Inflammation et cancer

Jean-Paul Sculier
Service des soins intensifs et urgences oncologiques
Oncologie thoracique
Institut Jules Bordet
Figure 2: Targeting of cancer's armed forces
Laboratory-Clinic Interface

The systemic inflammation-based Glasgow Prognostic Score: A decade of experience in patients with cancer

Donald C. McMillan*

*Academic Unit of Surgery, School of Medicine-University of Glasgow, Royal Infirmary, Glasgow G31 2ER, United Kingdom
### Table 1

Systemic inflammation based prognostic scores, the Glasgow Prognostic Scores.

<table>
<thead>
<tr>
<th>The Glasgow Prognostic Score (GPS)</th>
<th>Points allocated</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-Reactive protein $\geq 10$ mg/l and albumin $\geq 35$ g/l</td>
<td>0</td>
</tr>
<tr>
<td>C-Reactive protein $&gt;10$ mg/l</td>
<td>1</td>
</tr>
<tr>
<td>Albumin $&lt;35$ g/l</td>
<td>1</td>
</tr>
<tr>
<td>C-Reactive protein $&gt;10$ mg/l and albumin $&lt;35$ g/l</td>
<td>2</td>
</tr>
</tbody>
</table>

*The modified Glasgow Prognostic Score (mGPS)*

<p>| C-Reactive protein $\leq 10$ mg/l and albumin $\geq 35$ g/l           | 0                 |
| C-Reactive protein $&gt;10$ mg/l                                         | 1                 |
| C-Reactive protein $&gt;10$ mg/l and albumin $&lt;35$ g/l                    | 2                 |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Centre</th>
<th>Tumour site</th>
<th>n</th>
<th>HR (p-value)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crumley et al.</td>
<td>Glasgow, UK</td>
<td>Gastro-oesophageal</td>
<td>217</td>
<td>1.7 (&lt;0.001)</td>
<td>mGPS predicted survival independent of tumour site/stage/treatment</td>
</tr>
<tr>
<td>Proctor et al.</td>
<td>Glasgow, UK</td>
<td>11 sites</td>
<td>9608</td>
<td>1.9 (&lt;0.001)</td>
<td>mGPS predicted survival independent of tumour site</td>
</tr>
<tr>
<td>Proctor et al.</td>
<td>Glasgow, UK</td>
<td>11 sites</td>
<td>8759</td>
<td>1.7 (&lt;0.001)</td>
<td>mGPS predicted survival superior to NLR, PLR, PI, PNI</td>
</tr>
<tr>
<td>Shafique et al.</td>
<td>Glasgow, UK</td>
<td>Prostate</td>
<td>897</td>
<td>1.8 (&lt;0.05)</td>
<td>mGPS predicted survival superior to NLR</td>
</tr>
</tbody>
</table>

HR multivariate hazard ratio for incremental change of GPS/mGPS.
Table 3
Studies (n = 28) of the prognostic value of the GPS/mGPS in patients with operable cancer (n > 8,000).

