



Surgery

SURGICAL MANAGEMENT IN PATIENTS WITH SYNCHRONOUS COLORECTAL LIVER METASTASES – A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT While colorectal cancer is a major contributor to morbidity and mortality in the Caucasian population, there is a significant incidence of synchronous liver metastases (SCLM) in patients presenting with colorectal cancer. Surgery is the mainstay in management of colorectal cancer and is performed predominantly with a curative intent. The timing and sequencing of the surgical resection of tumour and the metastases has been established as highly important in improving prognosis. However, there is limited information around the effectiveness of each approach. The current review aims to identify data around simultaneous and staged resection in patients with SCLM to evaluate if there is a significant difference in either approach. PubMed and EASE's searcher® database were searched, a modified PRISMA checklist was used to identify relevant data from the search results and fifteen studies were finalized to be included in the quantitative analysis, defined by inclusion and exclusion criteria, and scored with the use of MINORS criteria. Various outcomes of interest are analysed and Meta-analysis is performed with the use of Odds Ratio or Weighted Mean Difference. In conclusion, it is noted that the analysis did not show a statistically significant difference in the outcomes with either intervention. There are distinct methods of thought around which method to employ in various patient scenarios, and this is left to the discretion of the treating specialist. Research suggests further enquiry into the use of neoadjuvant and adjuvant chemotherapy to treat the underlying metastases in association with the primary tumor.

KEYWORDS : Synchronous Colorectal Metastases, SCLM, Systematic Review, Simultaneous Resection, Stages Resection

INTRODUCTION

The statistics of colorectal cancer from the USA, UK and Australia, indicate a high incidence of colorectal cancer in the population(1). In the UK, colorectal cancer is the second most common cause of cancer death(1). While the incidence of colorectal cancer is similar in men and women, rectal cancer is more common in men and colonic cancer in women. Colorectal cancer is the third leading cause of cancer-related deaths in the United States when men and women are considered separately, and the second leading cause when both sexes are combined(2).

Studies show that at the time of initial presentation, between 15% - 25% of the patients with colorectal cancer have liver metastases, i.e. synchronous liver metastases. Liver is the most common metastatic site, as shown with the incidence of liver metastases at presentation, and also development of metastases as the disease progresses.

The need for timing of surgery and sequencing two sites add to the complexity of management in these cases. Traditionally, a staged approach was preferred, with the resection of the primary tumor done initially, followed by a hepatectomy (colorectal-first approach). However, in certain cases, if the liver is marginally resectable, there is value in taking the liver-first approach. Alternatively, where it is technically possible, a combined approach may be taken with a simultaneous resection of both the primary colorectal and the metastatic liver tumour.

There is limited randomised controlled trial evidence to establish the efficacy of one approach over the other. However, with increasing number of multi-center and cohort studies being published, there is a need to pool the data to determine if there is a difference between staged approach and simultaneous approaches in SCLM. The current study aims to aggregate available data around staged and simultaneous resection in patients with SCLM with the aim to identify, through meta-analysis, if one approach shows evidence of having significantly higher prognostic outlook.

METHODOLOGY

A process was designed to identify all relevant studies to include in the current review, as shown in Fig 1. Based on accessibility and scope, PubMed and EASE 'searcher' databases were finalized to run the search. Electronic searches were run from January 1990 to April 2015, with the aim to limit including studies that are skewed towards staged procedures constrained by resources available. The following terms were used: "surgical outcomes", "synchronous liver metastases", "simultaneous resection", "concurrent resection", "staged resection" and "delayed resection". Language was restricted to English. Medical Subject Headings (MeSH) search was repeated in PubMed for the above keywords.

