Extreme Aggressiveness and Lethality of Gastric Adenocarcinoma in the Very Young

Brian R. Smith, MD; Bruce E. Stabile, MD

Objective: To determine whether very young patients with gastric adenocarcinoma as compared with older patients with the disease have a biologically more aggressive form of the disease, presenting at an advanced stage and conferring unusually poor perioperative and long-term outcomes.


Main Outcome Measures: Histologic features, frequency of stage IV disease, frequency of curative gastric resection, postoperative mortality, and long-term survival in very young and older patient groups.

Results: Of 350 total patients, 30 (9%) were aged 35 years or younger. Very young patients (aged ≤35 years) as compared with older patients (aged >35 years) more often had diffuse-type tumor histologic findings (93% vs 69%, respectively; \( P = .003 \)), adjacent organ invasion (74% vs 29%, respectively; \( P = .001 \)), nodal metastases (94% vs 70%, respectively; \( P = .046 \)), distant metastases (81% vs 50%, respectively; \( P = .003 \)), and stage IV disease (90% vs 64%, respectively; \( P = .007 \)). Potentially curative gastrectomy was accomplished in 58% of older patients but only 17% of very young patients (\( P = .001 \)). Nontherapeutic operations were performed in only 6% of older patients but 33% of very young patients (\( P = .003 \)) related to advanced-stage disease. Mean survival was 33.4 months among older patients compared with only 11.6 months for very young patients (\( P = .02 \)).

Conclusions: Very young patients (aged ≤35 years) with gastric adenocarcinoma have significantly higher incidences of diffuse-type tumor histologic findings and both locally advanced and metastatic disease at presentation. These findings confirm a more aggressive tumor biology that results in often futile surgical interventions and an unusually grave prognosis. Strategies for earlier diagnosis together with effective new therapies are desperately needed to attenuate the extreme lethality in these uniquely unfortunate patients.

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While gastric adenocarcinoma in the general population remains a deadly disease with poor outcomes, younger patients may have a particularly poor prognosis. Whereas the average patient age at presentation is approximately 60 years, the relatively high mortality is largely attributable to the advanced stage of disease at diagnosis regardless of age. Clinical observation has suggested that very young patients have a far worse prognosis than their older counterparts. As a logical extension of this observation, we hypothesized that examination of cohorts of very young patients with gastric adenocarcinoma would reveal a biologically more aggressive form of the disease that correlates with distinctly inferior surgical results and long-term survival.

With regard to perioperative outcomes, the recognized liabilities of nontherapeutic laparotomy were anticipated to be manifestly exaggerated in this youthful population. Thus, there may be 2 distinct adverse factors operative in the very young, namely an excessive early postoperative mortality and severely limited longevity consequent to an aggressive tumor biology and advanced disease. To validate this hypothesis, a 15-year retrospective study of all patients diagnosed with gastric adenocarcinoma at a single institution was undertaken.

METHODS

A retrospective review that included all patients diagnosed with gastric adenocarcinoma at Harbor-UCLA Medical Center between January 1, 1993, and December 31, 2007, was conducted.
ducted. The medical center serves a large metropolitan area of southwestern Los Angeles County, California, with a patient population that is predominantly immigrant. A total of 350 such patients were encountered during this study period, and their clinical and pathologic information was culled from the hospital cancer registry database and from individual medical records.

Specific details retrieved from the database included patient demographics, gastroscopic or surgical biopsy results, operative interventions, and clinical follow-up. Patients with diagnoses of gastric carcinoid tumor, lymphoma, and gastrointestinal stromal tumor were excluded. Specific information such as reports of endoscopic ultrasonography and abdominal computerized tomography, clinical and pathologic tumor staging, and gastric resective or other operative or interventional procedures for cure or palliation was acquired through individual medical record review. Outcome measures of interest included patient age at diagnosis, histologic tumor type, TNM stage, disease stage, surgical resectability, operation performed, completeness of resection, postoperative complications and deaths, and long-term survival. To define the appropriate age groups for comparison, the distribution of frequencies of stage IV (essentially incurable) disease by 5-year age cohorts was examined. The resulting natural age separation was used to define the very young and older patient groups. For purposes of age group comparisons, the data related to very young patients were compared with those of older patients. Statistical analyses were performed using the Fisher exact test for categorical data and the unpaired t test for comparison of group means. Kaplan-Meier actuarial survival curves were generated for both age groups and compared. $P \leq .05$ was considered statistically significant. The institutional review board at Harbor-UCLA Medical Center approved the project.

