



## PERSPECTIVE

# Tumor Stage-Based Tailored Therapeutic Strategy: Rational Approach or New Trend?

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### ABSTRACT

Currently, many patients with gastric cancer are overtreated or undertreated. Gastrectomy with less (D1) or more (D2) extensive lymph node dissection usually followed by adjuvant treatment is the standardized treatment in all stages-cancer, early or late. However, there is little scientific evidence that aggressive treatment, as compared with less extensive surgery, provides better clinical outcome especially in earlier-stages cancer.

Since the principal goal for a curative (R0) resection in early stage-cancers can be achieved with a less extensive surgery, a trend towards a tumor stage-based extent of surgery with or without adjuvant treatment seems to be rational. Such a strategy has already been started in Japan.

Here, we highlight the risks (local, distant recurrences, death) and benefits (lower adverse-effects profile), of a tumor stage-oriented therapeutic strategy, as well as whether decision-making based on tumor stage is evidence-based or not.

Studies with new biologic markers, as gene expression signature, provide currently promising data that microarrays, in addition to other classic predictors, will be used in the future towards improvement of outcome prediction and treatment in both survival and quality of life (QOL) by reducing the rate of overtreatment or undertreatment of the patients with gastric cancer.

**E**xtensive, aggressive surgery in all stages of epithelial cancer has been accepted axiomatic in the management of the most common solid tumors including breast, prostate, colon and stomach. However, for the superiority of radical surgery especially in early stages of the disease there is little or no scientific evidence from randomized trials. Over the last decades several randomized trials for other solid tumors, mainly for breast cancer, have provide proof that long-term survival is similar after a limited surgery (breast conservation treatment) or extensive surgery (mastectomy).<sup>1</sup>

The concept of a less aggressive treatment approach has been widely discussed during the last decade also for early-stage gastric cancer. Complete removal of the primary tumor by surgery –curative or R0 resection in the AJCC/UICC-TNM classification<sup>2</sup> - has been established standard in the surgical management of gastric cancer. When the disease is identified at an early-stage cancer, this principal goal of surgery for an R0 resection is achievable by a less extensive surgery. This creative thoughtful concept represents an important advance towards a patient's lower morbidity and better quality of life, and has recently received increasing attention.<sup>3</sup> However, precondition for the clinical implication of a tailored treatment according to the tumor stage is the

availability of long-term survival data that provide scientific evidence supporting that this treatment strategy does not associated with any increase of treatment failure and death.

Indeed, the cause of treatment failure and death after complete tumor resection is the local recurrence and the formation of secondary tumor(s) at distant organs (distant recurrence). Risk-reducing recurrence is therefore the principal goal of therapeutic strategy. Morbidity and QOL should also be considered for treatment decision-making and is known that the less the extent of surgery the lower the rates of operative morbidity and mortality and the greater the benefits in QOL.

How can be reduced the risk of local and distant recurrence in gastric cancer? Two are the main ways. An R0 resection and an effective adjuvant treatment necessary to eliminate disseminated cancer cells which are responsible for distant recurrence.

Curative resection is the treatment of choice but the extent of this surgical procedure remains controversial.<sup>3</sup> Small tumors can be resected completely with a limited surgery leading to a better QOL and there are promising

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data for patients with small mucosal cancers treated by endoscopic mucosal resection (EMR) from specialized institutions from Japan.<sup>4</sup> However, there are not still long-term follow-up data whereas survival results with extensive surgery in early stage-cancers are excellent not only in Japan<sup>5</sup> but also in the West.<sup>6</sup>

Furthermore, relevant basic research strongly supports the important role of clear surgical margins not only for local tumor control but also for the combat of lymphatic spread and lymph node metastases. Padera et al. found that functional lymphatic vessels in the tumor margin are sufficient for lymphatic metastasis and therefore the authors suggest that the tumor margins should be treated aggressively by local treatment, such as surgery and radiation, to combat lymphatic dissemination.<sup>7</sup>

The optimal extent of lymph node dissection continues to be controversial. Randomized trials in the West comparing limited, D1 lymph node dissection with extended, D2 lymph node dissection<sup>8,9</sup> failed to confirm the superiority of D2 dissection in any nodal stage, early or late, suggested by multiple inconclusive Japanese and western studies.<sup>3,5</sup> However the western randomized trials are limited by inappropriate design and conduction.<sup>10</sup> Furthermore, because approximately 30% of the patients with a curable tumor have positive the level II nodes (N2 disease in the Japanese anatomical classification), and thus an in fact R0 resection can be achieved only by a D2 and not a D1 node dissection,<sup>10</sup> decision about the optimal extent of node dissection remains non-evidence-based.

Decision for an additional organ resection such as the spleen or the pancreas also seems to be strongly depended on the tumor stage. Splenectomy or pancreaticosplenectomy has been previously performed in all stages-cancer but this aggressive surgery increased operative morbidity and mortality without survival improvement.<sup>3,8,9</sup> Accumulating evidence supports that prophylactic resection of the spleen, pancreas or other organ does more harm than benefit,<sup>3</sup> but in advanced T4 cancers extensive radical surgery is the only way to be achieved an R0 resection. This aggressive surgical approach can be performed safely and can improve overall survival according to a recent report from specialized institution.<sup>11</sup> Whether this primary extensive surgery or a neo-adjuvant treatment for tumor reduction and subsequent surgical resection for localized advanced disease is more beneficial remains unclear and is investigating in randomized trials.

