Diagnostic Laparoscopy as an Effective Tool in Evaluation of Intra-abdominal Malignancies

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ABSTRACT

Accurate diagnosis and staging are crucial in defining an effective plan of management in intra-abdominal malignancies. Despite the availability of a wide array of imaging techniques, a high incidence of nontherapeutic procedures have been observed. Laparoscopy finds its utility in reducing this discrepancy by an accurate assessment of the extent of the disease. This review article explores applications of laparoscopy in the staging and diagnosis of abdominal malignancy and its comparative advantages against imaging studies and conventional laparotomy.

Keywords: Diagnostic laparoscopy, Gastrointestinal tract, Gynaecology, Malignancy, Metastasis, Staging.

INTRODUCTION

Unresectable tumors are undesirable diagnostic surprises during laparotomies for surgeons. A well-staged diagnosis and an assessment of resectability in abdominal malignancies are necessary determinants for the definition of an effective treatment strategy since laparotomies in patients with improperly staged, and non-resectable tumors will increase mortality and morbidity, cost as well as reduce the quality of life in the remaining lifetime. So laparoscopy can play a complementary role in diagnosis and staging of abdominal malignancy and its extent.1

The last three decades have witnessed tremendous improvements in laparoscopic equipment and technique, which has now led to a wider application of laparoscopy and an increasing interest in the use of laparoscopy as a staging tool.2

Despite ever evolving, sophisticated radiological diagnostic modalities like (CT), magnetic resonance imaging (MRI), A diagnosis of unresectable, metastatic diseases has been made at exploratory laparotomy for many patients with gastric, hepatic, pancreatic malignancy. Visualization of primary tumors, identification of hepatic metastasis, regional nodal metastasis and intra-peritoneal metastasis, which at times may not be efficiently spotted by imaging modalities, are possible with laparoscopy.1

If laparoscopic finding results in an unresectable disease, then further management can be planned, such as neoadjuvant chemotherapy, radiotherapy, etc. It will give a tissue diagnosis and can have a biopsy where the definitive treatment or surgery is not possible.3 Thus, it is recommended that diagnostic laparoscopy for a staging of abdominal malignancy be performed at the time of planned laparotomy or in cases where in spite of preoperative imaging resectability is in doubt.3

Many authors have stressed the importance of laparoscopic ultrasonography during diagnostic laparoscopy for abdominal malignancy since it gives the surgeon valuable information that would be difficult to obtain from a little laparoscopic visual exploration.

Since the introduction of laparoscopic staging, lavage of the peritoneal cavity has been added to the procedure for identification of early peritoneal seeding and eventual metastases, with free cancer cells found in the peritoneal lavage fluid as an effective indicator.

Unnecessary surgery, diagnostic delays, ineffective treatment leading to prolonged operative and in-patient stay which may affect the quality of life, in the long run, can be avoided by effectively using diagnostic laparoscopy. It finds its utility and efficacy as a preoperative tool for timely diagnosis, accurate staging, assessment, and evaluation of intra-abdominal malignancies as a determinant of standard treatment for more regular use.

BACKGROUND

Diagnostic laparoscopy is a minimally invasive modality for the diagnosis of intra-abdominal diseases through direct visual inspection. Tissue biopsies, acquisition of culture, peritoneal lavages along with a variety of therapeutic interventions are possible during the procedures.4,5

The main advantages of diagnostic laparoscopy over traditional open laparotomy are as follows:

- Reduced morbidity
- Reduced postoperative pain
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- Reduced in-patient stay permitting patient selection for curative resection or a neoadjuvant chemotherapy

This review article provides a comprehensive description of the role of diagnostic laparoscopy in the evaluation of patients of abdominal malignancies.

**Historical Perspective**

Over the past decade, the use of laparoscopy has expanded into virtually every surgical discipline, with surgical oncology being no exception. Much of the early work of Jacobaeus in 1910 focused on the diagnosis of malignant diseases.6

**Setup and Equipment**

As with any surgical procedure, an appropriate setup of the operating room is critical for an efficient, safe and effective laparoscopy. For most procedures, the patient is placed supine on the operating table with the surgeon positioned on the right side. The camera operator stands on the opposite side of the patient, with monitors placed above the operative field.

