinical practice with respect to metastatic colorectal cancer differs from the other two most common cancers, breast and lung, in that routine surveillance is recommended with the specific intent of detecting liver and lung metastases and undertaking liver and lung resections for their removal. We trace the history of this approach to colorectal cancer by reviewing evidence for effectiveness from the 1950s to the present day. Our sources included published citation network analyses, the documented proposal for randomised trials, large systematic reviews, and meta-analysis of observational studies. The present consensus position has been adopted on the basis of a large number of observational studies but the randomised trials proposed in the 1980s and 1990s were either not done, or having been done,

were not reported. Clinical opinion is the mainstay of current practice but in the absence of randomised trials there remains a possibility of selection bias. Randomised controlled trials (RCTs) are now routine before adoption of a new practice but RCTs are harder to run in evaluation of already established practice. One such trial is recruiting and shows that controlled trial are possible.

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Key words: Colorectal cancer; Metastasectomy; Liver resection; Pulmonary metastasectomy; Oligometastatic state

Core tip: In this review we examine the present position with respect to liver and lung metastasectomy for colorectal cancer and explore the history of how these clinical practices were adopted. We find that these practices are based on observational and largely retrospective data. The mechanistic rationale and the basic science are insufficient for proof of effectiveness. Although randomised studies have been proposed none have been completed so current practice does not reach the standards required for acceptance of other therapies. We provide an update of the present position and propose a way ahead.

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INTRODUCTION

Data on incidence and mortality from the World Health Organization's GLOBOCAN database shows that colorectal cancer is one of the commonest cancers world-

wide. Its position in the ranking varies from country to country but colorectal cancer is usually ranked in the top three most frequent cancers for both sexes^[1]. In 2008, over 1.2 million new cases of colorectal cancer have been recorded worldwide. In 2013, it is projected that there will be approximately 600000 deaths from colorectal cancer worldwide. The possibility of cure is dependent on early diagnosis, however at presentation 15%-25% of patients have metastases and it is estimated that 50%-60% of patients with colorectal cancer will develop metastases during the course of their disease.

Current practice in the management of colorectal cancer has developed from the continuous effort to reduce the incidence and mortality from this disease. Early diagnoses, aggressive treatment and screening programs have all aimed at reducing mortality. However prognosis remains poor, especially for those patients that will develop metastases.

Current clinical guidance from the United Kingdom's National Institute for Health and Clinical Excellence (NICE)^[2] and from America's National Comprehensive Cancer Network (NCCN)^[3,4] make recommendations for surveillance strategies to identify recurrence and for further imaging to evaluate liver and/or lung metastases. This allows for early detection of metastases. Both guideline publishing bodies recommend liver metastasectomy where possible and NCCN guidance is unequivocal in making similar recommendations for pulmonary metastasectomy: "Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required"^[3,4].

"Required" is a strong word and suggests no uncertainty. It should be noted that NCCN is an alliance of the world's leading cancer centres whose members, both individually and as institutions, have financial interests in cancer treatments. The UK's NICE publishes guidance in line with international agreed standards of impartiality^[5]. Current NICE guidance (2011) takes a similar stance to NCCN with respect to liver metastasectomy but is more guarded with respect to lung metastases: "There is uncertainty about the role of metastasectomy for the treatment of resectable lung metastases and this is being investigated in the PulMiCC trial"^[2]. PulMiCC is an acronym signifying Pulmonary Metastasectomy in Colorectal Cancer, a multicentre randomised trial funded by Cancer Research UK^[6].

In this review we examine the history of how the present positions with respect to liver and lung metastases have been reached, what is the current practice, and what is the evidence behind it. The authors share a commitment to obtaining and implementing the best evidence in the care of patients with advanced and metastatic cancer while bringing their own different perspectives on the question. The three thoracic surgeon authors come from different health care environments and in this review have worked with a methodologist with an interest in this subject. The surgeons do not necessarily agree on what might be the best clinical management of individual patients, either with each other or with the published

guidance, but we do agree that it is important to recognise that there are boundaries beyond which metastasectomy does not improve survival or patients' well-being. Research in defining those boundaries is needed.

