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Systematic Review

Combined clinical and surgical strategies for advanced colorectal cancer with hepatic metastases: impact on survival and quality of life: a systematic review

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ABSTRACT

We aim to evaluate in this systematic review the impact of combined clinical and surgical strategies on survival and quality of life in patients with advanced colorectal cancer and hepatic metastases (CRLM). We designed and followed our search on PubMed, Cochrane Library, Embase, and Google Scholar for studies published between 2010 and 2024. Inclusion criteria encompassed studies reporting survival rates and quality of life outcomes in patients who went through clinical or surgical management for CRLM and our data extraction and quality assessment were performed using standardized tools and risk of bias of included RCTs was accessed using Cochrane risk of bias tool. We found liver-first approach demonstrated improved 3-year overall survival (69%) for synchronous CRLM compared to combined or classic approaches with 54.4–60.4%. Neoadjuvant chemotherapy facilitated tumor downstaging but was associated with liver injury when prolonged beyond five cycles and those patients with metachronous CRLM, surgical resection come with maximum survival rate with five-year survival rates reaching 60% in selected cases and quality of life outcomes was improved in patients achieving curative resection. After all research, it can be can conclude that combined clinical and surgical strategies and tailored sequencing of treatment can enhance survival and quality of life for CRLM patients. Early multidisciplinary interventions and optimized chemotherapy regimens are critical in balancing oncologic outcomes and treatment-related risks.

Keywords: Colorectal neoplasms/therapy, Liver neoplasms/secondary, Neoadjuvant therapy/methods, Survival rate/statistics and numerical data, Quality of life/psychology

INTRODUCTION

Colorectal cancer (CRC) is one of the most significant global health problems; it is ranked as the third most frequently diagnosed cancer among men and second in women. Statics says that it accounts for approximately 10% of all cancers diagnosed annually. It is the second leading cause of cancer-related deaths worldwide.[1] Despite advancements in early detection, the treatment modalities and comprehensive management strategies among 25%-50% of patients with CRC will develop colorectal liver metastases (CRLM) either synchronously or metachronously. The fact about colorectal cancer is that the liver is its most common site of metastasis.

Global incidence of CRC is notable with substantial geographic variation and according to epidemiological studies, overall incidence of synchronous CRLM ranges between 13.8%-17.1% while metachronous CRLM occurs in approximately 7.6%-15.1% of cases.

Estimated statics results represented that 76%-85.3% of metachronous metastases are detected within one year of the primary diagnosis and up to 97.5% are identified within three years.[1-3]

Interestingly, CRLM is more common in males and left-sided colonic cancer due to embryological derivation of the tumor. Also, 2% of the patients develop CRLM between five to ten years after the surgical resection of the primary tumor emphasizing the importance of long-term follow-up methods. Pathogenesis of CRLM involves a complex interplay of tumor biology and the hepatic microenvironment and CRC cells disseminate primarily through the portal vein allowing metastatic seeding in the liver.

Molecular pathways such as WNT/β-catenin signaling or KRAS mutations and VEGF-mediated angiogenesis are commonly known contributing factors which helps in CRLM progression. Liver's unique dual blood supply is coupled with its immunosuppressive environment which further facilitates the growth of metastatic deposits.[4]

Management of CRLM has undergone significant evolution because of science and its technological innovations. Historically liver surgery was rarely attempted due to technical challenges and poor outcomes but now modern multidisciplinary approaches have transformed this field.