### RESULTS

A total of 350 patients with gastric adenocarcinoma were identified from the 15-year study interval. The mean age at presentation was 56.4 years (range, 20-94 years), and 55% were men. Ethnic proportions were as follows: Hispanic, 50%; Asian, 30%; African American, 11%; and white, 9%. The mean follow-up for all patients was 16.5 months.

Although advanced-stage disease was common throughout the study population, the age cohort distribution of stage IV disease demonstrated 35 years as the threshold age that separated those patients with unusually advanced disease from those with less advanced disease (Figure 1). Therefore, the 30 patients (9%) aged 35 years or younger were classified as very young, and the 320 patients (91%) older than 35 years were classified as older. Ethnicity, sex, and year of presentation had no influence on disease stage. However, patients classified as very young more often had diffuse-type tumor histologic findings as well as the components of advanced-stage disease such as transmural primary tumors with adjacent organ invasion (T4), nodal metastases (N1-3), and distant metastases (M1). All of these indicators of more aggressive tumor biology were significantly more common in the very young (Table).

A total of 188 patients (54%) underwent operation, with similar rates of operation in both age groups (60% in very young patients vs 53% in older patients; $P=.57$).
However, gastric resection was accomplished in only 56% of very young patients compared with 86% of older patients \( (P = .003) \). Notably, gastrectomy with negative histologic margins \((R0)\) and curative potential was achieved in 58% of older patients but was possible in only 17% of very young patients \((P = .001)\). In 3 of the 4 very young age cohorts, no patients could be afforded an \( R0 \) resection \((\text{Figure 2})\). With the exception of only 1 older age cohort \((\text{aged 81-85 years})\) in which no gastric resections were performed, only the very young age cohorts had R0 resection rates of 25% or less. Furthermore, nontherapeutic laparotomies were performed in only 6% of older patients but in 33% of very young patients owing to their very advanced stage of disease \((P = .002)\). The postoperative morbidity rates were similar \((33\% \text{ for very young patients vs } 29\% \text{ for older patients}; \ P = .79)\), but the mortality rate for very young patients was significantly greater than that of their older counterparts \((22\% \text{ vs } 2\%, \text{ respectively}; \ P = .003)\). Of note, 2 of the 4 postoperative deaths among the very young patients followed nontherapeutic laparotomies for unresectable tumors. The mean long-term survival was significantly greater for older patients at 33.4 months \((95\% \text{ confidence interval, 27.4-39.4 months})\) compared with only 11.6 months \((95\% \text{ confidence interval, 5.9-17.4 months})\) for very young patients \((P = .02)\). Overall actuarial survival was likewise significantly greater among older patients \((\text{Figure 3})\).

### Table. Tumor Histologic Findings and Staging Data

<table>
<thead>
<tr>
<th>Tumor Histologic Findings or Staging</th>
<th>No./Total No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aged ≤35 y ((n=30))</td>
</tr>
<tr>
<td>Diffuse-type tumor histologic findings</td>
<td>28/30 (93)</td>
</tr>
<tr>
<td>Tumor invasion of adjacent organs, T4</td>
<td>17/23 (74)</td>
</tr>
<tr>
<td>Lymph nodal metastases, N1-3</td>
<td>16/17 (94)</td>
</tr>
<tr>
<td>Distant metastases, M1</td>
<td>21/26 (81)</td>
</tr>
<tr>
<td>Stage IV disease</td>
<td>26/29 (90)</td>
</tr>
</tbody>
</table>

COMMENT

Although it is the second leading cause of cancer deaths worldwide, gastric adenocarcinoma ranks only 14th in cancer frequency in the United States.\(^2\) Disparities in the global epidemiology of gastric adenocarcinoma have led to significant variance in the clinical outcomes of patients described as young. The mere definition of young has been widely interpreted to include patients ranging from younger than 30 years to up to 50 years.\(^3,4\) Because our interest in this study was to determine whether very young patients with gastric adenocarcinoma have a more severe form of the disease, we initially investigated the frequencies of stage IV cancer along the continuum of 5-year age cohorts. There was an obvious cutoff at age 35 years that differentiated those with excessively advanced disease from those with less though still relatively advanced disease. As a result, our definition of very young has been confined to age 35 years and younger. Not surprisingly, among patients with gastric adenocarcinoma reported in the literature and arbitrarily described as young, there has been wide variation in their proportion, ranging from 6.8% to 14.8% of the entire patient population.\(^1,7\) In our study, the age groups were defined by a natural separation based on disease stage at presentation. Nevertheless, the subset of very young patients constituted 9% of our study population and is not inconsistent with the findings of earlier reported series that used more arbitrary definitions of youthfulness.