"SECOND LOOK" CANCER SURGERY AND CARCINOEMBRYONIC ANTIGEN MONITORING

The concept of further surgery to rescue patients whose cancer has recurred after primary resection is not new or even recent. In 1954 Wangenstein *et al*^[7] from Minneapolis reported their experience with "second-look" abdominal operations for stomach and colorectal cancers. These were operations performed electively, about six months after resection of a primary cancer at which lymph node metastases had been found. The report included information on 103 patients with stomach, colon or rectal cancer who had up to six re-look operations. Among 64 patients with colorectal cancer, resectable recurrence was found in 29 providing an opportunity for further surgery which was intended to cure. It should be noted that in 55% no recurrence was found so these patients went through an operation and no further resection was done. Conversely in a report from Philadelphia in 1959, in which clinical evidence of cancer was the trigger for a second-look operation, 55 of the 93 patients were found to have inoperable disease; waiting for clinically evident recurrence led to 59% of unavailing operations^[8].

Which if either was appropriate appears to have remained unresolved. During the 1970s there were reports of five-year survival rates of about 30% attributed to the effect of second look laparotomy in selected patients^[9-12]. Other surgeons were unable to confirm the effectiveness of second-look surgery^[11] but it may well be that there was a degree of reporting bias in the favour of publishing better results. In 1980 Cochrane *et al*^[13] reviewed 406 patients operated on between 1958 and 1962 and despite a policy of regular follow up comprising 2319 clinical examinations over 15 years they could only identify one patient for whom second-look surgery might have been curative. They could not justify routine second-look laparotomy in asymptomatic patients but operating when disease was evident was clearly futile and raised a question about the value of clinical surveillance.

By the end of the 1970s, in an attempt to detect recurrences while still asymptomatic, attention turned to surveillance with the tumour marker carcinoembryonic antigen (CEA) in the hope that curative resection of recurrence might be more frequently possible^[14-18]. A randomised controlled trial (the CRC/NIH funded CEA second-look trial, CEASL) was run from 1982 to 1993 using elevation of CEA levels to trigger reinvestigation^[19,20]. No survival benefit was demonstrated in the study: "the only demonstrable product (of CEA monitoring...) for most patients would seem to be the needless anxiety produced by premature knowledge of a fatal disease"^[21]. CEASL has now been published in full^[22]

as the first restored trial in the (Restoring Invisible and Abandoned Trials) initiative^[23].

LIVER RESECTION FOR METASTATIC COLORECTAL CANCER: THE HISTORY OF ADOPTION

The emphasis in the earliest second-look laparotomy reports was on lymph node metastases and anastomotic recurrence^[7,8] but this era in which CEA-prompted second-look surgery was explored was of great importance in setting the scene for the advances in liver metastasectomy for colorectal cancer. Liver metastases evident at the time of primary surgery, or appearing at an interval, presented a frustrating obstacle to surgical cure^[24]. There had been some surgery on these metastases from as early as the 1940s^[25-27] and liver resection for metastases was included in Wangenstein *et al*'s 1954 report but it was in the 1970s and 1980s that liver resection started to gather momentum^[27-39]. Full mobilisation of the liver was included in the 1982 protocol of the CEA second-look trial^[40]. There followed a concerted effort to tackle the problem of liver recurrence and as a result hepatic resection is now included in the standard of care^[24].