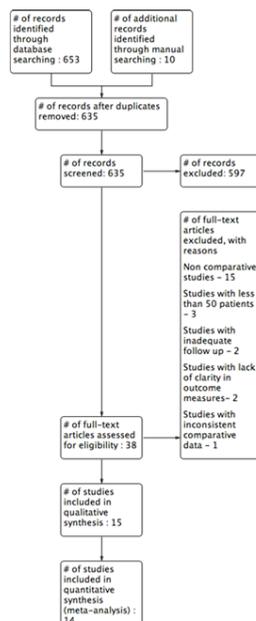


Figure 1 - PRISMA Flow Diagram to Identify Studies for Review

With no prospective, randomised controlled studies, observational studies were accepted. Comparative cohort studies were included, but all case series and case reports were excluded from the data pile. Studies with fewer than 20 patients were also excluded. Only English publications were short-listed, with no geographic restrictions. Studies with data before 1990 were excluded. Only comparative studies were included. To avoid complicating the analysis, liver-first and colorectal-first approaches were both designated as staged resection. Studies dealing with simultaneous or staged resection individually were excluded.

Guidelines to identify studies that compared surgical outcomes are based on PRISMA guidelines, as outlined in Table 1(9). Table 2 illustrates categories to isolate studies eligible for the current systematic review, identifies any potential risks of bias to be addressed later, and outlines the individual scores of the finalised studies in line with the MINORS criteria. Studies rated 13 and above were rated high quality. Descriptive analysis is carried out for the identified outcomes of interest to report characteristics of all the trials (Table 3).

Table 1: PRISMA Guidelines for Selection of Studies for Review

| Topic | Checklist item |
|-------------------------|---|
| Structured summary | Structured summary is outlined, including background, objectives, sources of data, criteria of eligibility, interventions, methodology, results, limitations, and conclusion |
| Objectives | Explicit objective statement is provided with reference to participants, interventions, comparisons, and objectives (PICO) |
| Eligibility criteria | Study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) are outlined. Rationale explained. |
| Data collection process | Method of obtaining data and process around extracting published data are outlined. |
| Data items | Variables and assumptions around data collection and extrapolation made are specified. |
| Risk of bias | Potential bias identified and method for assessing and contravening risk of bias are outlined. |
| Synthesis of results | Methodology around data synthesis and conclusions are clear and specific, and reproducible. |

With no retrospective cohort studies, there is risk of publication bias, coupled with the fact that the common clinical outcomes isolated for comparison across various studies are measured inconsistently.

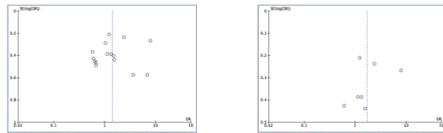


Figure 2- Funnel Plot illustrating heterogeneity among all published studies to the left and high quality studies to the right

Heterogeneity within the studies (Fig. 2) included in the current review was assessed by the P values of the outcomes, with P<0.102 considered

statistically significant. Funnel plots are used to evaluate any publication bias. Analyses of Odds Ratio (OR), Weighted Mean Difference (WMD) and funnel plots are conducted through the RevMan software V5.3. In the analyses, random effect models were used when the Cochrane I2 test was significant. The current analysis is performed in line with the recommendations outlined in the PRISMA checklist(9). Meta-analysis is performed with RevMan software V5.3. The main measure used is the Odds Ratio (OR), as the outcomes are dichotomous. Continuous Variables are assessed with Weighted Mean Difference (WMD), with 95% confidence interval.

Continuous variables are reported as medians converted to means with the technique described by Hozo et al(10). All statistical tests are two sided, with P<0.05 considered statistically significant outcome.