Despite appropriate extent of surgery, recurrence often occurs particularly in advanced-stage cancers.<sup>6</sup> Cancer cells escape the primary tumor and via blood and lymphatic vessels establish secondary tumors (recurrence) at distant organs. The need for effective adjuvant chemotherapy is clear but until now research efforts to establish a standard adjuvant treatment have been failed.<sup>12</sup> Recently, a randomized trial demonstrated that postoperative chemoradiotherapy after "curative" limited (D0 or D1) node dissection improves survival.<sup>13</sup>

Taking into account the data available becomes clear that decision about extent of surgery and use of adjuvant

treatment has increasingly been oriented to the tumor stage of the individual patient, suggesting the importance of a accurate pretreatment prediction of tumor spread (staging). However, despite advances in imaging technology -endoscopic ultrasonography, computer tomography, magnetic resonance imaging and positron emission tomography-, which have substantially increased the accuracy of tumor depth (T-stage) and distant metastasis (M-stage), prediction of nodal status is not just high as to allow with safety decision about extent of lymphadenectomy.

Ideally, if the tumor-stage could be accurately predicted before treatment, optimal surgery might be focused on the minimum extent of surgery needed to accomplish an R0 resection with sufficient resection of tumor margins. This tumor stage-oriented procedure then involves a wide spectrum of treatments from minimally invasive approaches (EMR, laparoscopic approach, function-preserving gastrectomy) to aggressively extensive resections. But such strategy prerequisites a numerous of conditions including the availability of expertise teams of surgeons, oncologists and endoscopists as well as of modern diagnostic and therapeutic technology. In many regional hospitals in the western World a change of standard D1 resection to less or more extensive resections is and will be remain challenging.

An optimal management of gastric cancer should meet the criteria of recurrence-prevention, low morbidity and a good QOL. A tailored tumor stage-based extent of surgery and adjuvant treatment may meet all these criteria but decision-making remains non-evidence-based. Under the condition that the principal goal of treatment of gastric cancer should be a complete resection not only of the primary tumor but also of positive perigastric nodes the following tumor stage-based treatment may be proposed.

### **Early-stage cancer (T1Nx)**

(a) Small (tumor size < 2 cm), mucosal, well differentiated or intestinal-type cancers: Endoscopic mucosal resection offers excellent quality of life without increasing risk of recurrence or death.<sup>4</sup> EMR is now advocated as the primary treatment of choice in Japan.<sup>14</sup> The detailed histological examination of the resected specimen will determine whether an additional secondary treatment is needed or the patient will remain under a close follow-up.

(b) For the remaining patients including those with mucosal cancers (> 2cm or all diffuse-type cancers) and all submucosal cancers a conventional open D1 gastrectomy is sufficient for an R0 resection in most cases; D2 dissection may rarely (affected level II nodes) be needed. Limited functions-preserving surgery and laparoscopic wedge resection are promising but still investigating. Adjuvant treatment is not required.

### **Non early-stage cancers (T2-3N0-2M0)**

These patients are at high risk of having metastatic disease in level II nodes (N2 disease) and thus the primary goal of surgery for curative resection is

achievable only by D2 lymph node dissection, but whether D2 dissection results in a survival benefit is still highly debated.<sup>3,8-10</sup> D1 dissection seems sufficient for node-negative disease but the prediction of nodal status remains inaccurate. Adjuvant chemoradiotherapy has been suggested effective after “curative” limited (D0 or D1) node dissection,<sup>13</sup> but the effect of this adjuvant treatment on patients undergoing D2 dissection is unclear.

#### Locally advanced gastric cancer (T3-T4,N0-2M0):

Survival of patients with localized unresected or non-curatively resected tumors is poor. Neo-adjuvant (preoperative) chemotherapy may reduce tumor mass enabling due a D2 dissection a potentially curative resection that may prolong survival.<sup>3,12</sup> Ongoing trials will establish whether this strategy as well as intra-peritoneal chemotherapy improve the patient’s outcome.

A new era towards a tumor stage-based less or more extensive surgery with or without use of more or less aggressive multimodality adjuvant treatment in the management of gastric cancer has already been started. However, we need much more evidence-based data to establish the optimal treatment of the individual patient according to the tumor stage.

Classic prognostic indicators, such as the TNM classification system<sup>2</sup> imperfectly predict the clinical outcome of a patient with gastric adenocarcinoma. Some early-stage tumors recur whereas some advanced-stage tumors do not develop recurrence after treatment.<sup>6</sup>

Exciting recent research using DNA microarrays provides promises for a highly accurate prediction of distant metastases and survival. Recent studies showed that DNA-microarray data distinguished primary breast tumors<sup>15</sup> and multiple other solid tumors<sup>16</sup> into a “good” and “poor” prognosis genetic signature. Interestingly, this gene-expression profile predicts clinical outcome much better than classic predictors as TNM stage. These data raise strong hope that new microarray studies in gastric cancer will determine a combined staging system consisted of microarrays and the conventional TNM-system that will accurately predicts the clinical outcome regarding local or distant failure and survival. This will open the way for a tailored treatment targeting the individual patient with gastric cancer reducing an overtreatment or undertreatment and improving both survival and QOL.

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