The development of surgical skill and confidence in resecting the liver was central to this advance but so was the debate around what would be required for proof of effectiveness. Adson of the Mayo Clinic wrote in 1984 "...there is no good way of knowing whether survival rates at two or three years should be attributed to removal of hepatic lesions or to the natural history of the disease"^[26]. Mayo surgeons subsequently provided a power calculation for a randomised trial^[38]. To have a 90% likelihood of demonstrating a significant difference between two randomized patient groups, it was calculated that 36 randomised patients would be sufficient when they used 1% as the anticipated rate in their power calculation. This was based on the 25% 5-year survival rates being reported following liver resection compared with the near zero survival anticipated without liver resection. If survival were 5% without resection, 74 patients would have been sufficient^[38]. The Erlangen group's argued that a trial was both unnecessary and unethical^[41]. This argument prevailed and the trial was not done. Liver resection became the standard of care and is now recommended in American and British clinical guidelines^[2-4]. The case for a trial of liver resection could still be made; many patients (probably most) who have liver resection go on to have further recurrence^[42]. There is no evidence that they have lived longer or better as result of this surgery.

PULMONARY METASTASECTOMY: WHERE LIVER SURGEON LEADS, SHOULD THORACIC SURGEONS FOLLOW?

The report of the International Registry of Lung Metas-

tases (IRLM)^[43] is a landmark in the history of lung metastasectomy. It is a collection of 5206 metastasectomy cases from 18 centres in Europe and North America including operations from as far back as 1945. Early single institution reports tended to bundle all their pulmonary metastasectomy operations into one paper, usually with colorectal cancer at the top of the frequency table with a tail of smaller numbers of other cancers^[44]. The IRLM subdivided the analysis into four groups: epithelial cancers, sarcoma, germ cell, and melanoma. This was an important distinction because it highlights the different oncological considerations. Rather than making general statements about pulmonary metastasectomy, in this article we will confine our further considerations to evidence obtained specifically in colorectal cancer.

The venous drainage of the mid-gut is *via* the hepatic portal vein. There is a disproportionately high rate of liver-first and liver-only metastases for colorectal cancer compared with other carcinomas and there is a further differential between cancer of the colon and of the rectum, the rectal cancers having a proportionally higher rate of lung-first metastasis^[45,46]. Liver resection was a natural extension of the second-look surgery approach because the capillary bed of the liver was regarded as providing a first filter containing metastases. In contrast, lung metastases were regarded as evidence that metastases had escaped that first filter and that the disease was systemic and beyond surgical cure. At the outset of the practice of second-look surgery for colorectal cancer, if pulmonary metastases were discovered, they were regarded as a contraindication to a second-look laparotomy because their presence precluded regaining control of the disease by resection of recurrence in the abdomen^[7].

The promulgation of pulmonary metastasectomy as a routine practice in the oncological management of colorectal cancer came about as an extension of GI oncological custom and practice^[47]. This is evident in a recommendation for pulmonary metastasectomy which appeared in a colorectal cancer guidance in 2004^[48]. The only citation given in support was to a paper by the Erlangen group confined to liver metastasectomy^[39]. Liver metastasectomy remains without RCT evidence but there is a consensus of belief in its effectiveness and a strong tendency to believe that this can be extrapolated to pulmonary metastasectomy. To quote Primrose: "the state of the art on metastasectomy in thoracic surgery is a decade behind that in liver surgery"^[49]. We do not find that it is as simple as this.

CITATION NETWORK ANALYSIS

Citation network analysis allows us to get a better understanding of how a belief comes to be accepted and how a practice was adopted by analysing what authors choose to cite and what to omit. The citation of prior publications that support the authors opinions tends to inflate authority of evidence by so called information cascades^[50]. In the course of a systematic review and quantitative synthesis, 51 case series of pulmonary me-

tastasectomy operations for colorectal cancer were identified as providing data usable for analysis^[51]. The analysis showed a pattern of mutually supporting citation which creates a distorted impression of evidence. Only two reports cited a paper overtly critical of the practice^[52]. The paper had appeared in a leading thoracic surgical journal and had metastasectomy in the title so it would have been found on any reasonable search. Conversely 14 papers out of 51 cited a lecture summary of Blalock^[53] from 1944 given to the Boston Medical Society paper. It has an opaque title and would not have been found on a search. It includes reference to Blalock's first pneumonectomy which coincidentally was a colorectal cancer metastasis. It is human nature to prefer to cite those who support us rather than those who are in opposition to our views but it is a way of distorting the weight of evidence. Recruiting the great name of Blalock is a bonus.

