

## Management of liver metastases from gastric carcinoma: Where is the evidence?

Hichem Jerraya, Ahmed Saïdani, Mehdi Khalfallah, Ibtissem Bouasker, Ramzi Nouira, Chedly Dziri.

Department "B" of General Surgery, Charles Nicolle's Hospital. Tunis El Manar University – Faculty of medicine of Tunis.

H. Jerraya, A. Saïdani, M. Khalfallah, I. Bouasker, R. Nouira, C. Dziri.

H. Jerraya, A. Saïdani, M. Khalfallah, I. Bouasker, R. Nouira, C. Dziri.

Analyse factuelle des traitements des métastases hépatiques des adénocarcinomes gastriques

Management of liver metastases from gastric carcinoma: Where is the evidence?

LA TUNISIE MEDICALE - 2013 ; Vol 91 (n°01) : 1-5

LA TUNISIE MEDICALE - 2013 ; Vol 91 (n°01) : 1-5

### R É S U M É

**Prérequis :** Les métastases hépatiques des adénocarcinomes gastriques sont souvent la traduction d'une maladie néoplasique évoluée ce qui a justifié pendant longtemps l'indication d'une chimiothérapie palliative. Cependant, inspirés par les bons résultats des différentes modalités thérapeutiques des métastases hépatiques des cancers colorectaux plusieurs chirurgiens se sont intéressés aux métastases hépatiques des adénocarcinomes gastriques. Les différents moyens thérapeutiques utilisés sont la chirurgie, la destruction par radiofréquence, la chimiothérapie intra artérielle hépatique et la gastrectomie palliative.

**But :** Répondre de façon factuelle aux questions suivantes relatives aux métastases hépatiques des adénocarcinomes gastriques :

1. Quelles sont les indications de la chirurgie ?
2. Quelle est l'utilité de la destruction par radiofréquence ?
3. Quelle est la contribution de la chimiothérapie intra artérielle hépatique ?
4. Quel est l'intérêt de la gastrectomie palliative ?

**Méthodes :** Une recherche bibliographique sur Pubmed de Janvier 1990 à décembre 2011 a été conduite en prenant comme mots clés « cancer gastrique » et « métastases hépatiques ».

**Résultats :** La chirurgie d'une métastase hépatique unique dont la taille est inférieure à 5 cm et non associée à une autre localisation métastatique offre de meilleurs résultats en termes de survie à 5 ans que la chimiothérapie palliative. La chimiothérapie intra artérielle hépatique offre une alternative à la chirurgie en cas de malade inopérable et peut être proposée comme traitement néo adjuvant à la chirurgie. L'intérêt de la destruction par radiofréquence et de la gastrectomie palliative reste à prouver.

**Conclusion :** La chirurgie constitue une bonne indication pour une métastase hépatique des adénocarcinomes gastriques unique dont la taille est inférieure à 5 cm et non associée à une autre métastase extra hépatique.

### S U M M A R Y

**Background:** Liver metastatic of gastric carcinoma are often the synonym of advanced neoplastic disease which has long justified the indication of palliative chemotherapy. However, inspired by the good results of the management of liver metastases of colorectal cancers, several surgeons have focused on the treatment of liver metastases of gastric carcinoma. The different therapeutic modalities used are surgery, radiofrequency ablation, hepatic arterial infusion and palliative gastrectomy.

**Aims:** To provide evidence based answer to the following questions regarding liver metastases from gastric carcinoma:

1. What is the indication of surgery?
2. Does radiofrequency ablation useful?
3. What is the contribution of the hepatic arterial infusion?
4. Is there any benefit to palliative gastrectomy?

**Methods:** A literature search on PubMed database over the period from January 1990 to December 2011 was conducted using as key words "gastric cancer" and "liver metastases".

**Results:** Surgery of a single liver metastasis smaller than 5 cm and not associated with another metastatic site offers better results in terms of 5-year survival rate than palliative chemotherapy. Intra hepatic arterial chemotherapy offers an alternative to surgery in inoperable patients and can be proposed as neo adjuvant treatment to surgery. The interest of radiofrequency ablation and palliative gastrectomy remains unproven.

**Conclusion:** Surgery is a good indication for single liver metastasis of gastric carcinoma less than 5 cm and not associated with another extra hepatic metastasis.

