

# Distant nodal metastasis: is it always an unresectable disease?

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**Abstract:** This article aims at analyzing the published literature concerning the treatment of patients with gastric cancer and distant nodal metastases, actually considered metastatic disease. A systematic search was undertaken using Medline, Embase, Cochrane and Web-of-Science libraries. No specific restriction on year of publication was used; preference was given to English papers. Both clinical series and literature reviews were selected. Only 11 papers address the issue of surgery for nodal basins outside the D2 dissection area. From these papers, in selected cases extended surgery may prove useful in prolonging survival, when a comprehensive therapeutic pathway including chemotherapy is scheduled. In conclusion, in presence of nodal metastases outside the loco-regional nodes, surgery may be considered for metastatic nodes in stations 13 and 16, in selected cases.

**Keywords:** Gastric cancer; stomach; staging; TNM; nodal metastases

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## Introduction

Stage IV gastric cancer is defined as metastatic disease (7<sup>th</sup> TNM Edition, 2010) (1), and surgery is usually considered not appropriate, outside from the palliative setting; however, a significant amount of patients are actually treated by surgery, with a theoretical curative intent and in selected cases with good long-term survival.

Lymph node stations 1–12 + 14v are defined as regional gastric lymph nodes by the 2011 Japanese Classification of Gastric Cancer, 3<sup>rd</sup> English Edition (2,3); metastases to any other nodes (stations 13 and 17, pancreatic head, station 14a, superior mesenteric artery, station 15, middle colic artery, station 18, pancreatic tail and station 16, periaortic, are classified as M1.

The present paper analyzes the available literature, focusing the attention on the stage IV subgroup defined by the presence of distant nodal metastases, and critically

discusses the most employed clinical pathways.

## Materials and methods

### Search methods

A systematic search of literature was performed using Medline, Embase, Cochrane and Web-of-Science libraries. No year of publication restrictions were considered. Search terms were: stomach, gastric cancer, metastases, stage IV, periaortic nodes, nodal metastases, nodal classification. Preference was given to English publications. All references in selected articles were further screened.

### Study selection

Articles were chosen on the basis of the abstract, if its content was related to the clinical results of surgical

treatment of patients with distant nodal metastases. Papers with pathological classifications, genetic and proteomic assessment, risk factors for nodal metastases, congress presentations and letters to the editor were excluded.

### Data extraction

A data extraction form was created and filled in, including study design, number of patients, intervention type/with special reference to nodal dissection (D1 *vs.* D2 *vs.* D3), post-operative complications, overall and disease free survival. For statistical analysis, it was considered significant  $P < 0.05$ , when published.

### Results

The titles and abstracts of 84 articles were screened separately by two authors (Gian Luca Baiocchi, Sarah Molfino) for eligibility. In addition, 68 articles were excluded because their abstracts were unavailable ( $n=12$ ), because they were irrelevant to the goal ( $n=42$ ), or because metastases rate was described, without reference to the treatment ( $n=14$ ). This resulted in 16 articles, 5 of which were further excluded after full text examination (1 was only available in the abstract form, 2 were comments to other papers, 2 included also patients without distant nodal metastases, without the possibility of extracting the subgroup which the paper is committed on). The remaining 11 articles were fully analyzed (4-15).

Official Japanese guidelines suggest to limit the D2 lymphadenectomy to stations 1–7, 8a, 9, 10, 11p, 11d and 12a (when total gastrectomy is necessary) and to stations 1–7, 8a, 9, 11p, 12a (in cases of need of distal gastrectomy). Most extended lymphadenectomy (variably called D2+ or D3) is not included in the 2010 Japanese guidelines (2,3). However, some rare series from Western Centers suggested at pathological analysis that distant, not locoregional nodes are in some cases involved by cancer as the only tumor burden. A study performed by the Italian Research Group for Gastric Cancer (IRGGC) analyzed the incidence of lymph nodal metastases in every singular nodal basin, and related those data with the T stage and the site of the primary tumor: station 16 nodes were involved in 38% of T4-upper third, in 30% of all upper third cancers, in 12% of middle third cancers and in 9% of distal third cancers (4). Another study showed that almost half of these cases were negative for further peritoneal and haematogenous disease, so they may be,