OPEN QUESTION OF "OLIGOMETASTATIC DISEASE"

In 1995 Hellman and Weichselbaum^[54] proposed a clinical state of oligometastatic disease. According to this theory "anatomy and physiology may limit or concentrate these metastases to a single or a limited number of organs". This oligometastatic state may make localized forms of cancer treatment, such as metastasectomy, a curative treatment option for a selected group of patients^[55]. The therapeutic opportunity represented by oligometastases^[56] was implicit from the outset: "recognition of the existence and implications of a state of oligometastases is necessary to invite active clinical investigation of new and potentially curative therapeutic strategies"^[54].

The attitude to pulmonary metastases from sarcoma illustrates their line of thought. It was for osteogenic sarcoma that pulmonary metastasectomy was first advocated as a clinical policy^[57]. In sarcoma, metastases are predominately to the lung and if there has been adequate local resection of the primary cancer with clear margins, pulmonary metastasectomy offered the chance of removal of all the cancer and a possibility of cure^[58]. Furthermore these are often young patients with potentially many years ahead to them^[59]. Pulmonary metastasectomy for sarcoma was recommended as the standard of care in a paper from Memorial Sloan-Kettering Cancer Center (MSKCC) in 1971^[57]. A report in 1979 from the same institution on a series of 35 pulmonary metastasectomy operations for colorectal cancer is regarded as the seminal paper for pulmonary metastasectomy in the growing movement for surgery of recurrent colorectal cancer^[60].

As pulmonary metastasectomy became accepted oncologists increasingly asked for this surgery. Torkel Åberg in 1980 challenged the belief in its effectiveness. He reported 25% 5-year survival in a small series of patients (3/12) who would have been candidates for metastasectomy but did not have this surgery. Åberg is infrequently cited^[61] and whether this is because the evidence was insufficient or that the point of view was unwelcome,

surgeons were not deterred from offering their patients pulmonary metastasectomy in the belief that it is a curative therapy. Between 1986 and 1992 several surgical follow-up studies were published, dedicated to colorectal cancer, some with ten year follow up^[47,62-69]. Remarkable outcomes in patients with hepatic and pulmonary metastasectomies, multiple metastases, and with repeated resections were published then and subsequently. It was the MSKCC reports^[60,70] that marked the introduction of pulmonary metastasectomy for colorectal cancer into clinical practice rather than the pneumonectomy case report of Blalock^[53] in 1944 which was only coincidentally for a colorectal cancer metastasis.

Currently a multistep model of metastasis is gaining attraction, in which primary tumors contain cells with differing metastatic potential^[71-73]. The likelihood of metastases occurring, as well as the number and sites of these metastases, may reflect the stage of tumor development. In this context it is essential from a clinical perspective to identify whether limited metastases represent a true oligometastatic state or a transitional state leading to disseminated metastases. In the latter case local control would not translate into improved survival. However hypothetically appealing, the idea of an oligometastatic state needs further empirical investigation^[74].

WILL BETTER MARKERS ENABLE US TO TARGET CURABLE PATIENTS?

The leaders of the European Society of Thoracic Surgeons (ESTS), recognising that resection of metastases in the lung from a wide range of primary sites had become a routine part of the daily clinical practice of a thoracic surgeon, set up the Lung Metastasectomy Project in 2006^[75]. One of the ESTS projects first investigations and its first published output was a survey of its members' views on which patients should be offered surgery^[76,77]. Only a third of surgeons responding to the ESTS survey used biomarkers in making their decision^[77]. In patients with colorectal cancer there is a strong statistical association between elevation of CEA and shorter survival. It has been repeatedly demonstrated that this association applies in patients who have had pulmonary metastasectomy^[51] and it has been confirmed in a meta-analysis^[78]. However this is a general prognostic feature and while elevated CEA makes long survival improbable, normal CEA does not identify a patient as being curable by pulmonary metastasectomy^[79].