### Mots - clés

Cancer gastrique, métastases hépatiques, résection hépatique, traitement

### Key - words

Gastric cancer; hepatic metastases; hepatic resection; treatment

The gastric adenocarcinoma is the second leading cause of cancer death with approximately 737.000 deaths per year [1]. Its prognosis is poor with a 5-year survival rate less than 30% [2]. This unfortunate prognosis becomes even more compromised if the gastric tumor was associated with liver metastases since the 5-year survival rate does not exceed in this case the 10% and the median survival without any treatment is about 3 to 5 months [2, 3]. Unfortunately this situation is not uncommon as liver metastases are present in 4 to 11% of gastric adenocarcinomas [4-8]. The poor prognosis of gastric adenocarcinoma is widely explained by the multiplicity of the routes of the tumor spread. Indeed, in contrast to colorectal cancers in which liver metastasis are mainly done through blood, the spread of gastric adenocarcinoma to liver is done both through blood and serosal invasion of the primary tumor, than via lymphatics.

The lymphatic dissemination results from the phenomenon of lymphatico-venous communication and lymph flow reflux by lymphatic obstruction. This pathway is at the origin of hepatic and peritoneal metastasis [9]. The multiplicity of these spread mechanisms explains that at time of diagnosis, liver metastases of gastric adenocarcinoma are rarely isolated and are most often associated with other visceral sites.

Regarding the concept that liver metastases of gastric adenocarcinoma (LMGA) are synonymous with generalized neoplastic disease, they were considered for a long time as a contraindication to a curative treatment and only a palliative chemotherapy was given with a median survival of approximately 7 months [10].

However, encouraged by the results of treatment of liver metastases of colorectal cancers, many authors reported an increasing number of prolonged median survivals (38 to 60 months) after curative treatment of LMGA in selected subjects [5,6,8,11]. Several therapeutic methods are available but none is consensual.

**This article aimed to provide evidence based answer to the following questions:**

1. What is the indication of surgery in the treatment of LMGA?
2. Does radiofrequency ablation (RFA) useful in the treatment of LMGA?
3. What is the contribution of the hepatic arterial infusion (HAI) in the treatment of LMGA?
4. Is there any benefit to palliative gastrectomy?

---

## METHODS

A literature search was conducted in the PubMed database over the period from January 1st 1990 to December 31st 2011, by taking as language of publication French and English. The keywords used were "gastric cancer" and "liver metastasis". We retained the original articles that are interested in the therapeutic methods of hepatic metastases from gastric adenocarcinoma other than systemic chemotherapy ie: surgical resection, radiofrequency ablation, hepatic arterial infusion and palliative gastrectomy. Editorials, case reports, abstracts and reviews were excluded. All selected articles were analyzed qualitatively

and conclusions were classified according to levels of evidence and grades of recommendations according to the classification of Anaes [12].

---

## RESULTS

By introducing the key words "gastric cancer" and "liver metastasis" on the Pubmed database, we obtained 281 publications. Only 35 articles match the eligibility criteria mentioned above and were used in this work. Only one article reported a prospective non-comparative study, the others publications were retrospective.

### **1. What is the indication of surgery in the treatment of LMGA?**

Twenty-one retrospective studies have focused on the resection of LMGA [4-8, 11, 13-27]. They included a number of cases that varies from 10 to 101. The indication of surgery was taken in 19 studies only if LMGA was not associated with other extrahepatic metastases and whenever liver resection was possible taking into account technical, anatomical and oncological requirements. In the two remaining studies, cases of liver metastases associated with extrahepatic localizations were included whenever a curative resection of all of the metastatic lesions could be considered [23, 27]. Taking into account all these criteria, the resectability rate of LMGA was low and only 10 to 20% of patients underwent resection of the primary cancer as well as liver metastases [4-6, 22].

Indeed, in the series of Koga [6], there were 247 cases of liver metastases among 5520 cases of gastrectomy for gastric adenocarcinoma. Among the 247 LMGA, only 42 liver resections were performed which corresponded to a resectability rate of 17%. The 5-year survival rate in the different series varies from 0 to 42% [6, 19] and the median survival ranges from 9 to 37 months [16, 23]. Approximately 2/3rd to three quarters of patients developed liver recurrence [6, 20, 22]. This high rate of recurrence within 2 years after hepatic resection suggests the presence of intrahepatic micrometastases around liver metastases at the time of surgery [28].