Table 2 - MINORS' checklist for Quality Assessment to isolate Risk of Bias

| EVALUATION OF INCLUDED STUDIES USING MINORS CRITERIA | | | | | | | | | | | |
|--|------|-----------|-------------------------------|-----------------------------|------------------------|--------------------------------|--------------------------------|----------------------|------------------------------|-----------------------|---------------|
| First Author | Year | Clear Aim | Inclusion of Consec. Patients | Prospective Data Collection | Appropriate End Points | Unbiased Evaluation of Outcome | Baseline Equivalence of Groups | Statistical Analysis | Appropriate Follow-Up Period | Loss of Follow-Up <5% | eralOvl Score |
| Turrini(12) | 2007 | 2 | 2 | 1 | 1 | 1 | 1 | 2 | 1 | 2 | 13 |
| Reddy(13) | 2007 | 2 | 2 | 1 | 1 | 1 | 1 | 2 | 1 | 2 | 13 |
| Moug(14) | 2010 | 1 | 2 | 1 | 1 | 2 | 2 | 2 | 2 | 0 | 13 |
| Mayo(15) | 2012 | 2 | 1 | 1 | 2 | 2 | 1 | 2 | 1 | 1 | 13 |
| Luo (16) | 2010 | 1 | 2 | 1 | 1 | 2 | 2 | 2 | 2 | 0 | 13 |
| Chua (17) | 2004 | 2 | 2 | 1 | 1 | 1 | 1 | 2 | 1 | 2 | 13 |
| Brouquet(8) | 2010 | 2 | 2 | 2 | 1 | 2 | 1 | 2 | 1 | 0 | 13 |
| Capusotti (18) | 2007 | 1 | 2 | 2 | 1 | 1 | 1 | 2 | 1 | 1 | 12 |
| Weber (19) | 2003 | 2 | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 0 | 10 |
| Thelen (20) | 2007 | 2 | 0 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 10 |
| Martin II (21) | 2008 | 1 | 2 | 1 | 1 | 1 | 2 | 2 | 0 | 0 | 10 |
| Kaibori (22) | 2010 | 2 | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 0 | 10 |
| de Haas (23) | 2010 | 1 | 1 | 1 | 1 | 2 | 1 | 2 | 1 | 0 | 10 |
| Slupski (24) | 2009 | 1 | 1 | 1 | 1 | 0 | 1 | 2 | 1 | 0 | 8 |
| Vassiliou (7) | 2007 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 8 |

Table 3 - Outcomes of Interest reported across various studies

| Author | Number of patients | | Operative time (min) | | Blood Loss (ml) | | Hospital Stay (days) | | No of patients reporting post op morbidity | | Mortality | |
|-----------------|--------------------|--------|----------------------|--------|-----------------|--------|----------------------|--------|--|--------|-----------|--------|
| | Simult | Staged | Simult. | Staged | Simult. | Staged | Simult. | Staged | Simult. | Staged | Simult. | Staged |
| Brouquet et al | 72 | 70 | n.r. | n.r. | 300 | 600 | n.r. | n.r. | 19 | 17 | 10 | 6 |
| Capusotti et al | 70 | 57 | n.r. | n.r. | n.r. | n.r. | n.r. | n.r. | 36 | 37 | n.r. | n.r. |
| Chua et al | 64 | 32 | 430 | 427 | 890 | 889 | | | 33 | 13 | 0 | 0 |
| de Haas et al | 55 | 173 | n.r. | n.r. | n.r. | n.r. | n.r. | n.r. | 11 | 25 | 0 | 1 |
| Kaibori et al | 32 | 42 | n.r. | n.r. | 670 | 1107 | n.r. | n.r. | 12 | 6 | 0 | 0 |
| Luo et al | 129 | 276 | 255 | 415 | 400 | 650 | 8 | 14 | 47 | 54 | 2 | 6 |
| Martin II et al | 70 | 160 | 180 | 235 | 300 | 350 | 10 | 18 | 39 | 88 | 1 | 3 |
| Mayo et al | 329 | 675 | n.r. | n.r. | n.r. | n.r. | n.r. | n.r. | 64 | 20 | 13 | 4 |
| Moug et al | 32 | 32 | n.r. | n.r. | 475 | 425 | n.r. | n.r. | 11 | 19 | 0 | 0 |
| Reddy et al | 135 | 475 | n.r. | n.r. | 400 | 361 | 8 | 6 | 44 | 135 | 1 | 2 |
| Slupski et al | 28 | 61 | 250 | 200 | 950 | 620 | 12 | 9 | 4 | 8 | | |