The Heidelberg group used immunohistochemical techniques in the surgical specimens of pulmonary metastatic lesions to investigate the expression of vascular endothelial growth factor-D, FBJ murine osteosarcoma viral oncogene homolog B (FOS-B), and melanoma antigen-A^[80]. Among the 39 patients studied, three-year survival was strongly associated with low pre-operative CEA but of the novel markers only FOS-B came close to significance ($P = 0.059$).

There continues to be interest in circulating tumour

cells the discovery of which must in itself indicate metastatic potential^[81]. Researchers in Santiago de Compostela have characterised the genetic make-up of these circulating tumour cells related to cell movement and adhesion, cell death and proliferation, and cell signalling and interaction in five patients. It is too early and probably far too complicated as yet to see this as helpful in identifying suitable patients or metastasectomy^[82].

The Chicago group who first proposed the oligo-metastatic concept have reported that progression of colorectal lung metastases is associated with specific micro-RNAs. Whether this work will help identify patients who can be cured by metastasectomy is yet to be shown^[74].

CURRENT "REAL WORLD" PRACTICE

Of the 146 surgeons responding to the ESTS survey, 93% were not concerned by an inter-operative interval of less than a year, 85% would operate for multiple metastases and 70% did not look at preoperative markers which included CEA. This very liberal interpretation of available evidence was of some concern but a survey cannot capture what actually happens; there is no means of verification.

Two year prospective data on 543 patients have since been captured in a registry study of Grupo Español de Cirugía Metástasis Pulmonares de Carcinoma Colo-Rectal de la Sociedad Española de Neumología y Cirugía Torácica. The median interval was 28 mo, 55% were solitary metastases and the majority of patients had normal/low CEA^[83]. This represents an estimated 60% of clinical practice in Spain and it is believed to be representative in the time frame of the data collection.

The reality in clinical practice is more in line with the meta-analysis results of Gonzalez *et al*^[78] than surgeons perception of current practice when surveyed on Survey Monkey^[77]. We now turn to an analysis of the available evidence.

REPORTED OUTCOMES OF PULMONARY METASTASECTOMY: SYSTEMATIC REVIEWS

Evidence available to the ESTS project included the first systematic review published in 2007^[84]. Twenty studies including 1684 patients who had a metastasectomy between 1980 and 2004 were analysed. The review was conducted to describe criteria for selecting patients with pulmonary metastases in an attempt to identify patients who would benefit from surgical resection. The reviewers found no randomised trials. They remarked on the overall poor standard and incompleteness of reporting and noted that these were highly selected series including the best prognosis patients. Nevertheless the survival rates reported, amongst patients having pulmonary metastasectomy, were 40%-60% at five years, far higher than the most op-

timistic expectations for patients with advanced colorectal cancer. The group in Heidelberg updated their analysis with reports from 1990 to 2007 for the Metastasectomy Project report in 2010^[85]. Fifteen studies which included 1539 patients were analysed.

In comparing reports from the different groups there was a notable improvement of overall survival rates with time. This may reflect the fact that surgery is becoming more and more part of multi-modality treatment regimes. Thus, with efficient diagnostic staging algorithms and modern multi-drug chemotherapy more long-term survival can be expected^[86]. In accordance with the now established principles in the management of hepatic and pulmonary metastasectomy more recent studies explore the effects of post-metastasectomy adjuvant chemotherapy in an attempt to further improve long-term survival^[87,88].

