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


Department “B” of General Surgery, Charles Nicolle’s Hospital. Tunis El Manar University – Faculty of medicine of Tunis.

SUMMARY

Background: Liver metastases 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.

Key-words
Gastric cancer; hepatic metastases; hepatic resection; treatment

Mots-clés
Cancer gastrique, métastases hépatiques, résection hépatique, traitement
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**

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