<table>
<thead>
<tr>
<th>Study</th>
<th>Centre</th>
<th>Tumour site</th>
<th>n</th>
<th>HR (p-value)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>McMillan et al.</td>
<td>Glasgow, UK</td>
<td>Colorectal</td>
<td>316</td>
<td>1.7 (&lt;0.001)</td>
<td>mGPS predicted survival independent of stage/treatment</td>
</tr>
<tr>
<td>Leitch et al.</td>
<td>Glasgow, UK</td>
<td>Colorectal</td>
<td>233</td>
<td>2.1 (&lt;0.001)</td>
<td>mGPS predicted survival superior to WCC/lymphocytes</td>
</tr>
<tr>
<td>Ishizuka et al.</td>
<td>Tochigi, Japan</td>
<td>Colorectal</td>
<td>315</td>
<td>1.5 (&lt;0.01)</td>
<td>GPS predicted survival independent of stage/treatment</td>
</tr>
<tr>
<td>Crozier et al.</td>
<td>Glasgow, UK</td>
<td>Colorectal</td>
<td>188</td>
<td>2.2 (&lt;0.05)</td>
<td>mGPS predicted survival independent of emergency presentation</td>
</tr>
<tr>
<td>Roxburgh et al.</td>
<td>Glasgow, UK</td>
<td>Colorectal</td>
<td>244</td>
<td>2.3 (&lt;0.001)</td>
<td>mGPS predicted survival independent of Petersen Index</td>
</tr>
<tr>
<td>Moyes et al.</td>
<td>Glasgow, UK</td>
<td>Colorectal</td>
<td>455</td>
<td>1.8 (&lt;0.01)</td>
<td>mGPS predicted post-operative infective complications</td>
</tr>
<tr>
<td>Roxburgh et al.</td>
<td>Glasgow, UK</td>
<td>Colorectal</td>
<td>287</td>
<td>2.7 (&lt;0.001)</td>
<td>mGPS predicted survival independent of tumour inflammatory infiltrate</td>
</tr>
<tr>
<td>Ishizuka et al.</td>
<td>Tochigi, Japan</td>
<td>Colorectal</td>
<td>300</td>
<td>2.1 (&lt;0.05)</td>
<td>GPS predicted survival independent of CLIP score</td>
</tr>
<tr>
<td>Ishizuka et al.</td>
<td>Tochigi, Japan</td>
<td>Colorectal</td>
<td>156</td>
<td>24.5 (&lt;0.05)</td>
<td>GPS predicted survival in T1/T2 stage disease</td>
</tr>
<tr>
<td>Kobayashi et al.</td>
<td>Tokyo, Japan</td>
<td>Oesophageal</td>
<td>65</td>
<td>NR (&lt;0.001)</td>
<td>GPS predicted survival independent of lymph node status</td>
</tr>
<tr>
<td>Polterauer et al.</td>
<td>Vienna, Austria</td>
<td>Cervical</td>
<td>244</td>
<td>NR (&lt;0.05)</td>
<td>GPS predicted survival independent of FIGO stage</td>
</tr>
<tr>
<td>Kobayashi et al.</td>
<td>Tokyo, Japan</td>
<td>Colorectal</td>
<td>63</td>
<td>3.1 (&lt;0.01)</td>
<td>GPS predicted survival independent of number of liver metastases</td>
</tr>
<tr>
<td>Knight et al.</td>
<td>Manchester, UK</td>
<td>Pancreas</td>
<td>99</td>
<td>4.3 (&lt;0.05)</td>
<td>GPS predicted post-operative morbidity</td>
</tr>
<tr>
<td>Richards et al.</td>
<td>Glasgow, UK</td>
<td>Colorectal</td>
<td>320</td>
<td>1.8 (&lt;0.001)</td>
<td>mGPS predicted survival independent of POSSUM</td>
</tr>
<tr>
<td>Nohoe et al.</td>
<td>Koga, Japan</td>
<td>Gastric</td>
<td>232</td>
<td>4.1 (&lt;0.001)</td>
<td>mGPS predicted survival independent of tumour stage</td>
</tr>
<tr>
<td>Mog et al.</td>
<td>Kilmarnock, UK</td>
<td>Colorectal</td>
<td>206</td>
<td>1.6 (&lt;0.05)</td>
<td>mGPS predicted survival independent of LNR</td>
</tr>
<tr>
<td>Roxburgh et al.</td>
<td>Glasgow, UK</td>
<td>Colorectal</td>
<td>302</td>
<td>1.6 (&lt;0.001)</td>
<td>mGPS predicted survival independent of comorbidity indices</td>
</tr>
<tr>
<td>Vashisht et al.</td>
<td>Hamburg, Germany</td>
<td>Oesophageal</td>
<td>495</td>
<td>3.0 (&lt;0.001)</td>
<td>GPS predicted peri-operative morbidity and survival</td>
</tr>
<tr>
<td>Ishizuka et al.</td>
<td>Tochigi, Japan</td>
<td>Hepatocellular</td>
<td>300</td>
<td>2.1 (&lt;0.05)</td>
<td>GPS predicted survival independent of post-operative mortality</td>
</tr>
<tr>
<td>Dutta et al.</td>
<td>Glasgow, UK</td>
<td>Oesophageal</td>
<td>112</td>
<td>4.3 (&lt;0.001)</td>
<td>mGPS predicted survival independent of LNR, NLR and PLR</td>
</tr>
<tr>
<td>Jamieson et al.</td>
<td>Glasgow, UK</td>
<td>Pancreas</td>
<td>135</td>
<td>2.3 (&lt;0.001)</td>
<td>GPS predicted survival independent of margin status/adjuvant therapy</td>
</tr>
<tr>
<td>Ishizuka et al.</td>
<td>Tochigi, Japan</td>
<td>Hepatocellular</td>
<td>398</td>
<td>2.5 (&lt;0.05)</td>
<td>GPS predicted survival independent of CLIP score</td>
</tr>
<tr>
<td>Lamb et al.</td>
<td>Glasgow, UK</td>
<td>Renal</td>
<td>169</td>
<td>5.1 (&lt;0.001)</td>
<td>GPS predicted survival independent of established scoring systems</td>
</tr>
<tr>
<td>La Torre et al.</td>
<td>Rome, Italy</td>
<td>Pancreas</td>
<td>101</td>
<td>1.8 (&lt;0.01)</td>
<td>mGPS predicted survival independent of LNR and margin status</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>Guangzhou, China</td>
<td>Gastric</td>
<td>324</td>
<td>1.4 (&lt;0.01)</td>
<td>GPS predicted survival independent of TNM stage, NLR and PLR</td>
</tr>
<tr>
<td>Jamieson et al.</td>
<td>Glasgow, UK</td>
<td>Pancreas</td>
<td>173</td>
<td>1.8 (&lt;0.01)</td>
<td>mGPS predicted survival independent of LIR</td>
</tr>
<tr>
<td>Ishizuka et al.</td>
<td>Tochigi, Japan</td>
<td>Colorectal</td>
<td>271</td>
<td>2.0 (&lt;0.05)</td>
<td>mGPS predicted survival in patients with normal CEA</td>
</tr>
<tr>
<td>Dutta et al.</td>
<td>Glasgow, UK</td>
<td>Gastric</td>
<td>120</td>
<td>2.2 (&lt;0.01)</td>
<td>mGPS predicted survival independent of LNR, NLR and PLR</td>
</tr>
<tr>
<td>Jiang et al.</td>
<td>Tokyo, Japan</td>
<td>Gastric</td>
<td>1710</td>
<td>1.8 (&lt;0.01)</td>
<td>mGPS predicted survival independent of TNM stage</td>
</tr>
</tbody>
</table>

