Expression of Insulin-Like Growth Factor II mRNA-Binding Protein 3 in Human Esophageal Adenocarcinoma and Its Precursor Lesions

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Context.—Insulin-like growth factor II mRNA-binding protein 3 (IMP3) is an oncofetal protein highly expressed in fetal tissue and malignant tumors but only rarely within adult benign tissues. The expression of IMP3 in esophageal adenocarcinoma (EAC) and its precursor lesions including distinctive type Barrett mucosa (BM, intestinal metaplasia) and esophageal columnar dysplasia (ECD) is largely unknown.

Objective.—To characterize the patterns of IMP3 expression in EAC and its precursor lesions.

Design.—Samples from 132 cases of EAC, 28 cases of ECD (16 high-grade dysplasia and 12 low-grade dysplasia cases), 28 cases of BM without dysplasia, and 138 cases of nonneoplastic esophageal mucosa without dysplasia or BM within formalin-fixed, paraffin-embedded tissue microarray blocks were examined. Tissues were stained with mouse monoclonal anti-IMP3 antibody. The intensity (1–3+) and percent (0%–100%) of positive cytoplasmic and/or membranous IMP3 staining cells were determined.

Results.—Most of EAC cases (93 of 132; 70%) showed cytoplasmic and membranous IMP3 staining. Poorly and moderately differentiated EAC showed statistically significant higher IMP3 expression compared with well-differentiated EAC (P < .001). A subset of ECD cases (7 of 28; 25%) was positive for IMP3, including 3 low-grade dysplasia cases (focal 1+ IMP3 staining) and 4 high-grade dysplasia cases (more diffuse 1–2+ IMP3 staining). No IMP3 staining was observed in any nonneoplastic esophageal mucosa and BM tissues without dysplasia.

Conclusions.—This study suggests that IMP3 may play a role in the carcinogenesis of EAC and has diagnostic utility in differentiating neoplastic and nonneoplastic lesions of the esophagus.

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also includes IMP1 and IMP2 and is identical to the KH domain containing protein overexpressed in cancer protein.\textsuperscript{31} IMP3 is shown to be expressed in various human and mouse tissues, such as developing epithelium, muscle, and placenta during early stages of embryogenesis but is not expressed or expressed in low to undetectable levels in adult tissues.\textsuperscript{22,23} IMP3 is reported to be involved in cell growth, adhesion, invasion, and migration and is a prognostic marker associated with metastatic progression as demonstrated in several studies of renal cell carcinoma.\textsuperscript{24–26,33–35}

The prevalence and significance of IMP3 in EAC and its precursor lesions including distinctive type BM and dysplasia are largely unknown. In this microarray study, we characterized the expression of IMP3 in EAC and its precursor lesions. In addition, correlations between IMP3 expression in EAC and various clinical parameters, such as stage, margin status, lymph node status, and overall survival, are examined.

**MATERIALS AND METHODS**

**Study Groups**

After receiving institutional review board approval, we retrieved esophagectomy and biopsy specimens with adequate material from the archive of the Department of Pathology at University of Rochester Medical Center. These specimens consisted of a total of 132 cases of EAC, 28 cases of ECD (16 high-grade dysplasia and 12 low-grade dysplasia cases), 28 cases of BM without dysplasia or carcinoma, and 138 cases of nonneoplastic esophageal mucosa (NNEM) without dysplasia or BM. Three cases of high-grade dysplasia were evaluated in which this diagnosis was the only finding. The other dysplasia cases were obtained from specimens that also contained invasive carcinoma. To avoid potential treatment effects, we excluded specimens exposed to preoperative treatment. All tissues had been fixed in 10% neutral buffered formalin, routinely processed, and embedded in paraffin. Hematoxylin-eosin–stained sections of BM without dysplasia or carcinoma, and 138 cases of nonneoplastic esophageal mucosa (NNEM) without dysplasia or BM. Three cases of high-grade dysplasia were evaluated in which this diagnosis was the only finding. The other dysplasia cases were obtained from specimens that also contained invasive carcinoma. To avoid potential treatment effects, we excluded specimens exposed to preoperative treatment. All tissues had been fixed in 10% neutral buffered formalin, routinely processed, and embedded in paraffin. Hematoxylin-eosin–stained sections from each case were reviewed by 2 pathologists, and from each case we selected 2 to 3 sections with representative and adequate amount of lesional tissue to be included in the tissue microarray (TMA).