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|------------------------|----|-----|------|------|------|------|------|------|----|----|---|---|
| Thelen et al | 40 | 179 | 260 | 208 | n.r. | n.r. | 20 | 19 | 7 | 45 | 4 | 2 |
| Turrini et al | 57 | 62 | 325 | 356 | n.r. | n.r. | 18 | 15 | 12 | 19 | 2 | 3 |
| Vassiliou et al | 25 | 78 | 260 | 340 | n.r. | n.r. | 12 | 20 | 13 | 48 | 0 | 0 |
| Weber et al | 35 | 62 | n.r. | n.r. | n.r. | n.r. | n.r. | n.r. | 8 | 19 | 0 | 0 |

RESULTS

Capusotti et al(18) reported similar survival in both procedures, but a multivariate analysis showed prognostic factors in determining the survival in combined resection to be gender, stage of the tumour (T4 showing worse prognosis) and metastatic infiltration. Capusotti et al(18), de Haas et al(23), Broquet et al(8), and Luo et al(16) reported significantly poorer survival outcomes in patients with more than 3 metastases with combined resection, calling the need to evaluate the role of neo-adjuvant therapy in such cases. Broquet et al(8) also report a significant effect of liver tumor size >3 cm associated with poor postoperative survival following simultaneous resection. Chua et al(17) reported poorer prognosis in patients with stage IV cancer, but significantly shorter hospitalization for simultaneous resection (a factor of the cancer itself rather than the timing of the surgical intervention). They report concurrent diagnosis of tumor and metastases in patients with stage IV colorectal cancer resulting in the use of simultaneous resection with curative intent. Management of patients in this study is overseen by experienced specialist surgeons, which likely influenced the better prognostic outcome. de Haas et al also report a statistically lower progression-free survival in the simultaneous resection group. However, these results could be skewed as a higher percentage of patients in the staged group received pre-operative chemotherapy. Kaibori et al(22) incorporate the occurrence of new metastases in patients undergoing staged resections and conclude that staged hepatic resection could be useful in detection of occult metastases, potentially reducing post-operative recurrence, and reiterate the need for neo-adjuvant chemotherapy in staged procedures.

Slupski et al(24) describe the effect of associated treatment and the size of the colorectal margins (< or > 3cm) on the surgical outcome, however the TNM staging of the primary tumor did not show a significantly different outcome between either resection. Results from the comparison of post-operative mortality by Thelen et al(20) show simultaneous resections having a significantly higher mortality rate. However, it is noted that the mortality was limited to patients who underwent a major hepatectomy and there were nil deaths in patients with minor hepatectomies. Thelen et al(20) advocate the use of staged resections where there may be a need for a major hepatectomy to reduce mortality. In the same comparison, Turrini et al(12) report that there is no significant difference between the procedures when a major hepatectomy is needed, but bring out the issue of patients with staged procedures being undertreated.

Table 4 - Summary of outcomes in identified studies

| Outcome or Subgroup | Studies | Participants | Statistical Method | Effect Estimate |
|---|---------|--------------|---|---------------------|
| I. Postoperative Morbidity | 15 | 6933 | Risk Difference (M-H, Random, 95% CI) | 0.06 [0.02, 0.11] |
| a. Morbidity in all studies | 15 | 4050 | Risk Difference (M-H, Random, 95% CI) | 0.05 [-0.01, 0.11] |
| b. Morbidity in High Quality Studies | 7 | 2883 | Risk Difference (M-H, Random, 95% CI) | 0.08 [0.01, 0.15] |
| II. Postoperative Mortality | 12 | 4963 | Odds Ratio (M-H, Random, 95% CI) | 2.83 [1.44, 5.56] |
| a. Mortality in all studies | 12 | 3294 | Odds Ratio (M-H, Random, 95% CI) | 2.46 [1.04, 5.80] |
| b. Mortality in High Quality Studies | 5 | 1669 | Odds Ratio (M-H, Random, 95% CI) | 3.64 [0.99, 13.37] |
| III. Intraoperative Blood Loss | 5 | 747 | Std. Mean Difference (IV, Random, 95% CI) | -0.26 [-1.09, 0.57] |
| IV. Length of Hospital Stay | 5 | 873 | Std. Mean Difference (IV, Random, 95% CI) | -0.76 [-1.99, 0.47] |
| V. 5 Year Survival | 10 | 2070 | Odds Ratio (M-H, Fixed, 95% CI) | 1.12 [0.87, 1.44] |