Latest research has reported about surgical resection that it is only potentially curative treatment for CRLM which is offering 5-year survival rates of up to 60% among these patients. Techniques such as portal vein embolisation, staged hepatectomy, and combining resection with tumor ablation have expanded the number of patients eligible for surgery.[5]

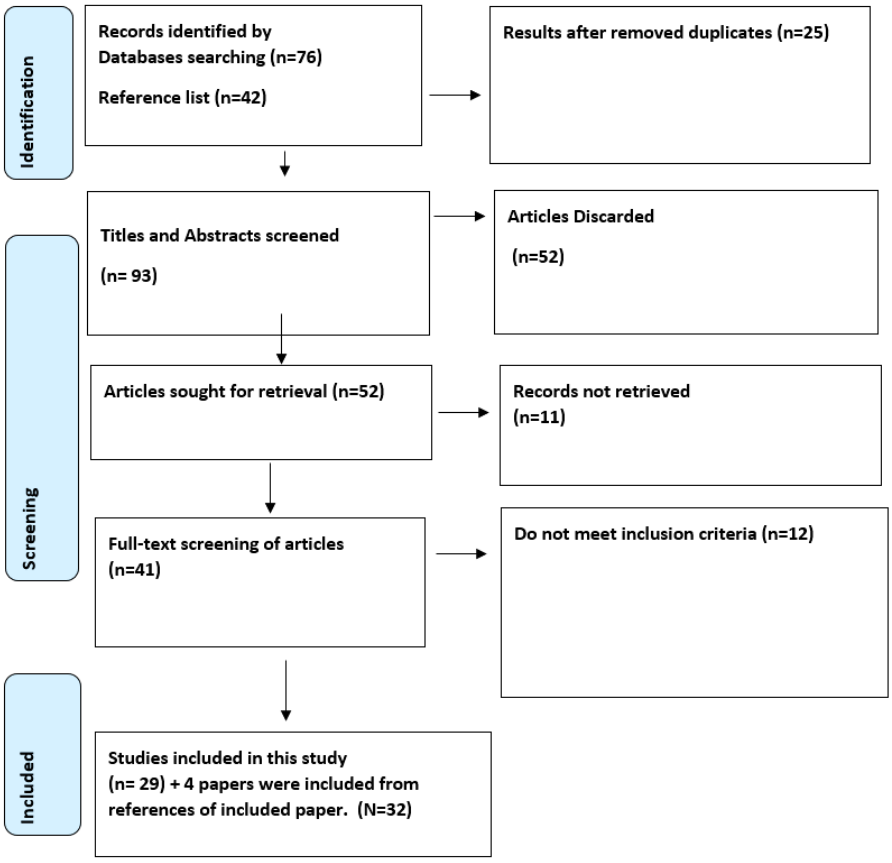

Figure 1: PRISMA flow chart.

In patients with US CRLM, systemic chemotherapy, EGFR/VEGF targeted agents and locoregional treatments including SBRT or SIRT when possible, enhance survival and may alter an otherwise US case to resectable. Various surveillance approaches employed after primary CRC resection are influential in identifying early CRLM.

Surveillance using carcinoembryonic antigen (CEA) or computed tomography (CT) increases detection rates of recurrent disease and surgical interventions with curative intent but now studies have shown mixed results regarding overall survival benefits.

Meta-analyses of randomized trials suggest that while intensive surveillance improves resection rates that it does not conclusively enhance survival rate for long-term.

CRLM impacts survival outcomes and quality of life in CRC patients as research has demonstrated that among patients who develop CRLM there were only 25% are operable and of these, 25-50% achieve long-term survival more than 10 years and these results stress for urgency of improving systemic therapies and surgical techniques as well as early detection methods.[6,7]

METHODS

Search strategy

Methodology section includes systematic search strategy in the following databases: (PubMed, Cochrane Library, Embase, and Google Scholar). These were searched using a combination of keywords each joined by a Boolean operator.

Risk of bias assessment

The Cochrane Risk of Bias Tool was applied to evaluate randomized controlled trials. Bias domains (d1 to d5) were assessed as low, moderate, or high risk. The evidence level for each study was graded based on the GRADE approach.

Table 1: Search strategy.