Additionally, full sections from 13 resection cases of EAC and 1 resection case of high-grade dysplasia and intestinal metaplasia were also stained with IMP3 to confirm our microarray results. All 14 full section cases contained NNEM.

Esophageal adenocarcinoma and ECD cases were graded and classified based on the World Health Organization classification.\textsuperscript{36} Well-differentiated EACs are characterized by predominantly glandular or papillary structures, while poorly differentiated EACs are characterized by only rare glandular structures. Moderately differentiated EACs are those with intermediate glandular differentiation. In our sample set of EAC cases, if more than 1 sample from 1 EAC case was present in our microarray, the highest tumor grade was reported. These results from the microarray were compared with the original reported grading and those with discrepant grades were omitted from the outcome evaluation.

Survival and tumor characteristics data, if available, including length of follow-up, time from diagnosis to death, lymph node status, tumor site, margin status, and the American Joint Committee on Cancer stage grouping, were retrieved and deassociated with patient identifiers. The EAC cases included 57 well-differentiated, 32 moderately differentiated, and 43 poorly differentiated EACs. Of these EAC cases, 1 case was from the proximal esophagus, 15 cases were from the mid esophagus, 41 cases were from the distal esophagus, and 67 were from the gastroesophageal junction. One hundred and seven EAC cases had negative margins while 17 EAC cases had positive margins. Fifty-two EAC cases were negative for lymph node metastasis and 75 EAC cases were positive for lymph node metastasis. The EAC cases included 19 stage I (7 with submucosal invasion and 12 limited to the lamina propria), 41 stage II, 53 stage III, and 11 stage IV cases.

**Construction of TMAs**

The TMAs were constructed by using a manual tissue arrayer device from Beecher Instruments (Sun Prairie, Wisconsin). The areas of tissue with adequate amount of representative tissue were marked in the paraffin blocks, and two to three 1-mm diameter cores from each case were included in their respective arrays.

**Immunohistochemistry**

Immunohistochemistry was performed using mouse monoclonal anti-IMP3 antibody (1:80, Dako, Glostrup, Denmark). Briefly, 4-μm thick microarray sections from routinely processed, formalin-fixed, paraffin-embedded tissues were transferred to glass slides, deparaffinized in xylene, and rehydrated in a graded series of ethanol. Heat-induced epitope retrieval was performed. The tissue was then treated with 3% H₂O₂ and then rinsed with TWEEN-20 buffer. A few drops of diluted normal blocking serum were placed on the tissue and incubated at room temperature. The serum was then blotted off, and the slides were incubated with primary antibody directed against IMP3 (1:80, 45-minute incubation at 4°C). The sections were then treated with a cocktail of biotinylated anti-rabbit immunoglobulin (Ig) G and antimouse IgG and IgM (Ventana, Tucson, Arizona) for 30 minutes, followed by avidin-biotin-peroxidase complex (Ventana) for 30 minutes. Sections were then rinsed, developed with diamino-benzidine and hydrogen peroxide (10 minutes), counterstained with Mayer hematoxylin, and cover slipped. Representative sections of pancreatic adenocarcinoma tissue were used as a positive control. Negative controls were performed by replacing the primary antibody with nonimmune IgG. Positive and negative controls reacted appropriately.