A basic set of equipment is necessary for safe and effective laparoscopy. The basic tray consists of scissors, a grasper, and a dissector. Reusable ports are also used as well as suction irrigation device. Since electrosurgery is used during the procedure, all instruments are insulated to the tip.7

Laparoscopic telescopes are either forward viewing (0°) or oblique (30°). Oblique views are essential to visualize relatively inaccessible regions of the abdomen. The telescope has an eyepiece at the proximal end, serves as the site of attachment for the camera.

Veress needle is used to gain access to the peritoneal cavity. The ability to obtain tissue safely for pathological evaluation is important. Both cup and grasping forceps are effective instruments, achieving an adequate specimen. Cup forceps help in reduction of the amount of tumor spillage by maintaining the entire specimen within the jaws of the forceps. As the prevalence of minimal-access surgery for staging purposes increases, new equipment and techniques continue to emerge, laparoscopic ultrasound and ultrasound-guided biopsy being essential examples.7,8

**LIMITATIONS IN DETECTING METASTATIC DISEASE BY CT AND MRI**

**Computed Tomography**

The CT scan has undergone a revolutionary evolution over the last twenty years with new developments that have improved data acquisition, processing, and image handling. Conventional CT has been replaced by dynamic thin-section CT, spiral CT, Multidetector CT. CT is accurate in assessing abdominal malignancy, But there are certain limitations:9

- It has a limited role in the assessment of local vascular invasion, and there is difficulty in distinguishing whether the tumor is touching vascular structures or invading them, e.g., portal vein and superior mesenteric artery involvement in pancreatic carcinoma.
- It is relatively non-specific for predicting resectability.
- Tumors less than 1 cm in diameter are difficult to detect, thereby reducing the efficacy in detection of peritoneal metastatic deposits, small liver metastasis, and peritoneal micrometastases.
- It cannot distinguish between reactive lymphadenopathy and malignant deposits.
- Lastly, due to faulty techniques and human error.

There are definite concerns about the potential for a false positive diagnosis of unresectability resulting in a repudiation of surgery or a false positive diagnosis of resectability resulting in an unnecessary trip to the operating room. These limitations can be potentially overcome by incorporating other imaging modalities, especially diagnostic laparoscopy with laparoscopic ultrasonography and biopsy.

**Magnetic Resonance Imaging**

Abdominal MRI is rapidly evolving but currently provides essentially the same information as CT scan.

Its limitations involve image artifacts from respiration, aortic pulsation, bowel peristalsis and lack of ideal contrast material for the gut lumen. Recent advances have improved abdominal imaging with MRI, but it has not replaced high-quality CT scanning.10

**Laparoscopic Ultrasonography**

Laparoscopic ultrasound (LUS) probes offer a possible solution allowing the surgeon to perform laparoscopic diagnostic procedures with the use of ultrasound, thereby improving the accuracy of predicting resectability up to as high as 98% in some studies.11,12

**Staging of Intra-abdominal Cancers**

Staging laparoscopy is useful in the evaluation of intra-abdominal malignancy in the following aspects:4,13-15

- Precise staging of the tumor
- Avoidance of unmerited, non-therapeutic laparotomy in patients with metastatic diseases
- For exclusion of metastatic disease and extraction of tissue biopsy antecedent to the initiation of neoadjuvant chemotherapy
- For procuring tissue for diagnosis (lymphomas) or peritoneal lavage fluid for cytology to exclude the
presence of otherwise undetectable peritoneal metastasis.
- Diagnosis of locally advanced disease (fixed tumor or vascular invasion) where no evident distant metastasis is found.
- Development of tailor-suited palliative treatment in patients with advanced or metastatic disease catering to the requirements.
- For assessment of treatment response or disease progression before a definitive laparotomy.

A detailed discussion of the utility of staging laparoscopy for individual cancer types is beyond the scope of this article; however, a brief overview is provided below.

**Esophageal Cancer**

Presentation of Esophageal cancer is often accompanied by locally advanced tumors, as well as lymph nodes and distant metastases, which is a predictor of a poor prognosis. Studies suggest that preoperative chemotheraphy and radiation followed by surgical resection has been shown to improve survival, however, as with other gastrointestinal malignancies, preoperative imaging may point towards a resectable tumor even though a significant percentage of esophageal cancers (20–65%) are found unresectable at the time of exploratory laparotomy.