These poor results have motivated the search of the best candidates for liver resection. Thus, several prognostic factors influencing survival after resection of LMGA were determined in the different series. The most included variables were clinicopathological features of primary gastric tumor, number and distribution of liver metastases, synchronous or metachronous character of metastases and resection margin.

The number of liver metastases is an independent factor influencing survival [5,6,8,20]. Indeed, the 5-year survival rate after resection of a single LMGA is significantly higher and it is about 55% [5,6]. Unilobar distribution of liver metastases is also associated with a better survival after resection especially if their size is less than 4 cm [22]. Other studies have concluded that the size of metastases smaller than 5 cm was related to better survival [5, 16, 27].

As concern extrahepatic disease associated to LMGA, this situation constituted a poor prognosis with significantly lower median survival compared to cases in which resection of

isolated LMGA was performed (7 vs. 23 months respectively) [23, 27].

The results concerning the surgical margin of LMGA are conflicting as some authors consider that anatomical hepatic resection with a surgical margin of at least 10 mm is an important factor influencing survival [15, 17, 23], while others reported that both the resection margin and the type of liver surgery did not affect survival rates [4, 7, 22].

The time of LMGA resection represents another controversial subject. Some authors reported poor results in terms of survival after surgery for synchronous metastases [4, 17, 19]. Indeed, in the series of Ambiru et al [17], the synchronous character of LMGA is the only independent factor of poor prognosis. However, in a recent study published in 2009, Ueda [8] reported that the survival rate at 5 years was 60% after surgical resection of synchronous LMGA.

Other factors related to the primary gastric tumor were associated in some series with a poor prognosis after resection of LMGA as the size larger than 6 cm [26], the invasion of the serosa [6, 7, 14, 24], the lymphatic and the venous invasion [14, 20] and the type of lymphadenectomy less than D2 [26].

In summary, surgery of LMGA offers better long-term results than palliative chemotherapy. Surgery should be considered, whenever the liver metastasis is single, smaller than 5 cm and not associated with other extra hepatic metastases however the level of evidence is low (**level 5, Grade of recommendation C**).

## **2. Does radiofrequency ablation (RFA) useful in the treatment of LMGA?**

Only few studies have evaluated the RFA alone in the treatment of LMGA. These are three retrospective studies including small numbers of cases [29-31]. Median survival is 30.7 months in one study [30]. However, Kim et al [29] reported a tumor recurrence rate of 100% with a median survival of 11 months only.

Although the RFA of LMGA is feasible, the high tumor recurrence rate justifies additional prospective studies to better assess the long-term results of this technique and to verify if there is a benefit compared to palliative chemotherapy. In the light of these data RFA cannot be recommended as a treatment for LMGA (**Level 5, Grade of recommendation C**).

## **3. What is the contribution of the hepatic arterial infusion (HAI) in the treatment of LMGA?**

Two retrospective studies have examined the results of the HAI in the treatment of LMGA [32, 33], while a non-comparative prospective study evaluated the HAI in combination with RFA [34]. In Ojima's study [33], although the response rate to the HAI was 83%, no improve in survival was noted. However, in the prospective study of Yamakado et al [34], the HAI has helped to reduce both the size and the number of liver metastases which have been totally destroyed in a second time by RFA. This combination therapy yielded a median survival of 16.5 months.

Regarding these results, the HAI is an effective tool to reduce the number and the size of LMGA with a view to consider further treatment by surgery or radiofrequency (**Level 4, Grade of recommendation C**). However comparative trials are needed.

## **4. Is there a benefit to palliative gastrectomy?**

Eight studies evaluated the impact on survival of palliative gastrectomy in metastatic and locally advanced gastric adenocarcinoma. All these studies are retrospective [35-42]. Seven studies found a benefit in terms of median survival after palliative gastrectomy, ranging from 3 to 11 months [35-41]. Only one study did not find any difference in survival between patients who underwent palliative resection and non operated patients [42].

The low level of scientific evidence of these studies (**Level 5**) and their conflicting results do not allow to evaluate the interest of palliative gastrectomy. Thus, gastrectomy cannot be indicated as a palliative treatment in asymptomatic patients with LMGA (**Grade of recommendation C**).