**Scoring of Immunoreactivity of EAC, ECD, BM, and NNEM**

Semiquantitative assessment of expression levels of IMP3 protein analytes in the cytoplasm of target cells was determined by a pathologist using bright-field microscopy. The intensity of positive staining was accessed and graded from 1+ to 5+, with 1+ being weakly positive cyttoplasmic and/or membranous staining, 3+ being strongly positive cytoplasmic and/or membranous staining, and 2+ being intermediate staining between 1+ and 3+. Intensity of 0 was assigned to cases with no evidence of specific staining. The approximate percent (0%–100% in increments of 5%) of positive staining cells, defined as at least 1+ intensity of staining, within a lesion was evaluated. If more than 1 sample per case was available for evaluation, the intensity grade and percent of positive staining cells were averaged. A case was regarded as positive when there was at least 1+ staining intensity in at least 5% of the lesional cells.

**Statistical Analyses**

Independent 2-tailed Student t test was used to determine the statistical significance of differences in expression levels among different EAC tumor grades and between EAC and ECD. Independent 2-tailed Student t test was also used to determine the statistical significance of differences in expression levels in EAC between TMA and full section staining. Pearson χ² test was used to determine statistical significance of differences in frequency of positive IMP3 expression among EAC, ECD, BM, and NNEM. Semiquantitative IMP3 staining expression level was correlated with histologic or clinical parameters, and the respective Pearson product moment correlation (r) was determined. Pearson χ² was used to determine the statistical significance of differences in frequency of positive IMP3 expression in subsets of EAC with varying clinical and histologic...
Figure 1. A, Benign squamous esophageal mucosa with negative staining for insulin-like growth factor II mRNA-binding protein 3 (IMP3). B, Distinctive type Barrett mucosa with negative staining for IMP3. C, Low-grade esophageal columnar dysplasia in a background of Barrett mucosa with focal weak positive IMP3 staining only in the focus of low-grade esophageal columnar dysplasia. Inset, Another representative area of low-grade dysplasia with weak positive IMP3 staining. D, Focus of high-grade esophageal columnar dysplasia with strong positive staining for IMP3. E, Well-differentiated esophageal adenocarcinoma with variegated positive staining for IMP3. F, Poorly differentiated esophageal adenocarcinoma with strong positive staining for IMP3 (original magnifications ×100 [A] and ×200 [B through F and C, inset]).
parameters. IMP3 expression level was also correlated with patient survival data. Survival curves were estimated using the Kaplan-Meier product-limit method, and the significance of differences between survival curves was determined using a log-rank test where the P value for the \( \chi^2 \) statistics was determined. Multivariate analysis of IMP3 expression level, patient age, sex, lymph node status, American Joint Committee on Cancer stage, margin status, tumor site, and histologic grade on survival was performed using the Cox proportional hazards regression modeling. MedCalc (Mariakerke, Belgium) software was used for statistical analysis and P values less than .05 were considered statistically significant.

RESULTS

Microarray Results

No IMP3 staining was observed in any of the NNEM and BM uninvolved by dysplasia (Figure 1, A and B). Benign gastric oxyntic glands showed consistent nonspecific cytoplasmic blush staining for IMP3. A minority (7 of 28; 25%) of dysplasia cases was positive for IMP3 (Figure 1, C and D). Three low-grade ECD cases showed positive (+ in <15% of lesional cells) staining for IMP3, and 4 high-grade ECD cases without associated carcinoma showed more diffuse and stronger positive (1–2+ in 5%–80% of lesional cells) staining for IMP3.