There is a significant value of diagnostic laparoscopy in staging oesophageal cancer because of its utility in the identification of patients who may or may not be likely to benefit from preoperative chemotherapy, therefore avoiding unnecessary laparotomy or thoracotomy which may have eventually yielded negative findings.

Placement of feeding tubes can be performed at the same time as the staging laparoscopy, to improve the nutritional status of these patients and to prevent the need for additional, technically difficult procedures like percutaneous endoscopic gastrostomy (PEG).

Staging laparoscopy has shown an accuracy of 75–80% in identification of peritoneal metastasis with sensitivity and specificity of 64% and 70% compared to ultrasonography (40–50%) and computerized tomography (45–60%). Addition of LUS and video thoracoscopy has shown to improve the utility of diagnostic laparoscopy in oesophageal cancer.

Lymph node staging is an important independent indicator of prognosis in patients with oesophageal cancer. Metastasis to thoracic lymph nodes is unvaryingly involved because of lymph node spread, despite the level of the primary tumor.

Hagen et al. showed improved survival for patients undergoing complete lymphadenectomy associated with esophagectomy for distal third and gastroesophageal junction tumors. Appropriate therapy can be determined by actual tumor node metastases (TNM) status, defined by preoperative assessment of thoracic and abdominal lymph nodes.

Krasna et al. reported on similar diagnostic accuracy for thoracoscopy and laparoscopic staging procedures (93% and 94%, respectively). Celiac lymph nodes were missed by standard non-invasive techniques in six of 20 patients, who underwent laparoscopy and thoracoscopy.

Watt et al. comparatively evaluated the accuracies of laparoscopy, sonography and computerized tomography in detection of intra-abdominal metastases in patients diagnosed with oesophageal cancer and adenocarcinoma of the cardia. Laparoscopy had a noteworthy higher significance and accuracy (sensitivity 88%; specificity 100%; accuracy 96%) than sonography or CT, with regard to hepatic status. Peritoneal masses were not detected by sonography or CT, while those were correctly identified by laparoscopy in eight of nine patients before surgery with no false-positives and one false-negative result, giving a sensitivity of 89%, specificity of 100%, and accuracy of 98%.

An additional study by Dagnini et al. supports laparoscopy as an effective procedure in the staging of esophageal cancer before the therapeutic intervention, with false-negative findings estimated at 4.4%.

**Gastric Cancer**

Neoadjuvant chemotherapy preceding definitive surgical resection has improved survival among gastric cancer patients with tumors (T3-T4N1), as reported by studies.

In those trials, the benefit of survival was derived by gastric cancer patients with locally advanced tumors or lymph node metastases; however, the 5-year survival rate is poor in the presence of unresectable disease or disseminated metastases (<20%). Hence, it is vital to identify patients of gastric cancer who may benefit from neoadjuvant chemotherapy and those with advanced or metastatic tumors who are not likely to benefit from therapeutic laparotomy.

Several investigators reported that diagnostic laparoscopy has an accuracy of 89 to 100% for staging, aids in the identification of occult metastasis or unresectable disease, and helps to avoid nontherapeutic laparotomy in 13 to 57% of gastric patients despite a negative preoperative imaging workup.

There has been reported uniquely high sensitivity (90 to 96%) of diagnostic laparoscopy for identifying metastasis to liver, peritoneum, and lymph nodes as compared with either ultrasonography (23–37%) or CT (28–52%). Diagnostic laparoscopy with the US further improves identification of liver metastasis and peritoneal lavage cytology enhanced identification of occult peritoneal metastasis by 10–15% in pancreatic cancer.
Therefore, laparoscopy can now play a pivotal role in the management of gastric cancer by accurately defining those patients who are suitable for immediate gastric resection and lymphadenectomy or patients with the advanced local disease who may benefit from preoperative neoadjuvant chemotherapy. Gastric serosal infiltration, metastases in lymph nodes, adherence to adjacent structures, peritoneal carcinomatosis, ascites and the presence of liver metastases are the inherent characteristics to evaluate in the staging of gastric cancer.

The distinction between local and disseminated disease is essential, and knowledge of these parameters dictates the most appropriate intervention.27 Possik et al.28 reported from a cohort of 360 patients that laparoscopic examination assessed tumor fixity in 255 patients and had a sensitivity of 87% for the detection of hepatic metastases and 83% for peritoneal dissemination.