Search criteria	Search strings
Keywords	Advanced colorectal cancer, hepatic metastases, survival rates, quality of life, clinical strategies, surgical interventions, chemotherapy, targeted therapy, immunotherapy, prognosis, patient outcomes, metastasis, adjuvant therapy, neoadjuvant therapy, liver resection, ablation, systemic therapy, hepatic resection, treatment response, survival analysis, recurrence
Search string 1: colorectal cancer and hepatic metastases	("colorectal cancer" OR "colon cancer" OR "advanced colorectal cancer") AND ("hepatic metastases" OR "liver metastases" OR "liver tumor" OR "hepatic lesions")
Search string 2: survival and recurrence	("survival rates" OR "recurrence-free survival" OR "overall survival" OR "progression-free survival") AND ("quality of life" OR "patient outcomes" OR "health-related quality of life" OR "functional outcomes")
Search string 3: surgical interventions and treatment modalities	("liver resection" OR "hepatic resection" OR "liver surgery" OR "hepatic ablation" OR "liver transplantation") AND ("advanced colorectal cancer" OR "colon cancer")
Search string 4: therapeutic approaches	("chemotherapy" OR "systemic therapy" OR "targeted therapy" OR "immunotherapy") AND ("hepatic metastases" OR "liver metastases") AND ("colorectal cancer")
Search string 5: prognosis and clinical strategies	("prognosis" OR "clinical strategies" OR "treatment response") AND ("advanced colorectal cancer" OR "hepatic metastases") AND ("overall survival" OR "recurrence-free survival")
Search string 6: adjuvant and neoadjuvant therapies	("adjuvant therapy" OR "neoadjuvant therapy" OR "chemoradiation" OR "chemotherapy regimen") AND ("liver metastases" OR "hepatic metastases") AND ("colorectal cancer")

Table 2: Study inclusion and exclusion criteria.

Criteria	Details
Inclusion criteria	
Population	Patients diagnosed with advanced colorectal cancer with hepatic metastases.
Intervention	Clinical and surgical management strategies.
Outcomes	Survival rates, recurrence-free survival, and quality of life.
Study types	Randomized controlled trials, cohort studies, and meta-analyses.
Exclusion criteria	
Outcomes	Studies without survival or quality of life outcomes.
Type of study	Non-human studies or reviews lacking original data.
Sample size	Case series with <10 participants.

Table 3: Data extraction.

Aspect	Details
Key variables	Survival rates (overall and recurrence-free).
	Quality of life indices (using validated scales).
	Adverse events linked to interventions.
Process	Data were independently extracted by two reviewers using a pre-defined template to minimize bias.

Table 4: Quality assessment.

Study ID	Domain 1 (Randomization)	Domain 2 (Allocation concealment)	Domain 3 (Blinding)	Domain 4 (Outcome reporting)	Domain 5 (Other bias)	Overall risk of bias
1	Low	Low	Moderate	Low	High	Low
2	Low	Low	Moderate	Moderate	Low	Moderate
3	Low	Low	Low	Moderate	Low	Low
4	Low	Moderate	Moderate	High	Moderate	High
5	Low	Low	High	Low	Low	Low
6	Low	Low	Moderate	Moderate	Moderate	Moderate

Table 5: Grading evidence levels.

Evidence level	Criteria	Studies count
High	Consistent findings from RCTs with low risk of bias; directly applicable population.	3
Moderate	Evidence from RCTs with some limitations or well-done cohort studies.	2
Low	Evidence from cohort studies with significant bias or indirect evidence.	1

RESULTS

In the Table 6 depicted factors influencing hepatectomy resectability and surgical planning. Moreover, provided the description of factors which influencing hepatectomy resectability and surgical planning. Also, Table 7 depicted Summary of treatment sequencing and outcomes. Table 8 shown surgical management of CRLM.

Table 6: Factors influencing hepatectomy resectability and surgical planning.