Most EAC cases (93 of 132; 70%) showed positive cytoplasmic and membranous IMP3 staining (Table 1). Higher level of IMP3 expression was found in moderately differentiated EAC (mean intensity, 1.5 ± 0.17; mean percent of positive staining, 43 ± 5.7) and poorly differentiated EAC (mean intensity, 1.7 ± 0.17; mean percent of positive staining, 48 ± 5.5) compared with well-differentiated EAC (mean intensity, 0.86 ± 0.12; mean percent of positive staining, 22 ± 3.7). Moderately and poorly differentiated EAC cases showed statistically significant higher levels of IMP3 expression compared with well-differentiated EAC cases (P < .001). Moderately and poorly differentiated EAC cases (>80%) also more frequently showed positive IMP3 expression compared with well-differentiated EAC cases (53%). No significant difference in IMP3 expression levels was observed between moderately and poorly differentiated cases. These results are illustrated and summarized in Figure 1, E and F, and Tables 1 and 2. A comparison of clinical and pathologic parameters by IMP3 expression levels is summarized in Table 3. Although the difference in frequency of IMP3-positive EAC was not statistically significant between younger (<65 years) and older (>65 years) patients, EAC in younger patients (<65 years) showed higher IMP3 expression level compared with EAC in older (>65 years) patients (P = .03, 2-tailed Student t test). Although not statistically significant, positive IMP3 expression in EAC also appeared to be associated with higher stage and positive lymph node involvement. IMP3 expression in EAC only showed statistically significant correlation with tumor differentiation (r = 0.37, P < .001).

Multivariate analysis showed that tumor stage was the only variable predictive of overall survival (P < .001;
Table 3. Significance of Difference in Frequency of Insulin-Like Growth Factor II mRNA-Binding Protein 3 (IMP3) Expression in Esophageal Adenocarcinoma (EAC) and Correlation With Clinical and Pathologic Parameters

<table>
<thead>
<tr>
<th>Pathologic or Clinical Parameter</th>
<th>IMP3+ EAC Cases, No./ Total (%)</th>
<th>Frequency IMP3+ EAC, P Value (df)*</th>
<th>Correlation Coefficient $r$, (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differentiation</td>
<td></td>
<td></td>
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<tr>
<td>WD</td>
<td>30/57 (53)</td>
<td>$&lt;.001$ (2)</td>
<td>0.37 ($&lt;.001$)</td>
</tr>
<tr>
<td>MD</td>
<td>28/32 (88)</td>
<td>$&lt;.001$ (2)</td>
<td>0.32 ($&lt;.001$)</td>
</tr>
<tr>
<td>PD</td>
<td>35/44 (81)</td>
<td>$&lt;.001$ (2)</td>
<td>0.35 ($&lt;.001$)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>$&lt;65$</td>
<td>4/5/9 (76)</td>
<td>0.20 (1)</td>
<td>$&lt;.01$ (.06)</td>
</tr>
<tr>
<td>$\geq65$</td>
<td>43/67 (64)</td>
<td>$&lt;.001$ (2)</td>
<td>0.35 ($&lt;.001$)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>74/107 (69)</td>
<td>0.67 (1)</td>
<td>$0.02$ (.06)</td>
</tr>
<tr>
<td>Female</td>
<td>19/25 (76)</td>
<td>$&lt;.001$ (2)</td>
<td>0.32 ($&lt;.001$)</td>
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<tr>
<td>Tumor location</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Proximal</td>
<td>1/1 (100)</td>
<td>0.74 (3)</td>
<td>0.12 (.19)</td>
</tr>
<tr>
<td>Mid</td>
<td>9/15 (60)</td>
<td>$&lt;.001$ (2)</td>
<td>0.01 (.9)</td>
</tr>
<tr>
<td>Distal</td>
<td>29/41 (70)</td>
<td>0.71 (1)</td>
<td>0.02 (.85)</td>
</tr>
<tr>
<td>GEJ</td>
<td>48/67 (72)</td>
<td>$&lt;.001$ (2)</td>
<td>0.32 ($&lt;.001$)</td>
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<tr>
<td>Margin status</td>
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<tr>
<td>Negative</td>
<td>77/107 (72)</td>
<td>0.75 (1)</td>
<td>0.01 (.9)</td>
</tr>
<tr>
<td>Positive</td>
<td>11/17 (64)</td>
<td>$&lt;.001$ (2)</td>
<td>0.37 ($&lt;.001$)</td>
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<tr>
<td>Lymph node status</td>
<td></td>
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<td></td>
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<tr>
<td>Negative</td>
<td>35/52 (67)</td>
<td>0.71 (1)</td>
<td>0.02 (.85)</td>
</tr>
<tr>
<td>Positive</td>
<td>54/75 (72)</td>
<td>$&lt;.001$ (2)</td>
<td>0.32 ($&lt;.001$)</td>
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<td>Stage</td>
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<tr>
<td>0</td>
<td>1/3 (33)</td>
<td>0.68 (4)</td>
<td>$&lt;.05$ (.57)</td>
</tr>
<tr>
<td>1</td>
<td>13/19 (68)</td>
<td>$&lt;.001$ (2)</td>
<td>0.37 ($&lt;.001$)</td>
</tr>
<tr>
<td>2</td>
<td>29/41 (70)</td>
<td>$&lt;.001$ (2)</td>
<td>0.37 ($&lt;.001$)</td>
</tr>
<tr>
<td>3</td>
<td>39/53 (74)</td>
<td>$&lt;.001$ (2)</td>
<td>0.37 ($&lt;.001$)</td>
</tr>
<tr>
<td>4</td>
<td>8/11 (73)</td>
<td>$&lt;.001$ (2)</td>
<td>0.37 ($&lt;.001$)</td>
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Abbreviations: df, degrees of freedom; GEJ, gastroesophageal junction; MD, moderately differentiated; PD, poorly differentiated; WD, well differentiated.