Kriplani and Kapur et al.29 found a comparable laparoscopic staging accuracy of 92%, with laparoscopy predicting resectability in 87% of patients studied. Several investigators have identified the usefulness of staging Laparoscopy as a necessary adjunct to radiography and sonography. The results suggest that laparoscopic staging may obviate exploratory surgery in a significant group of patients.30 Burke et al.31 published their study of 111 gastric cancer patients who were judged to be free of metastatic disease by pre-operative CT underwent laparoscopy, which diagnosed metastatic disease in 32 patients with an overall accuracy of 94%.

Ribeiro et al.32 demonstrated a utility of peritoneal lavage with laparoscopy while staging gastric cancer in patients since the data is easily available and enhances the accuracy of laparoscopy. They also showed that peritoneal cytology is useful in the identification of patients at high risk for peritoneal recurrence since it is of great value in detecting the microscopic intra-abdominal spread of gastric cancer.

Pancreatic Adenocarcinoma

Fifteen to forty percent patients with pancreatic cancer where tumors are reckoned resectable are found to have unresectable tumors because of extension of local tumor or presence of metastasis, despite advances in pre-operative imaging [including CT, endoscopic ultrasonography (EUS), MRI, positron emission technology (PET)]. Findings associated with metastatic cancer at the time of staging laparoscopy are large size of the tumor, adenocarcinoma of the pancreas as opposed to periampullary cancer or duodenal cancer, body and tail location, and preoperative serum levels of CA 19-9 higher than 150 U/Ml.33

Diagnostic laparoscopy has a median sensitivity (range), specificity, and accuracy of (93–100%), 88% (80–100%), and 89% (87–98%) respectively in the identification of unresectable, imaging-occult pancreatic adenocarcinoma. Total 5–7% of patients assumed to have resectable tumors on diagnostic laparoscopy are found to have unresectable tumors on open exploration, which may be ascribed to the occult vascular invasion, fixed tumors or presence of lymph node metastasis. Laparotomy with negative findings can avoid 4 to 36% patients, but not all cases.33

On combining with LUS, the diagnostic accuracy of diagnostic laparoscopy increases by 12–14%; albeit few surgeons and centers have the equipment and the skills necessary for the interpretation of LUS images. Identification of occult metastasis can be further improved with peritoneal lavage cytology in 7–15% of patients, but it is hindered due to the time constraints and unavailability of expert cytopathologists.34

John et al.35 in their prospective trial of 40 patients, demonstrated that Staging laparoscopy is essential in the detection of occult intra-abdominal metastases and that LUS improves the accuracy of laparoscopic staging with potentially resectable pancreatic and periampullary cancer.

Jimenez et al.36 found that laparoscopy diagnosed unsuspected metastases in 31.2% of patients with pancreas cancer, thus avoiding nontherapeutic Laparotomy. Reddy et al.37 suggested that unresectable disease can be detected by staging laparoscopy in 20–48% of patients felt to be resectable by CT scan.

Conlon et al.38 have reported an accuracy rate of 98% for staging laparoscopy in pancreatic cancer. In a series of 115 patients, they delineated good results in detection of extrapancreatic tumor extension where only six patients (9%) were deemed unresectable on laparotomy out of 67 patients with resectable disease on laparoscopy.

The need for a prophylactic bypass is an additional consideration regarding staging laparoscopy for pancreatic cancer. On examination of a prospective cohort of 155 patients with unresectable pancreatic adenocarcinomas who did not undergo enteric or biliary bypass at the time of laparoscopic staging, Espat et al.39 identified only three patients who required surgical bypass. Endoscopically placed stents achieved biliary decompression in these patients. They proposed advocating surgical biliary bypass just for patients with obstructive jaundice who fail endoscopic stent placement and open gastroenterostomy in patients who have a confirmed gastric outlet obstruction.

Laparoscopy has a significant contribution to the proper management of patients with pancreatic cancer, by abolishing nontherapeutic laparotomy and redirection.
of treatment plans and therefore, increased efficiency of resource utilization.

HEPATOBLIARY MALIGNANCIES

Primary Liver Tumors

In patients with primary liver tumors, staging laparoscopy is indicated when pre-operative imaging is suggestive of resectable disease and an adequate hepatic reserve. Diagnostic laparoscopy with LUS permits evaluation of entire hepatic parenchyma and permits identification of the size, location, and some liver tumors along with potential vascular invasion, even though the incidence of peritoneal metastasis in uncommon among these patients.