---

## **DISCUSSION**

---

The management of liver metastases from gastric adenocarcinoma is not consensual. If systemic chemotherapy is an irrefutable indication for LMGA associated with other extra hepatic metastases, the attitude for isolated liver metastases is still widely debated. Although the level of evidence is low, the results of surgery in this situation in terms of 5-year survival and median survival were superior to those obtained with systemic chemotherapy alone. This outcome is even more evident when surgery was indicated for single liver metastases whose size is less than 5 cm. Our findings join with those of three reviews [43-45] in which, the authors suggested that surgery of LMGA is reasonable in selected patients and should be considered as an option in the treatment of gastric adenocarcinoma with liver metastases. The encouraging results of surgery based on retrospective studies will be verified by a prospective study "The GYMSSA trial" which compared gastrectomy with metastasectomy and systemic chemotherapy vs. systemic chemotherapy alone [46].

RFA is a method widely applied for primary or secondary liver tumors [47]. It may be an alternative to surgical resection in inoperable patients. However, the size of liver metastases represents a determining factor for the radicality of destruction [48]. Indeed, lesions measuring less than 2.5 cm will be completely destroyed in more than 90% of cases, while for those whose size is greater than 5 cm, the destruction is complete in less than 50% of cases [47]. This explains the high percentage of tumor recurrence in the series of Kim et al [29]. So, although the interest of radiofrequency is increasing, the effectiveness, indications and limitations of this method in the treatment of LMGA must be evaluated by larger series.

With regard to HAI, this method can deliver high doses of cytotoxic agents to liver tumors with minimal systemic side effects [49]. The HAI is another alternative treatment for LMGA which are not accessible to surgery. Moreover, it can be used in order to obtain a reduction in tumor size in order to perform a surgical resection or radiofrequency destruction.

Regarding palliative gastrectomy, its defenders argue that this procedure improves the response of the residual tumor to chemotherapy. On the other hand, the reduction in tumor mass

decreases both metabolic consumption and the secretion of tumor-induced immunosuppressive cytokines [50-51]. However, studies that find a benefit in terms of survival after palliative gastrectomy, are all retrospective and include selection bias in favor of surgical patients. Prospective randomized studies are needed to evaluate the usefulness of palliative gastrectomy.