* Determined by Pearson $\chi^2$ test.

Figure 2, A). Univariate analysis also showed that stage, regional lymph node, and margin status were predictive of overall survival (Figure 2, B and C). IMP3 expression level does not appear to be associated with overall survival by univariate analysis (Figure 2, D). However, univariate analysis showed that in the subset of stages 3 and 4 EAC cases, 1-year overall survival was 50% for IMP3-positive cases and 30% for IMP3-negative cases, and in the subset of regional lymph node–positive EAC cases, the 5-year overall survival was 20% for IMP3-positive cases and 6% for IMP3-negative cases (Figure 2, E and F).

Esophageal adenocarcinoma cases showed statistically significant higher average intensity of IMP3 expression compared with ECD ($P < .001$). IMP3 was more frequently expressed in EAC compared with ECD, BM, and NNEM ($P < .001$). IMP3 was more frequently expressed in ECD compared with BM and NNEM ($P = .02$ and $P < .001$, respectively). These results are illustrated and summarized in Figure 1 and Tables 1 and 4. Cases of BM adjacent to high-grade dysplasia and intramuscosal EAC clearly demonstrated the lack of IMP3 staining within the BM and positive IMP3 staining within the dysplastic and neoplastic glands (Figure 3, A, and B).

Full Section Results

Thirteen full sections of EAC cases were also stained with IMP3 and 10 of these showed 1+ to 3+ intensity (mean, 1.27) positive staining in 10% to 100% (mean, 45%) of neoplastic cells (Table 5). The staining pattern was patchy, but no particular difference in staining was seen between neoplastic cells at different levels or depth of invasion. Two EAC cases with mucinous and goblet cell differentiation showed the most varied patchy staining pattern. One EAC case contained both well-differentiated and poorly differentiated areas. The poorly differentiated areas in this case showed positive but less intense staining for IMP3 compared with the well-differentiated area. Compared with the TMA results, the full section results showed no statistical difference in the percentage of positive cases of EAC for IMP3 (TMA, 70%; full section, 77%; Pearson $\chi^2$ test, $P = .86$, degrees of freedom of 1). Independent 2-tailed Student $t$ test showed no statistical difference in the intensity and percent of positive staining cells of EAC cases between TMA and full section staining (intensity, $P = .98$; percent of positive staining cells, $P = .35$).

A full section of high-grade ECD showed positive 2+ IMP3 staining in 80% of the lesion. Intestinal metaplasia unassociated with dysplasia did not show positive staining for IMP3 in this case. All 14 cases containing NNEM, including squamous epithelium, metaplastic columnar epithelium without goblet cells, and submucosal esophageal glands, showed no staining for IMP3. Benign gastric oxyntic glands consistently showed nonspecific cytoplasmic blush staining for IMP3. These results are summarized in Table 5.