Nontherapeutic laparotomy can be avoided in 25–40% of patients by combining diagnostic laparoscopy and LUS since it has a sensitivity of 63–67% for the identification of unresectable disease in patients with liver cancer. For lesions larger than 2 cm, diagnostic laparoscopy with LUS has a sensitivity of 96–100% over triphasic CT which is 35–40% sensitive. Although on diagnostic laparoscopy, there can be false negatives in 5 to 15% of primary liver tumors. 13,14

Biliary Tract Tumors

In nearly all patients with gallbladder cancer, hilar cholangiocarcinoma, or extrahepatic bile duct tumors without substantiation of unresectable or metastatic disease on preoperative imaging, staging laparoscopy may be indicated. The utility of diagnostic laparoscopy may be limited to those with T2–T3 cholangiocarcinoma due to the increased availability of EUS, since most patients with T1 cancers have a resectable disease.

In patients with gallbladder cancer and cholangiocarcinoma, diagnostic laparoscopy has a diagnostic accuracy of 48–60% and 53–60%, respectively. 13,14 An enhancement in the overall yield and accuracy may be achieved by combining diagnostic laparoscopy with LUS. 40

A study by D’angelica et al. 41 of 410 patients with radiographically resectable hepatobiliary malignancies was completed in 73% of patients and, in 84 (55%) of the 153 evaluated patients, SL identified the disease that precluded resection.

Hemming et al. 12 studied 168 patients who underwent laparoscopic staging for malignant tumors (chiefly hepatobiliary tumors) in the abdomen and reported 1.8% overall complication rate and no mortality. Several studies suggest that laparotomy can be avoided in a significant number of patients with hepatobiliary cancer when the disease is non-resectable on diagnostic laparoscopy. In-patient stay can be reduced by avoiding laparotomy, which may normally average 5–6 days post-laparotomy when compared with 1.5 days after laparoscopy.

Colorectal Cancer

Diagnostic laparoscopy may infrequently benefit patients with primary colorectal cancer without any evidence of systemic metastasis, essentially because of its low yield in the identification of occult or subclinical metastasis but also because of a preference to undergo colectomy (laparoscopic or open) with intent for cure or alleviation of bleeding, obstruction or perforation.

Diagnostic laparoscopy with intraoperative ultrasonography can be of paramount utility for the identification of the number and location of hepatic metastases and to rule out peritoneal or extrahepatic disease in patients of colorectal cancer with isolated liver metastases and no evidence of extrahepatic disease. A nontherapeutic laparotomy can be avoided in 25–45% if a staging laparoscopy is performed for these indications.

Diagnostic laparoscopy with LUS has a higher sensitivity and specificity of 98–99% to identify occult hepatic metastasis and to evaluate the porta hepatic and celiac lymph nodes with other GI cancers. 13,14

In a study by Jarnagin et al., 45 out of 104 patients underwent MIS staging, 25% of patients with the potentially resectable disease were found to have a disease at laparoscopy which precluded resection. Laparoscopy predicted an overall resectability in 68% of patients and avoided unnecessary laparotomy in 54%. An increased rate of resectability and reduced cost of hospitalization was observed in the group of patients who underwent laparoscopic staging.

Rahusen et al. 44 reported a 38% yield of staging laparoscopy showing unresectability. Later, those results were confirmed by Thaler et al. 47 that identified a 25% yield of SL in identifying radiographically occult disease which led to the decision of resection or no resection.

LYMPHOMA

Since the last 1960s, staging laparotomy was recommended for patients with Hodgkin’s disease and some patients with Non-Hodgkins lymphoma to identify the patients who were potentially curable with radiotherapy, and to precisely plan the fields of radiotherapy. 46

With the introduction of CT scan and CT-directed percutaneous biopsy, development of combination chemotherapy, progressive use of combined modality therapy, recognition of morbidity due to laparotomy and an emerging role of laparoscopy in new and recurrent lymphadenopathy, in staging of patients with histologically confirmed lymphoma and assessment of the response to treatment, the role of laparotomy has been reduced. A particular indication for laparotomy is where the percutaneous biopsy has yielded inadequate information.
A sampling of retroperitoneal lymph nodes, hepatic biopsy and direct visualization of the abdominal cavity in association with bone marrow aspiration or biopsy may accomplish laparoscopic staging.