Category	Description
Resectability	Classifications include resectable (complete tumor removal feasible with ≥20% FLR), borderline (technical/biological challenges), and unresectable (extensive liver involvement or major vascular invasion).[8]
Surgical goal	Complete tumor removal with curative intent; no role for debulking. Resect disappearing metastases as over 50% recur if left untreated.[9]
Future liver remnant	Adequate FLR depends on liver health: ≥20–25% for healthy, >30% for chemotherapy-injured liver, and >40% for cirrhotics. Conditions like fibrosis and steatosis impair liver regeneration.[10]
Preoperative imaging	Common modalities: CT (widely used), MRI (higher sensitivity/specificity), PET (adjunct for unclear lesions or elevated CEA). Advanced imaging like 3D volumetric analysis aids resection planning.[11]
Chemotherapy	Potentially converts unresectable disease to resectable, improving curative options.
FLR augmentation	Techniques like portal vein embolization, two-stage hepatectomy, and associating liver partition with portal vein ligation are used when FLR is inadequate.[12]
Liver resection limits	Up to 80% of a healthy liver can be resected in noncirrhotic patients.
Technical considerations	Assessment of tumor relationship to vascular inflow/outflow and biliary drainage is essential.
Biological factors	Disease progression, presence of extrahepatic disease, and molecular markers (RAS/BRAF mutations, MSI status) influence resectability.

Table 7: Summary of treatment sequencing and outcomes.

Category	Definition/approach	Key data/Findings	Outcomes
Synchronous CRLM	Liver metastases identified at or before diagnosis of primary colorectal tumor	Prevalence: 14–25% of colorectal cancer patients.	Treatment sequencing varies: Classic, combined, or liver-first. Combined surgery and neoadjuvant chemotherapy improve outcomes in selected cases.
Metachronous CRLM	Metastases discovered after resection of the primary tumor	Prevalence: 7–30% of colorectal cancer patients.	Simpler sequencing: Surgery alone or surgery with perioperative chemotherapy.
Chemotherapy first (Synchronous)	Initial chemotherapy before liver resection or colorectal surgery	Study: Liver-first approach associated with higher OS in bilobar metastases (3-year OS 69% vs. 54.4–60.4%; $p \leq 0.031$).	Improves liver-related prognosis while minimizing chemotherapy-related liver injury risks.
EORTC 40983 trial	Evaluated FOLFOX perioperative chemotherapy vs. surgery alone	Improved 3-year PFS with FOLFOX (36.2% vs. 28.1%; $p = 0.041$), but no OS difference (61.3 vs. 54.3 months). Increased complications in FOLFOX group (25% vs. 16%).	Highlighted DFS benefit but risks include peripheral neuropathy and liver injury.
JCOG0603 trial	Evaluated FOLFOX after hepatectomy vs. hepatectomy alone	Improved DFS (49.8% vs. 38.7%, $p = 0.006$). No OS difference (83.1% vs. 71.2%, $p = 0.42$). Similar perioperative complication rates between groups.[13]	Suggests better DFS with FOLFOX but no OS advantage; highlights need to balance risks.
Neoadjuvant chemotherapy	Administered before hepatectomy to downstage tumors	Treatment beyond 5 cycles associated with worse OS (HR = 1.723, $p = 0.034$) and PFS (HR = 1.808, $p = 0.004$).	Prolonged chemotherapy increases surgical risks without additional oncologic benefit.
Chemotherapy regimens	Oxaliplatin-based (sinusoidal injury); Irinotecan-based (steatohepatitis)	Regimen-specific injuries linked to surgical morbidity and mortality risks.	Tailored regimens needed to optimize liver function preoperatively.[13]

Table 8. Surgical management of CRLM.

Surgical Strategy	Indications	Key Outcomes	Limitations
Parenchymal-sparing hepatectomy	Unilobar/bilobar disease, small tumors, minimal invasion.	Lower morbidity and shorter hospital stays 33% recurrence rate Allows for repeat hepatectomy if needed.	Requires precise tumor location and sparing techniques.
One-stage hepatectomy (±PVE/HVE)	Disease requiring FLR hypertrophy due to small FLR (<30%).	Equivalent oncologic outcomes to parenchymal-sparing. Preferred for certain anatomical/tumor burdens.	Higher morbidity compared to parenchymal-sparing techniques.
Two-stage hepatectomy	Significant bilobar disease.	Median OS of 50 months Feasible for unresectable disease Allows hypertrophy and tumor clearance.	Requires two surgeries with risks of complication and incomplete hypertrophy.