That results are improving in line with the use of more effective chemotherapy does not however resolve the question of whether surgery itself is effective. In the most recent systematic review published in 2013 from Switzerland there were 94 surgical follow-up studies found in the search of papers for inclusion. Their meta-analysis confined to reports from 2001 to 2011 includes 2925 patients from 25 reports^[78]. There is no shortage of observational evidence; we are awash with data. But there were still no randomised trials or any other forms of control data. The same three prognostic factors emerge (number of metastases, interval since primary resection, and CEA) with larger numbers and better reporting in the more recent case series. The statistics are more robust and more stark: the reviewers found that more than one metastasis, an inter-operative interval shorter than about two years, and elevated CEA each double the hazard ratio for recurrence^[78]. The evidence based criteria on which pulmonary metastasectomy can be recommended with expectation of improving survival have become more stringent. For patients with more than one metastasis and recurrence evident within two years, there is now evidence to doubt survival benefit.

IS THERE SYMPTOMATIC BENEFIT FROM PULMONARY METASTASECTOMY?

In general patients having pulmonary metastasectomy are asymptomatic and it is therefore consistent that no mention has been made in these reports of symptomatic benefit. For individual patients with symptoms likely to be relieved by pulmonary metastasectomy, surgery should be considered as an individualised clinical decision, but for a policy of pulmonary metastasectomy there is no evidence of symptomatic benefit. The most inclusive review found no documented change in either symptoms or measurements of lung function amongst 51 surgical follow up studies including 3504 patients^[51]. There has been one prospective study of 177 patients which showed a measurable and significant decline of a range of standard lung function tests^[89]. Furthermore the quick and easy approach to metastasectomy, wedge resection

by videothoracoscopy must come under scrutiny. The researchers found that there was a decline in lung function proportional to the number of wedge resections^[90].

Patients offered pulmonary metastasectomy are usually asymptomatic and patients in the terminal stage of colorectal cancer do not die of, or with, respiratory problems that might have been pre-empted by pulmonary metastasectomy^[91]. There is a significant loss of patient reported quality of life^[92] and a palliative role for a policy of pulmonary metastasectomy in asymptomatic patients can be discounted.

IS COHORT SURVIVAL A CONSEQUENCE OF SURGERY OR A RESULT OF SELECTION?

There has been confirmation that several factors, already identified by the IRLM, and in subsequent studies, were consistently associated with more favourable outcomes amongst the reports in the systematic reviews^[51,78,84,85]. Amongst them were fewer metastases, longer interval since the primary cancer resection and non-elevated CEA. These are prognostic factors: they are features which are statistically associated with the outcome irrespective of treatment^[79].

Predictive factors are those that differentiate between patients who will or will not benefit from a particular treatment^[79] and R0 *vs* R1/2 resection should be considered in this respect. It is difficult matter to analyse because many authors include only R0 cases in evaluation of their outcomes^[84] precisely because failure to achieve R0 resection is a failure of the intent of the operation. Indeed, if survival were similar irrespective of R0/R1 resection, this would seriously undermine belief in its effectiveness. Only a minority of studies report an analysis of the R0 *vs* R1 resection and only some of them find it to be associated with a difference in survival. Even if significantly associated in some reports there is a risk that R1 might be confounded with other unfavourable factors.

In 2007 the *British Medical Journal* published an analysis which challenged the whole basis of metastasectomy^[93]. The alternative interpretation offered was that the selection of patients was so expertly done that the operated cohorts included patients who were naturally destined to survive beyond five years due to an inherently favourable prognosis. It was proposed that the attribution of survival benefit to surgery might be in fact a result of the selection of a proportion of patients inherently more likely to survive^[94]. The same argument had been made nearly thirty years earlier^[52,95].