Routine laparoscopic staging for Hodgkin's disease has shown unsuspected hepatic involvement in 6% of patients and occult splenic involvement in 13% and has allowed stage upgrading in 23% of patients undergoing laparoscopic evaluation. Involvement of the liver was present in 20% of patients of Non-Hodgkin's lymphoma, which further proves the greater systemic involvement of this type of lymphoma.

Conlon et al. reported a series of 55 laparoscopic procedures performed in patients with diagnosed or suspected lymphomas, in which the use of laparoscopy in the diagnosis of abdominal lymphomas was established. Patients undergoing radiotherapy and chemotherapy for lymphoma may be reassessed using laparoscopy for a second evaluation when imaging studies suggest recurrence in the abdominal cavity, as an addition to initial staging and diagnosis.

Minimally invasive procedures for lymphoma may offer a mean to minimize the interval between diagnosis, restaging, and beginning of chemo-radiotherapy when indicated, although this was not evaluated in prospective studies. Reduced pain, reduced inpatient hospital stay, sooner resumption of normal activities and ability to initiate chemotherapy earlier than after laparotomy make laparoscopy a better choice in the diagnosis and staging of a patient with lymphoma.

GYNECOLOGIC MALIGNANT DISEASE

Application of staging laparoscopy in gynecological malignancies has a promising future and is expected to metamorphose numerous aspects of its management.

Ovarian Cancer

Historically, laparoscopy was used for patients with ovarian cancer in one of two settings:

- Before the initiating chemotherapy in patients whose initial laparotomy was believed to be inadequate
- For reevaluation procedures to determine whether patients had persistent disease after completing their primary chemotherapy.

Ozols et al. reported a 55% false-negative rate for laparoscopy compared with laparotomy and underscored the need for laparotomy in patients who appear disease-free at laparoscopy.

Endometrial Cancer

In 1998, the staging of endometrial cancer changed from a clinical to a surgical system. Peritoneal washing, removal of the uterus and adnexa, and retroperitoneal lymph node sampling are done under surgical staging. Laparoscopic-assisted surgical staging has been proposed as an alternative to laparotomy by combining operative laparoscopy and vaginal hysterectomy, for patients early stage endometrial carcinoma.

Assessment of the intraperitoneal cavity, sampling through peritoneal washings and definite removal of the adnexa are possible in surgical laparoscopy.

Clinical outcomes and hospital charges were compared by Gemignani et al. for 320 patients with endometrial cancer staged by laparoscopy versus traditional laparotomy. An incidence of fewer complications, shorter inpatient stay, and overall reduced hospital charges was observed in patients who underwent laparoscopy in comparison to those who underwent laparotomy. There was no statistically significant difference noted in the recurrence rates between the two groups.

Port-site recurrence

There was an initial concern of higher rates of port site recurrence after staging laparoscopy despite the association of the procedure with a low (1–2%) rate of major morbidity.

Dobronte et al. first reported a case of port-site tumor recurrence 2 weeks after laparoscopy in a patient with malignant ascites. Albeit there has been no documentation of increased port site recurrence following staging laparoscopy as compared with laparotomy, with improved expertise and use of an impervious barrier bag for organ retrieval.

Hence, it may be concluded that laparoscopic staging appears safe from an oncologic point of view, since port site implantation is uncommon, differs from traditional open surgical incision recurrence and reflects biological behavior of the diseases instead of the type of surgery.

CONCLUSION

In spite of currently available standard radiological tests such as USG, CT and MRI which are useful in staging the abdominal malignancies, a significant percentage of cases prove to be inoperable because of metastatic or locally advanced disease. Hence diagnostic/staging laparoscopy is very useful in preventing non-therapeutic laparotomies in these patients and also helps in appropriate palliation of symptoms.

CLINICAL SIGNIFICANCE

Diagnostic laparoscopy helps in accurate staging of the tumor, avoidance of non-therapeutic laparotomies in patients with metastatic disease and thus, decreasing the morbidity in such patients. It also helps in the selection
of appropriate neoadjuvant therapy in advanced or metastatic disease, in palliation of symptoms, and an assessment of treatment response in the patient.

REFERENCES


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