Continued.

Surgical Strategy	Indications	Key Outcomes	Limitations
ALPPS	CRLM with <30% FLR, fast hypertrophy needed.	92% resection rate OS of 46 months (vs. 26 for two-stage) Similar complication rates to two-stage.	Requires expertise; high perioperative morbidity.
Orthotopic liver transplantation	Select patients with unresectable CRLM, favorable tumor genetics, and no disease progression.	5-year OS of 45.3% (compared to 12.5% with PVE and resection).	Scarcity of donors Not feasible for BRAF mutations or N2 nodal disease.
HAIC	Initially unresectable CRLM; adjuvant for hepatectomy.	52% conversion to resectable status. Up to 100% response rate in chemotherapy-naïve patients.	Specialized expertise required for pump placement and maintenance.
Repeat hepatectomy for recurrence	Patients with sufficient liver remnant and isolated recurrence.	5-year OS of 73% for repeat hepatectomy Improved survival in selected patients.	Reduced efficacy if time interval between resections is short.
Minimally invasive liver resection	Patients suitable for open hepatectomy, dependent on tumor size and location.	Reduced blood loss and shorter hospital stays Oncologically equivalent outcomes to open surgery.	Limited availability of expertise in some centers.[13]

Table 9: Advancements in colorectal cancer and hepatic metastases therapies.

Category	Technology/Advancement	Description	Impact
Genetic analysis	Next-generation sequencing (NGS)	Identifies unique tumor genetic changes to personalize treatment strategies.	Enables precision medicine for tailored therapies.
Non-invasive diagnostics	Liquid biopsies & ctDNA testing	Tracks cancer progression and treatment response using blood samples.	Reduces the need for invasive diagnostic procedures.
Immunotherapy	Checkpoint inhibitors & cancer vaccines	Enhances the immune system's ability to detect and attack cancer cells.	Improves survival and quality of life for patients.
Surgical innovations	Two-stage hepatectomy (TSH) & ALPPS	Advanced surgical techniques to resect multiple liver metastases while preserving function.	Increases surgical success rates and reduces recurrence risk.
Minimally invasive surgery	Robotic-assisted surgery & 3D imaging	Precision tools and imaging for safer, more effective surgeries.	Reduces surgical complications and recovery times.
Ablative therapies	Microwave ablation, irreversible electroporation, cryoablation	Non-invasive approaches to destroy tumors in complex locations.	Offers alternatives for patients unsuitable for surgery.
Targeted drug delivery	Nanotechnology	Delivers chemotherapy directly to cancer cells, minimizing impact on healthy tissues.	Reduces side effects and improves drug efficacy.
Advanced radiotherapy	Proton beam therapy	Precisely targets tumors with minimal exposure to surrounding tissues.	Lowers side effects while maintaining treatment effectiveness.
Post-surgical recovery	Enhanced recovery after surgery (ERAS)	Protocols designed to optimize post-operative recovery through multimodal care.	Accelerates recovery, reduces hospital stays, and minimizes complications.

Continued.

Category	Technology/Advancement	Description	Impact
Artificial intelligence	Surgical planning & recovery monitoring	AI-assisted tools for pre-surgical decision-making and post-treatment follow-ups.	Enhances efficiency, accuracy, and patient outcomes across treatment stages.
Innovative therapies	Photodynamic therapy	Uses light-sensitive drugs and specific light wavelengths to kill cancer cells.	Offers a targeted and less toxic treatment option.