## References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; 61:69-90.
2. Howlander N, Noone AM, Krapcho M et al. SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, [http://seer.cancer.gov/csr/1975\\_2008/](http://seer.cancer.gov/csr/1975_2008/), based on November 2010 SEER data submission, posted to the SEER web site, 2011.
3. Leong T. Chemotherapy and radiotherapy in the management of gastric cancer. *Curr Opin Gastroenterol* 2005; 21: 673-8.
4. Okano K, Maeba T, Ishimura K et al. Hepatic resection for metastatic tumors from gastric cancer. *Ann Surg* 2002; 235: 86-91.
5. Sakamoto Y, Ohyama S, Yamamoto J, et al. Surgical resection of liver metastases of gastric cancer: an analysis of a 17-year experience with 22 patients. *Surgery* 2003; 133: 507-11.
6. Koga R, Yamamoto J, Ohyama S, et al. Liver resection for metastatic gastric cancer: experience with 42 patients including eight long-term survivors. *Jpn J Clin Oncol* 2007; 37: 836-42.
7. Cheon SH, Rha SY, Jeung HC, et al. Survival benefit of combined curative resection of the stomach (D2 resection) and liver in gastric cancer patients with liver metastases. *Ann Oncol* 2008; 19: 1146-53.
8. Ueda K, Iwahashi M, Nakamori M, et al. Analysis of the prognostic factors and evaluation of surgical treatment for synchronous liver metastases from gastric cancer. *Langenbecks Arch Surg* 2009; 394: 647-53.
9. Kumagai K, Shimizu K, Yokoyama N et al. Gastrointestinal cancer metastasis and lymphatic advancement. *Surg Today* 2010; 40: 301-6.
10. Ajani JA. Evolving chemotherapy for advanced gastric cancer. *Oncologist* 2005; 10 Suppl 3: S49-S58.
11. Makino H, Kunisaki C, Izumisawa Y, et al. Indication for hepatic resection in the treatment of liver metastasis from gastric cancer. *Anticancer Res* 2010; 30: 2367-76.
12. Guide méthodologique. Analyse de la littérature et gradations des recommandations. Agence nationale d'accréditation et d'évaluation en santé (Anaes). 2000
13. Bines SD, England G, Deziel DJ, et al. Synchronous, metachronous, and multiple hepatic resections of liver tumors originating from primary gastric tumors. *Surgery*. 1993; 114: 799-805; discussion 804-5.
14. Ochiai T, Sasako M, Mizuno S, et al. Hepatic resection for metastatic tumors from gastric cancer: analysis of prognostic factors. *Br J Surg* 1994; 81: 1175-8.
15. Miyazaki M, Itoh H, Nakagawa K, et al. Hepatic resection of liver metastases from gastric carcinoma. *Am J Gastroenterol* 1997; 92: 490-3.
16. Fujii K, Fujioka S, Kato K, et al. Resection of liver metastasis from gastric adenocarcinoma. *Hepatogastroenterology* 2001; 48: 368-71.
17. Ambiru S, Miyazaki M, Ito H, et al. Benefits and limits of hepatic resection for gastric metastases. *Am J Surg* 2001; 181: 279-83.
18. Saiura A, Umekita N, Inoue S, et al. Clinicopathological features and outcome of hepatic resection for liver metastasis from gastric cancer. *Hepatogastroenterology* 2002; 49: 1062-5.
19. Zacherl J, Zacherl M, Scheuba C, et al. Analysis of hepatic resection of metastasis originating from gastric adenocarcinoma. *J Gastrointest Surg* 2002; 6: 682-9.
20. Shirabe K, Shimada M, Matsumata T, et al. Analysis of the prognostic factors for liver metastasis of gastric cancer after hepatic resection: a multi-institutional study of the indications for resection. *Hepatogastroenterology* 2003; 50: 1560-63.
21. Roh HR, Suh KS, Lee HJ, et al. Outcome of hepatic resection for metastatic gastric cancer. *Am Surg*. 2005; 71: 95-9.
22. Sakamoto Y, Sano T, Shimada K et al. Favorable indications for hepatectomy in patients with liver metastasis from gastric cancer. *J Surg Oncol* 2007; 95: 534-539.
23. Thelen A, Jonas S, Benckert C, et al. Liver resection for metastatic gastric cancer. *Eur J Surg Oncol* 2008; 34: 1328-34.
24. Tiberio GA, Coniglio A, Marchet A, et al. Metachronous hepatic metastases from gastric carcinoma: a multicentric survey. *Eur J Surg Oncol* 2009; 35: 486-91.
25. Choi SB, Song J, Kang CM, et al. Surgical outcome of metachronous hepatic metastases secondary to gastric cancer. *Hepatogastroenterology* 2010; 57: 29-34.
26. Tsujimoto H, Ichikura T, Ono S, et al. Outcomes for patients following hepatic resection of metastatic tumors from gastric cancer. *Hepatol Int* 2010; 4: 406-13.
27. Adam R, Chiche L. Chirurgie des métastases hépatiques de cancers non colo-rectaux, non endocrines. Rapport présenté au 107ème congrès français de chirurgie 2005. Monographie de l'Association française de Chirurgie – Ed Arnette.
28. Nomura T, Kamio Y, Takasu N, et al. Intrahepatic micrometastases around liver metastases from gastric cancer. *J Hepatobiliary Pancreat Surg* 2009; 16: 493-501.
29. Kim HO, Hwang SI, Hong HP, Yoo CH. Radiofrequency ablation

## CONCLUSION

The best treatment for hepatic metastases from gastric adenocarcinoma is still widely debated. Surgery is a good indication in well selected patients with single liver metastasis less than 5 cm (Level 5, Grade of recommendation C). However, this condition is not the most common. For the remaining majority of LMGA, there is not enough scientific evidence to indicate other therapeutic modalities (RFA, HAI and palliative gastrectomy). In this case, systemic chemotherapy remains the best hope for a longer survival and an improved quality of life.