The pooled data from high quality studies also demonstrates a much more symmetrical distribution, and the analysis shows the effect to be statistically significant (P=0.22). There is significant heterogeneity in the higher quality studies (I² = 55%), possibly because of the varied methodologies around data collection and procedural differences. Brouquet et al(8) isolated patients that could not be treated with surgical resection with a curative intent, which could potentially influence the outcome. Luo et al(16) describe the simultaneous resection recipients having fewer hepatic metastases and being treated less often with chemotherapy prior to surgery compared to staged resection. They also describe statistical differences in surgical procedures used. Turrini et al(12) describe potential under-treatment of patients in the staged resection group, owing to the time involved in the chemotherapy and multiple hospital visits. Thelen et al(20) note that three out of the four reported deaths occurred in patients over the age of 70.

The summary of the results from the meta-analysis of previously identified outcomes of interest are summarized in Table 4. There is no significant statistical difference in postoperative morbidity in patients following a simultaneous resection and a staged resection. The forest plot outlined shows a slight skew in favor of the staged procedure, with 23% of the population reporting complications post-operatively in a staged procedure compared with 31% following simultaneous resection.

Analysis of the results limited to studies scoring 13 on the MINORS criteria also did not yield statistically significant differences in morbidity between simultaneous and staged resection (Fig 3). There was, however, significant heterogeneity in these results (I² = 82%, P < 0.00001).

There is a clear skew towards higher mortality (Fig 4) in the simultaneous resection group, which can be seen as statistically significant (P=0.04)

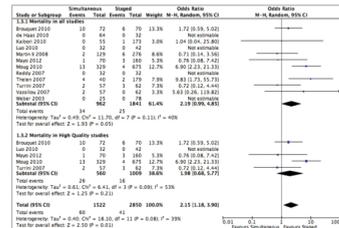


Figure 3 - Forest Plot depicting distribution of postoperative mortality comparing simultaneous versus staged resection

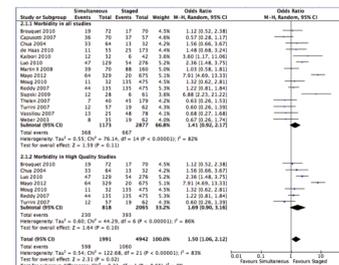


Figure 4 - Forest Plot depicting distribution of postoperative morbidity comparing simultaneous versus staged resection

Five studies reported data on intraoperative blood loss, and five studies reported length of hospital stay for both groups. There are no significant differences found in the simultaneous and staged resection groups for either event. The data collected over both these parameters showed significant heterogeneity (I² = 96%, P < 0.00001 for both). The volume of blood loss was lower in the simultaneous group by 250 ml, but this was not statistically significant, as shown by the forest plot in Fig. 5.