DISCUSSION

CRLM treatment sequencing exemplifies complexity of tailoring therapeutic approaches which is based on the characteristics of cancer and patient-specific factors such as patient's health and institutional expertise. Delineation between synchronous and metachronous CRLM is one of the critical contexts for determining treatment pathways. Management paradigms for synchronous CRLM are diverse and are ranging from classic approaches focusing on colorectal resection first to reverse strategies prioritizing liver metastases.[14] Growing data do confirm the first-pass hepatic effect; outpatients with multiple bilobar involvement benefit from the approach: 3-year survival is significantly higher (69%) compared to the combined or true (54,4—60,4%). The outcomes demonstrate that focusing on the liver as the primary site plays the primary prognostic function in regards to the patient's condition. However, this strategy is employed based on sound multidisciplinary planning, patients' fitness, and the utilization of neoadjuvant chemotherapy.[15] The research has stated that the potential benefits of liver-first strategy must be weighed against chemotherapy-associated liver injuries. Prolonged regimens which are exceeding five cycles can exacerbate risks without corresponding survival advantages. These include sinusoidal obstruction syndrome with oxaliplatin and steatohepatitis with irinotecan and both of which contribute to postoperative morbidity. There are persisting concerns of progression or unresectable disease during prolonged chemotherapy and these concerns underscore need for early surgical intervention.[16]

Treatment for metachronous CRLM, indeed appears more straightforward but it is no less nuanced, while surgery is recognized its cornerstone but perioperative chemotherapy demonstrates benefits in disease-free survival without extending overall survival as evidenced in the EORTC 40983 and JCOG0603 trials has confirmed this, and dichotomy between DFS and OS benefits require more refined patient selection process. It is emphasizing perioperative risks and patient quality of life. Lack of survival advantage from FOLFOX supports the research about overtreatment in populations without aggressive disease. The chemotherapy-first approach is generally challenged nowadays because it provoked damage to liver integrity and also has long-term consequences.

Combination of perioperative chemotherapy can reduce the tumor size to a certain extent but the side-effects including peripheral neuropathy are still a crucial issue. The rather limited PFS benefit noted in the outcome of the EORTC 40983 trial should be well-balance against the postoperative complication risks, predominantly where these have been observed with the use of chemotherapy; 25% versus 16%. These data indicate that systemic therapies must be used cautiously, especially in patients who are at a borderline for surgery.[17]

Management of colorectal liver metastases (CRLM) has evolved with advancements in surgical techniques and perioperative care and choice of surgical strategy is driven by the burden of the tumor's anatomical considerations and how patient's overall medical fitness is. Parenchymal-sparing hepatectomy has emerged as a preferred approach for patients with limited disease due to its ability to preserve liver function while maintaining oncologic efficacy. Because of a lower morbidity, this technique is preferable when subsequent resection is required due to disease recurrence. One-stage operatively resectable hepatic malignancies, extensive disease that necessitates preoperative hypertrophy of the future hepatic remnant through portal vein embolization.[18-20] For significant bilobar involvement the two-stage hepatectomy is curative approach by leveraging liver regeneration although it requires a complex two-step process. The introduction of ALPPS has shortened the timeline for hypertrophy and it is showing superior outcomes in select patients, though it is associated with higher morbidity and requires specialized expertise. ALPPS (Associating Liver Partition and Portal vein Ligation for Staged hepatectomy) is a new approach of liver surgery invented for treatment of liver malignancies.

It promotes healthy regeneration of the remaining liver before large tumors are resected; provides chances of first-time operations to patients who otherwise are considered to have no liver reserve for further invasive surgery. Emerging strategies such as orthotopic liver transplantation also provide hope for patients with otherwise unresectable disease but are hindered by organ scarcity and stringent criteria. In the same ways, hepatic arterial infusional chemotherapy (HAIC) also demonstrates remarkable response rates in converting unresectable CRLM to resectable status but necessitates specialized technical and maintenance expertise.[21,22]