MATHEMATICAL MODELLING WITH CANCER REGISTRY DATA

No comparison had ever been made with survival among unoperated patients with similar prognostic features to those operated on. This was put to the test in a math-

ematical model^[96]. Two large follow-up studies ($n = 144$ and 159) were identified that contained prognostic factors that also existed in a cancer registry with long term survival data^[67,97]. Cancer registry data were used to create a survival model for patients with a similar mix of primary colorectal cancer stage and survival to a time similar to the interval between primary resection and metastasectomy. The modellers designated this the “death free interval” (DFI) alluding to the more familiar meaning of “DFI” for “disease free interval” with which there was some equivalence in the mathematical model. The actual five-year survival for the two case series were 40% and 41%, in fact lower than the 55% and 50% estimated in the model. Even if the veracity of the model is doubted it does emphasise that not all of the 40%-50% five-year survival rates now being reported following pulmonary metastasectomy can be realistically attributed to the surgery.

TAKING AN EVIDENCE-BASED PERSPECTIVE

A report of the Lung Metastasectomy Project^[75] was published as a Supplement to the *Journal of Thoracic Oncology* in 2010. The leaders wrote “It rapidly became clear that although there was great experience in performing this surgery, the belief in its benefit relied on clinical case series and registry reports. Evidence fell well short of Evidence Based Medicine standards and robust guidance could not be produced on this basis^[75]. They pointed the way to a randomised controlled trial^[98].”

The pre-eminence of the randomised controlled trial (RCT) as a form of evidence however does not go unchallenged. Cooper argued that in the evaluation of surgical operations the RCT was a “square peg in a round hole^[99]”. Proponents of observational studies in surgery argue that they require less time, are less expensive, and avoid the ethical question of enrolling sometimes vulnerable patients in a randomization process. At a more philosophical level it has been argued that there isn’t “any practical reason for thinking of randomization as having unique epistemic power^[100]”. It is accepted by EBM gurus that the RCT is by no means the only form of acceptable “evidence^[101]”. While the general point is fully accepted that there may be many circumstances when observation and clinical impression serve well enough^[102] the specific point here is whether any one of the hundred or so follow up studies of pulmonary metastasectomy convincingly overcomes the central problem of selection bias^[103]. The problem is endemic in follow-up studies of patients who have been selected for a particular form of surgery^[104] and doing more of the same form of study does not resolve the problem.

The leaders of the ESTS study concluded “In the absence of a randomized controlled trial looking at the effectiveness of pulmonary metastasectomy on survival and quality of life, it is unlikely that the current practice will ever be influenced^[75]. This led to the PulMiCC trial^[98]. The trial is based on clinical practice in which

many patients with colorectal cancer metastasised to the lung are considered unsuitable for metastasectomy while others are deemed to be ideal candidates^[6,105,106]. Between these two groups of patients there are many less clear cut cases and the decision cannot be made by looking at evidence but by debate within the clinical teams and in discussion with the patient. Surgeons have even used the expression “gut feeling” to explain how their decisions are made. Randomisation may be as rational an approach when that degree of scientific uncertainty is evident.

CONCLUSION

The practice of liver and lung metastasectomy for colorectal cancer is based on observational and mainly retrospective data. The mechanistic rationale and the basic science do not yet constitute proof of effectiveness. Although randomised studies have been proposed, we are not aware of any that have been completed to inform current practice with an evidence based medicine standard. We propose that a randomised study to investigate the effectiveness of this practice is possible and that for lung metastasectomy the PulMiCC trial is already recruiting.

In present day surveillance CEA is used variably for detection of recurrence^[107,108]. Imaging with fast spiral computerised tomography and positron emission tomography (PET/CT) allows detection of metastases amenable to resection or ablation and, as important, PET also allows for exclusion of patients with widespread or locally recurrent disease. Intensive monitoring in three groups of patients monitored with CEA or CT or both has now been compared with clinical follow up in a randomised controlled trial^[109]. As in CEASL^[22,110] this did detect metastatic disease earlier providing an opportunity for more metastasectomy operations but there was no hint of survival benefit. This must surely raise doubt about liver metastasectomy as a routine therapeutic goal^[110,111] but as far as we are aware no randomised controlled trials are as yet underway; this seems to be the next best step.

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