- for metachronous hepatic metastases from gastric cancer. *Surg Laparosc Endosc Percutan Tech* 2009; 19: 208-12.
30. Kim HR, Ha Cheon S, Lee KH, et al. Efficacy and feasibility of radiofrequency ablation for liver metastases from gastric adenocarcinoma. *Int J Hyperthermia* 2010; 26: 305-15.
  31. An JY, Kim JY, Choi MG, et al. Radiofrequency ablation for hepatic metastasis from gastric adenocarcinoma. *Yonsei Med J* 2008; 49: 1046-51.
  32. Iwahashi M, Tanimura H, Nakamori M, et al. Clinical evaluation of hepatic arterial infusion of low dose-CDDP and 5-FU with hyperthermotherapy: a preliminary study for liver metastases from esophageal and gastric cancer. *Hepatogastroenterology* 1999; 46: 2504-10.
  33. Ojima H, Ootake S, Yokobori T et al. Treatment of multiple liver metastasis from gastric carcinoma. *World J Surg Oncol* 2007; 5: 70.
  34. Yamakado K, Nakatsuka A, Takaki H, et al. Prospective study of arterial infusion chemotherapy followed by radiofrequency ablation for the treatment of liver metastasis of gastric cancer. *J Vasc Interv Radiol* 2005; 16: 1747-51.
  35. Hartgrink HH, Putter H, Klein Kranenbarg E, Bonenkamp JJ, van de Velde CJ. Value of palliative resection in gastric cancer. *Br J Surg* 2002; 89: 1438-43.
  36. Saidi RF, ReMine SG, Dudrick PS, Hanna NN. Is there a role for palliative gastrectomy in patients with stage IV gastric cancer? *World J Surg* 2006; 30: 21-7.
  37. Samarasam I, Chandran BS, Sitaram V, et al. Palliative gastrectomy in advanced gastric cancer: is it worthwhile? *ANZ J Surg* 2006; 76: 60-3.
  38. Kim DY, Joo JK, Park YK, et al. Is palliative resection necessary for gastric carcinoma patients? *Langenbecks Arch Surg* 2008; 393: 31-5.
  39. Miyagaki H, Fujitani K, Tsujinaka T, et al. The significance of gastrectomy in advanced gastric cancer patients with non-curative factors. *Anticancer Res* 2008; 28: 2379-84.
  40. Lin SZ, Tong HF, You T, et al. Palliative gastrectomy and chemotherapy for stage IV gastric cancer. *J Cancer Res Clin Oncol* 2008; 134: 187-92.
  41. Chang YR, Han DS, Kong SH, et al. The value of palliative gastrectomy in gastric cancer with distant metastasis. *Ann Surg Oncol* 2012; 19: 1231-9.
  42. Li C, Yan M, Chen J, et al. Survival benefit of non-curative gastrectomy for gastric cancer patients with synchronous distant metastasis. *J Gastrointest Surg* 2010; 14: 282-88.
  43. Shirabe K, Wakiyama S, Gion T, et al. Hepatic resection for treatment of liver metastases in gastric carcinoma: review of the literature. *HPB* 2006; 8: 89-92.
  44. Kakeji Y, Morita M, Maehara Y. Strategies for treating liver metastasis from gastric cancer. *Surg Today* 2010; 40: 287-94.
  45. Liu J, Chen L. Current status and progress in gastric cancer with liver metastasis. *Chin Med J* 2011; 124: 445-56.
  46. Kerkar SP, Kemp CD, Duffy A, et al. The GYMSSA trial: a prospective randomized trial comparing gastrectomy, metastasectomy plus systemic therapy versus systemic therapy alone. *Trials* 2009; 10: 121.
  47. Chen MH, Yang W, Yan K, et al. Treatment efficacy of radiofrequency ablation of 338 patients with hepatic malignant tumor and the relevant complications. *World J Gastroenterol* 2005; 11: 6395-401.
  48. Iannitti DA, Dupuy DE, Mayo-Smith WW, Murphy B. Hepatic radiofrequency ablation. *Arch Surg* 2002; 137: 422-26.
  49. Ganeshan A, Upponi S, Hon LQ, Warakaulle D, Uberoi R. Hepatic arterial infusion of chemotherapy: the role of diagnostic and interventional radiology. *Ann Oncol* 2008; 19: 847-51.
  50. Pollock RE, Roth JA. Cancer-induced immunosuppression: implications for therapy? *Semin Surg Oncol* 1989; 5: 414-19.
  51. McCarter MD, Fong Y. Role for surgical cytoreduction in multimodality treatments for cancer. *Ann Surg Oncol* 2001; 8: 38-43.