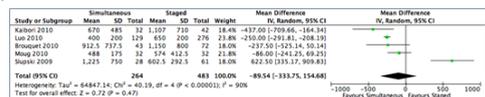


Figure 5 - Forest Plot depicting operative blood loss comparing simultaneous versus staged resection

Moug et al(14) collected case matched data from 32 consecutive

patients with CRC and hepatic metastases, from one center, with all patients operated on by a single team. This brings to attention the concern that there is a severe lack of randomisation in the current data sets. This could possibly explain the high heterogeneity, as the outcomes are being affected by confounding biases like surgeon's skill and hospital facilities. Slupski et al(24) specifically calculated blood loss in staged procedure as a combination of both procedures, while this is not clear in the other data

Fig. 6 demonstrates distribution around the length of hospital stay in the data collected. The argument that simultaneous resection leads to a decreased length of hospital stay could be demonstrated in the analysis of included studies. However, there is not enough evidence in the current review ($P=0.08$) to support this. There is high heterogeneity demonstrated in the data as well ($I^2=97\%$).

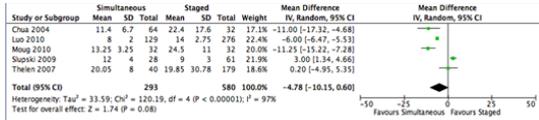


Figure - Forest plot depicting length of hospital stay comparing simultaneous versus staged resection

The five-year survival rate data shows less heterogeneity relative to the other outcomes studied ($I^2 = 21\%$), but still has an underlying bias, demonstrated in Fig. 7. There is no significant difference in the 5-year survival rates.

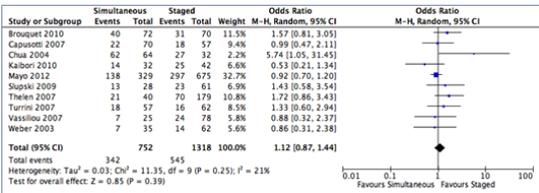


Figure 7- Forest plot depicting 5 year survival comparing simultaneous versus staged resection

DISCUSSION

Despite development of adjuvant therapies in treatment of cancer, surgery remains the primary treatment option with a curative intent in colorectal cancer(25)(26). A multidisciplinary approach is usually needed to incorporate all the factors involved in treatment, including chemotherapy and timing of surgery.

The timing or sequence of surgical interventions in SCLM is unclear. It seems common sense that in symptomatic patients with intact initial tumour, the colon is resected first. However, majority of intact colorectal cancer is asymptomatic, adding to the ambiguity.

There is no consensus around which procedure is advantageous. The argument advocating for staged resection is made on assessment of metastatic response to chemotherapy between procedures, allowing patients to have a better outcome post-surgery, or to evaluate the need for further surgery. In common surgical practice, simultaneous resection is avoided in patients with a high burden of complications from the initial neoplasm. Other contraindications include emergency colorectal surgery, low performance status or low chance of a radical resection(27). However, thought must be given to the published results around the postoperative complications following a staged procedure acting as a screening agent for further surgery.

Recent advancements in chemotherapy have significantly increased the survival rates in SCLM, when compared with surgical treatment alone. This could mean that the previous complication rates post-staged resections are overstated, negating any argument around preference for a staged procedure redundant. This review establishes simultaneous resection as a feasible and relatively safe procedure for patients with SCLM.

In patients with aggressive neoplastic disease, the argument is that treating patients with neoadjuvant chemotherapy could help differentiate patients with rapidly progressing disease who may not respond to surgery(28). However, there is evidence negating this theory, supported by a trial run by Lambert et al(29).

This review does not categorise staged resections, which may result in a bias if there is an underlying prognostic effect of one approach.

However, given the lack of data, this is not investigated further. In studies where there is a statistically significant poorer prognosis with simultaneous resection, there is an argument to be made for the need to assess the possibility of potentially occult disease. Kaibori et al(22) point out that the poorer outcome in simultaneous resections could be attributed to missing micrometastases during surgery, resulting in recurrence and reduced survival. This ties in with the need for neo-adjuvant chemotherapy and stronger post-operative tumour evaluation to determine optimal surgical plan. Also, the outcome data for simultaneous procedures should be interpreted with care, as the selection criteria is not universal.