COMMENT

In this study, we found that IMP3 is overexpressed in EAC and a subset of ECD but not in BM and NNEM. Low-grade ECD is noted to have only focal weak IMP3 expression in contrast to high-grade ECD, which showed more intense diffuse expression of IMP3. These results suggest that when positive, IMP3 staining is a very useful adjunct in differentiating difficult cases of neoplastic and dysplastic lesions versus BM and reactive lesions of the esophagus. Although TMA may not be completely representative, it is an efficient way to screen for tissue markers and studies have shown that TMA with 1, 2, and 3 cores will represent about 91%, 96%, and 98%, respectively, compared with whole section studies. Additional full section staining of limited cases showed similar results compared with our microarray results. Compared with our TMA results, the full section results showed no statistical difference in the percentage of positive cases of EAC for IMP3 (TMA, 70%; full section, 77%; Pearson $\chi^2$ test, $P = .86$, degrees of freedom of 1) and showed the same mean intensity of expression (mean, 1.27; independent 2-tailed Student $t$ test, $P = .98$) and similar percent of lesional cells with positive staining (TMA mean, 35%; full section mean, 45%; independent 2-tailed Student $t$ test, $P = .35$).

A recent study on IMP3 expression in EAC and ECD reported by Lu et al also showed similar findings in IMP3 expression pattern as in the present study. However, the percent of EAC cases with positive IMP3 expression was reported to be much higher than our findings (94% versus 70% of microarray cases and 77% of full section cases). Also we noted a more significantly increased IMP3 expression in EAC compared with ECD.
expression in moderately and poorly differentiated EAC compared with well-differentiated EAC than was reported by Lu et al. In contrast to our study, Lu et al. did report rare positive staining for IMP3 in BM (5 of 68; 7%). These differences may be due to sampling issues in a microarray study; however, the series by Lu et al. also included a significant number of biopsy cases, which also would have the same issues in limited sampling of lesional tissue. These results confirm that IMP3 can be a useful supplemental immunohistochemical marker in addition to routine light microscopy evaluation of difficult esophageal surgical cases.

The present study also demonstrated a stepwise increase in IMP3 expression in NNEM and BM, ECD, and EAC, suggesting that IMP3 expression may play a role in the pathogenesis of EAC. The correlation of higher levels of IMP3 expression with higher tumor grade and the significantly better overall survival seen in IMP3-positive versus IMP3-negative high-stage EAC cases indicate that IMP3 might also have potential prognostic value in certain subsets of EAC. The reported association of increased IMP3 expression levels and worse overall survival as observed in multiple renal cell carcinoma studies was not seen in the present study.

The role of the IGF pathway in esophageal carcinogenesis has not been well studied. IMP3 is a regulatory binding protein thought to be involved in the stabilization and intracellular trafficking of IGF-II mRNA to facilitate IGF-II production and is therefore believed to have similar roles in the modulation of other intracellular nucleotides. The modulation of the IGF cell signaling pathways is thought to be associated with the acquisition of malignant features in esophageal tumors. The signal transduction

![Figure 2](https://example.com/image2.png)

**Figure 2.** A, Overall survival (OS) curves for esophageal adenocarcinoma (EAC) estimated by the Kaplan-Meier product-limit method with the significance of the differences between survival curves of different stages as determined by the log-rank test; multivariate analysis of insulin-like growth factor II mRNA-binding protein 3 (IMP3) expression, age, sex, American Joint Committee on Cancer stage, tumor location, regional lymph node, and margin status by Cox proportional hazards regression modeling showed tumor stage is the only variable predictive of overall survival. B, Kaplan-Meier OS curve for EAC cases with positive regional lymph nodes and those with negative regional lymph nodes. C, Kaplan-Meier OS curve for EAC cases with positive and negative margins. D, Kaplan-Meier OS curve for EAC cases with positive IMP3 (any case with 1+ staining intensity in at least 5% of lesional cells) and negative IMP3 expression. E, Kaplan-Meier OS curve in high-stage (stages 3 and 4) subset of EAC cases with positive IMP3 and negative IMP3 expression. F, Kaplan-Meier OS curve in regional lymph node–positive subset of EAC cases with positive IMP3 and negative IMP3 expression.