Minimally invasive approaches use such as laparoscopic and robotic liver resections have already become adopted due to their favorable recovery profiles though their use is

contingent on the tumor's location and the center's expertise. Randomized clinical trials have evaluated primary tumor resection (PTR) versus systemic chemotherapy for instance, Dutch CAIRO4 study showed that there was no significant survival advantage of upfront PTR over systemic therapy (median OS: 20.1 vs. 18.3 months p=0.32) but systemic therapy resulted in fewer complications.[23]

Similarly, a trial so-called as JCOG1007 reported no overall survival benefit (median OS: 26.7 vs. 25.9 months with p=0.69) leading to trial termination. In systematic reviews advancements such as artificial intelligence (AI) and stereotactic body radiotherapy (SBRT) have shown promise and AI applications enhance diagnostic accuracy also predict recurrence risk while also help to facilitate more personalized plans for its unbeatable advancements and options.[24] Moreover, now there is integration of chemotherapy regimens like FOLFOXIRI has demonstrated superior conversion rates for borderline resectable metastases as research has reported.[25]

In unresectable cases, TransMet proved that liver transplantation with chemotherapy improves survival by potentially creating a new standard of care. The use of preoperative chemotherapy continues to be controversial and in spite of the evidence that has cast doubt on the role of the treatment in improving overall survival, its role in enhancing surgical parameters and in the staging of metastatic disease is now well established. Combined, these observations highlight the need for patient-tailored and interdisciplinary based interventions that incorporate contemporary technologies to improve the management of CRLM.[26]

Emerging technological innovations and future of cancer

Latest emerging technological innovations for advanced colorectal cancer treatment with hepatic metastases are now offering us a new hope for better survival rates. Current research reported that advancements of the next-generation sequencing (NGS) now allow doctors to identify unique genetic changes in tumors which gives us now more personalized treatments. Liquid biopsies and circulating tumor DNA (ctDNA) tests are making it easier to track how cancer responds to therapy without invasive procedures. Immunotherapy, on the other hand is evolving rapidly and there is new checkpoint inhibitors evolved and cancer vaccines are being used and are helping the immune system target cancer more effectively. For patients with liver metastases and surgical innovations like two-stage hepatectomy (TSH) and ALPPS are increasing the chances of removing multiple tumors while preserving liver function.

Emergence of robotic-assisted surgeries and 3D imaging systems are helping surgeons to operate with greater precision and safety now a days.[27-29] On the non-surgical front there are other therapeutic approaches which are emerging and at some places these are already being use such as like microwave ablation and irreversible electroporation and cryoablation. The emergence of these technological tools is providing less invasive options to treat tumors in delicate areas. New chemotherapy regimens tailored to individual patient needs improve outcomes before surgery while nanotechnology enables targeted drug delivery directly to cancer cells sparing healthy tissues.

The use of Artificial intelligence is beginning to play a critical role in everything from surgical planning to monitoring post-treatment recovery and it is being rapidly adapted for making care more efficient and accurate in the field of medicine and oncology. Photodynamic therapy and proton beam therapy offer new ways to minimize side effects while effectively targeting cancer and enhanced recovery after surgery (ERAS) protocols are now being used which are helping patients recover faster with fewer complications. All these these breakthroughs in 2024 are a represented a shift toward more personalized, precise and less burdensome treatments and their repid emergence is bringing hope to patients facing this complex disease.[30-32]

CONCLUSION

Our findings revealed that colorectal cancer with hepatic metastasis is a challenging disease and a multidisciplinary strategy is necessary for its care. Use of combined systemic medicines, surgical resection and cutting-edge methods to maximize results. The only curative treatment is still surgical resection which has a major positive impact on survival for some individuals. Resectability and recovery are enhanced by new tactics such liver-first initiatives and minimally invasive procedures.

Our research reported challenges such as liver damage from treatment and the possibility of recurrence. Optimizing survival and quality of life requires careful preoperative planning, long-term monitoring, and customized therapy sequencing. To significantly improve results in this complicated patient population, more research into therapeutics medicines, surgical approaches, and diagnostic techniques and individualized care techniques is necessary.

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