Turrini et al(12) discuss the need for adjuvant therapies and add that when treated with earlier intervention, simultaneous resection could provide prompt completion of surgical therapy. This is especially relevant in patients at high risk for microscopic disease, since they are more likely to need and respond to such adjuvant therapy.

There is an argument that removing all the neoplastic foci could potentially interrupt the progression of the disease, effectively halting the 'metastatic cascade'(23). The disadvantages are around potential morbidity caused by a longer anaesthesia, probable introduction of sepsis and increased risk of anastomotic leak.

In staged resections, there is a risk of progression of disease while patient is being treated for the primary tumor. This could mean that the metastases become unresectable by the time the patient recovers from initial surgery. Also, in a staged procedure, the post-operative morbidity could potentially mean that the patient is emotionally affected, not coming back for the second procedure. There are distinct limitations with simultaneous procedures as well, most important being the need for extensive hepatectomy, combined with resection of the primary tumor, resulting in higher postoperative morbidity or mortality.

There is evidence supporting the protocol to downsize the liver metastases with the use of neo-adjuvant chemotherapy, in patients with categorically 'unresectable' disease. This could allow metastases to become resectable, improving outcome and increasing eligibility for liver resection(30). The clinical status of the patient is paramount in making this decision and further management. Thelen et al(31) note the exclusion of patients from the study if the primary resection was undertaken at a different hospital. This can be overcome with a method that can enable data comparison and transparency.

Identifying the prognostic factors is also an important aspect in determining the course of treatment in SCLM. Size and number of hepatic metastases, age of the patient, stage of the primary CRC have been identified as having a significant outcome on the disease progression and overall prognosis. Conversely, the included studies note that these factors do not limit the use of hepatic resection for treatment. There is no significant difference in the 5-year survival rates, ranging from 25 – 40% overall survival post five years in either procedure. However, it has not been distinctly stated if any of the factors were considered in planning around which procedure to use. In patients with poor prognostic factors, a staged resection could be favored to improve post-operative morbidity – an outcome not substantiated by any evidence in this study.

This study is limited by the lack of randomisation in the underlying data. There is also associated inadequacy in interpreting the data, as the allocation methodology is unclear. Not all studies are case matched, with unequal populations groups reported. This is countered by pooling the data for meta-analysis. There are assumptions incorporated into the analysis, including the fact that outcomes are compared irrespective of the staging or location. Both factors have shown a prognostic effect on the disease, but in this analysis, no allowance has been made to explain the effects on mortality or postoperative morbidity.

Heterogeneity is an issue to consider. There is a need for a prospective, randomised trial to test the outcomes of each of the surgical procedures without bias. With logistical difficulties around setting up a study and running a trial, it can be tempting to use existing data irrespective of how old it may be. But, the progression of techniques and therapies mean that population data collected a decade ago does not give the right cross-sectional picture compared with recent data. The current review isolates studies conducted from 2000 and beyond to isolate this

problem. There is also the problem with collecting data in one center, as is the case with some of the studies in the review. This introduces a new confounding variable, around any inherent skew present in the hospital systems getting incorporated into the data.

CONCLUSION

The results from the current systematic review do not show a significant preference towards one procedure. This ambiguity establishes the need for further evidence. The studies in the current review demonstrate significant heterogeneity, potentially due to lack of standardisation around data collection and lack of randomisation. Most of the studies note that it is a surgeon's call about which procedure to use based on various factors that affect the postoperative prognosis. SCLM does not have a typical presentation, and therefore there is limited chance that one treatment protocol can be uniformly applied. Also, as with other cancers, the treatment is often holistic, incorporating a multidisciplinary team, with the disease prognosis not limited to the surgical technique.

Overall, it can be concluded that the management of SCLM is complex and multidisciplinary. A holistic, customized treatment regimen is required, incorporating a thorough assessment, patient preference, strong communication between surgical and oncological team, that is determined on a case by case basis.

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