The data presented herein and those of several other series suggest a biologically more aggressive form of gastric adenocarcinoma in very young patients.\(^5,4\) Specific histologic markers of aggressive biological behavior include poorly differentiated tumors with diffuse-type histologic findings and signet ring cells. Although the diffuse type of gastric adenocarcinoma is believed to be less common than the more differentiated intestinal type, it more often affects young patients and may be familial and dependent on an autosomal dominant, incomplete penetrance pattern of genetic inheritance.\(^10\) A high level of microsatellite instability has been commonly found in gastric adenocarcinomas and is known to be associated with mutations in the coding and noncoding regions of a variety of cancer-related genes.\(^7,11-17\) It is estimated that between 5% and 10% of gastric adenocarcinomas are genetic in origin.\(^18\) Most of these cancers are of the diffuse type, and the most substantiated germline mutation is that of the \(CDH1\) gene, which codes for the cellular adhesion molecule E-cadherin. The \(CDH1\) germline mutation is associated with hereditary diffuse gastric cancer in about one-third of affected families and manifests phenotypically as linitis plastica. As the very young patients in this study were significantly more affected with tumors of diffuse-type histologic findings, the implication of a genetic basis for the disease in this population appears to be strong.

Another indicator of the aggressive nature of gastric adenocarcinoma in young patients is the high rates of nodal and distant metastases found at diagnosis compared with those in older patients as well as the frequency of Linitis plastica involving all or most of the stomach at surgical exploration.\(^7,8\) Young patients also have been shown to have a higher incidence of the \(cagA-positive\) genotype of \(H\) \(pylori\) infection that is known to be more virulent than infection by bacterial strains not harboring the gene.\(^5,15,16\) Several studies have indicated that \(cagA-positive\) \(H\) \(pylori\) infection substantially increases the odds ratio for cancer development compared with \(cagA-negative\) \(H\) \(pylori\) infection.\(^7,17,18\) Although host genetic factors may play a more dominant oncogenic role in young patients, little doubt remains regarding the causal relationship between \(H\) \(pylori\) infection and the development of gastric adenocarcinoma.\(^18\) Best estimates suggest that the infection plays an important etiologic role in more than 50% of all gastric adenocarcinomas worldwide.\(^20\)

Despite our findings and those of previous studies that confirmed a more aggressive form of gastric adenocarcinoma in young patients, there have been 2 recent investigations from abroad that fail to support this conclusion.
clusion. Kulig et al. analyzed 214 affected Polish patients aged 40 years and younger. Compared with 3217 older patients, there were no differences in tumor stage, postoperative morbidity or mortality, or long-term survival, although the young patients had a higher frequency of diffuse-type tumor histologic findings. Similarly, Lee et al. demonstrated in 54 Korean patients aged 40 years and younger that higher frequencies of women, diffuse-type tumors, and proximal gastric location of primary tumors were the only differences between young and older patients. No differences were found with regard to TNM stage, tumor size, or cumulative survival. Unfortunately, no operative data were contained in this latter study. While neither of these investigations confirmed our findings, both used an older age threshold of 40 years that was chosen arbitrarily and may have inappropriately assigned lower-risk patients to the young age group. Furthermore, the Korean study did not compare the age groups for high rates of advanced T-stage tumors, nodal involvement, or distant metastatic disease. These markers of aggressive tumor behavior, together with a high frequency of diffuse-type histologic findings and low rates of resectability and survival, collectively provide the basis for our finding of a particularly malignant tumor biology in very young patients, at least in the United States.

Future considerations for prevention of gastric cancer that is genetically based, aggressive, and appears early in life should include prophylactic gastrectomy. Young members of families with a history of hereditary diffuse gastric cancer who harbor the CDH1 germline mutation are candidates for such a preemptive intervention. Because this cadre of patients represents only a very small minority of those affected, effective prevention for the majority awaits further elucidation of the genetic factors involved.

Along with improved surgical and nonsurgical therapeutics, simple awareness of the problem of the extreme aggressiveness of gastric adenocarcinoma in younger patients is desperately needed at this time. Such awareness, together with new and effective screening methods to detect early-stage tumors, will be required to impact the dismal outcomes in these unfortunate individuals.
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REFERENCES