from a theoretical point of view, suitable for R0 surgery (5). On the other side, a Chinese series of 872 cases aimed at analyzing the risk factors for survival in metastatic cases treated by surgery. The included period was 1993–2008. Both haematogenous and distant nodal cancer involvement were included. The authors finally concluded that patients with distant nodal-only disease (stage IV for nodal involvement) could be operated on and pathological R0 operation represented a significant prognostic factor for overall survival (6). The recent Regatta study seems to conclude in the opposite way, but it deserves some criticisms; the most important, which hampers its utility in the present paper, is that in the surgical group only gastrectomy + D1 lymphadenectomy was performed, thus the intervention was by definition R2, really palliative (7). Furthermore, a study specifically aimed at investigating if the surgical stress could worsen the oncological results *per se*, concluded in a negative way: the survival was 381 and 181 days, respectively, in patients undergoing and not undergoing surgery; hospital mortality was 3.4% and 15.9%, respectively (8).

### Discussion and conclusions

Stage IV tumours clearly have poor prognosis, thus the role of surgical treatment is limited. However, no prospective randomized studies are available (with the exception of the REGATTA trial, already mentioned); usually the oncologists would not send those patients for surgical consultation, mainly because post-operative morbidity and mortality are relevant in the setting of metastatic disease. On the other side, we are still unable to exclude the likelihood of medium term survival of a stage IV patient, undergoing R0 surgery and chemotherapy. In a recent paper from Korea including 273 patients with metastatic disease treated by chemotherapy first, 42 were received at the end R0 gastric + metastatic disease resection, and 12 (4.3% of the whole series) were alive without disease after a median follow-up of 29.1 months (9). Unfortunately, we have got only limited risk factors to be taken into consideration in the decision-making process: from a study published in 2012 including patients with distant metastases, at multivariate analysis nor the extent of liver disease, nor gender, age, tumor site, Borrmann type, T, N, P, the multiple metastatic sites, grading and extent of gastrectomy, were independently related to the overall survival (10). However, some recent papers underline that interesting survival rates may be expected in selected cases: from a wide

retrospective analysis of the MD Anderson Cancer Center files, 82 cases undergoing surgery out of 7,484 patients with stage IV gastric cancer [1995–2012] were recruited. The 5-years OS was 42% in patients with only positive cytology, 13% in patients with overt carcinomatosis, 34% in patients with distant metastatic nodes, and 20% in patients with hepatic metastases (11).

In this scenario, the case of patients with distant, periaortic and retropancreatic (stations 13 and 16, respectively) nodal metastases should be critically reviewed by a subgroup analysis. Those cases are one of the most important fields of divergence between Eastern and Western approach: while in Far East the dissection of nodes in these areas is nearly neglected, in Western Centers the nodal dissection is frequently enlarged to the retropancreatic and to the periaortic nodes. This is true especially for those centers having high volume of gastric cancer cases. We are observing an interesting phenomenon from a historical point of view; while 30 years ago the Japanese surgeons sustained an aggressive surgical approach to gastric cancer, which was subsequently accepted in the rest of the world, Western surgeons are actually more aggressive in this dissection nowadays than their Eastern counterpart. Other recently published papers, investigating Krukenberg tumors, margin infiltration and surgery in old patients, included as subgroup analysis number of patients with distant positive nodes, whose survival was not statistically different (when lymphadenectomy was done) from patients without nodal metastases in those basins (16–18).

In conclusion, the most recent guidelines suggest, in selected cases and in centers showing high volume and expertise, to take into consideration the dissection of distant nodes (especially periaortic nodes) (19,20). There is the need for a further RCT on this topic, comparing standard D2 and experimental D3 both in patients without and with evident nodal metastases in the periaortic area. Very far nodal metastases, such as axillary, inguinal and clavicular nodes, are clearly really haematogenous metastases, with poor prognosis and no-sense for surgical dissection.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest

to declare.

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