![Table 4](https://example.com/table4.png)

**Table 4. Significance of Differences in Frequency of Positive Insulin-Like Growth Factor II mRNA-Binding Protein 3 Expression in Esophageal Adenocarcinoma (EAC), Esophageal Columnar Dysplasia (ECD), Barrett Mucosa (BM), and Nonneoplastic Esophageal Mucosa (NNEM) Determined by Pearson χ² Test**

<table>
<thead>
<tr>
<th></th>
<th>χ² (df = 1)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>EAC versus NNEM</td>
<td>145</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>EAC versus ECD</td>
<td>18.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>EAC versus BM</td>
<td>44.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ECD versus NNEM</td>
<td>30.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ECD versus BM</td>
<td>5.88</td>
<td>.2</td>
</tr>
</tbody>
</table>

Abbreviation: df, degrees of freedom.
For these reasons, the isolated study of Am J Gastroenterol EAC case with well and poorly differentiated areas. Dis Esophagus Arch Pathol Lab Med—Vol 135, August 2011 Ann Thorac Surg + + + + + + + +. 100 + 90 Am J Surg Pathol Ann Surg Diffusely positive staining EAC cases ( >50%) of total EAC cases (%). | EAC mean % of staining cells/standard error 45/10.5 Table 5. Full Section Insulin-Like Growth Factor II mRNA-Binding Protein 3 (IMP3) Staining in Esophageal Adenocarcinoma (EAC) and Esophageal Columnar Dysplasia (ECD) Case Differentiation IMP3 Staining Intensity Percent of Positive IMP3 Lesional Staining High-grade ECD NA 2+ 80 EAC No. 1 Moderate 1+ 10 EAC No. 2 Moderate 2+ 100 EAC No. 3 Moderate 1+ 25 EAC No. 4 Poor 2+ 90 EAC No. 5 Poor 2+ 80 EAC No. 6 Well 0 NA EAC No. 7 Well 1+ 25 EAC No. 8 Poor 0 NA EAC No. 9a Poor 1+ 50 EAC No. 10a Poor 3+ 30 EAC No. 11 Moderate 1 80 EAC No. 12 Moderate 0 NA EAC No. 13a Poor 1–3+ 50 Positive EAC cases/total EAC cases (%) 10/13 (77) Moderate to strong intensity staining EAC (2–3+)/ total EAC cases (%) 5/10 (50) Diffusely positive staining EAC cases (>50%)/ total EAC cases (%) 4/10 (40) EAC mean intensity of staining/standard error 1.27/0.28 EAC mean % of staining cells/standard error 45/10.5 Abbreviation: NA, not applicable.

a Mucinous and patchy signet ring cell differentiation.

b EAC case with well and poorly differentiated areas.

c At least 1+ staining intensity in at least 5% of lesional cells.

pathway leading to the ultimate expression of IGF may be modulated by multiple factors, such as epithelial growth factor and IGF binding proteins, as well as other molecular pathways such as the PI3K/AKT/mTOR and Ras/Raf/MAPK pathways. 45 For these reasons, the isolated study of IMP3 is difficult to accurately assess for its specific role in carcinogenesis. Although our preliminary study did not show statistically significant predictive value of IMP3 for overall survival in this EAC series by univariable and multivariable analysis, the results suggest that IMP3 may have prognostic value in a high-stage subset of EAC cases. In summary, through this TMA study, we demonstrated the expression pattern of IMP3 in esophageal tissues. Further independent studies with larger case series are needed to validate and better characterize the role of IMP3 in esophageal carcinogenesis and EAC progression.

References


IMP3 in Esophageal Adenocarcinoma and Precursor Lesions—Feng et al