HR, multivariate hazard ratio for incremental change of GPS/mGPS; NR, not reported; LNR, lymph node ratio; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; CLIP, cancer of the liver Italian program; LIR, local inflammatory response; POSSUM.
Table 4
Studies \((n = 11)\) of the prognostic value of the GPS/mGPS, in cancer patients receiving chemo/radiotherapy \((n > 1500)\).

<table>
<thead>
<tr>
<th>Study</th>
<th>Centre</th>
<th>Tumour site</th>
<th>(n)</th>
<th>HR ((p\text{-value}))</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forrest et al.</td>
<td>Glasgow, UK</td>
<td>Lung (NSCLC)</td>
<td>109</td>
<td>1.9 ((&lt;0.01))</td>
<td>GPS predicted survival independent of ECOG-ps/platinum therapy</td>
</tr>
<tr>
<td>Crumley et al.</td>
<td>Glasgow, UK</td>
<td>Gastro-oesophageal</td>
<td>65</td>
<td>1.7 ((&lt;0.05))</td>
<td>mGPS predicted survival independent of ECOG-ps/platinum therapy</td>
</tr>
<tr>
<td>Kobayashi et al.</td>
<td>Tokyo, Japan</td>
<td>Oesophageal</td>
<td>48</td>
<td>5.9 ((&lt;0.01))</td>
<td>GPS predicted toxicity in patients receiving neoadjuvant therapy</td>
</tr>
<tr>
<td>Sharma et al.</td>
<td>London/Sydney</td>
<td>Colorectal</td>
<td>52</td>
<td>NR</td>
<td>GPS predicted toxicity and survival independent of stage/treatment</td>
</tr>
<tr>
<td>Ishizuka et al.</td>
<td>Tochigi, Japan</td>
<td>Colorectal</td>
<td>112</td>
<td>6.0 ((&lt;0.01))</td>
<td>GPS predicted survival in patients receiving adjuvant therapy</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>Kaohsiung, Taiwan</td>
<td>Oesophageal</td>
<td>123</td>
<td>3.4 ((&lt;0.001))</td>
<td>GPS predicted survival in patients receiving radiotherapy</td>
</tr>
<tr>
<td>Roxburgh et al.</td>
<td>Glasgow, UK</td>
<td>Colon</td>
<td>348</td>
<td>3.2 ((&lt;0.01))</td>
<td>mGPS predicted survival in patients receiving adjuvant therapy</td>
</tr>
<tr>
<td>Chau et al.</td>
<td>Sydney, Australia</td>
<td>Various</td>
<td>68</td>
<td>4.1 ((&lt;0.01))</td>
<td>GPS predicted survival in patients receiving docetaxel</td>
</tr>
<tr>
<td>Hwang et al.</td>
<td>Gwangui, South Korea</td>
<td>Gastric</td>
<td>402</td>
<td>1.8 ((&lt;0.01))</td>
<td>GPS predicted survival independent of performance status</td>
</tr>
<tr>
<td>Morimoto et al.</td>
<td>Yokohama, Japan</td>
<td>Hepatocellular</td>
<td>81</td>
<td>5.5 ((&lt;0.001))</td>
<td>GPS predicted survival in patients receiving sorafenib</td>
</tr>
<tr>
<td>Gioulbasanis et al.</td>
<td>Heraklion, Greece</td>
<td>Lung (metastatic)</td>
<td>96</td>
<td>1.9 ((&lt;0.01))</td>
<td>GPS predicts toxicity and efficacy in platinum-based treatment</td>
</tr>
</tbody>
</table>

HR, multivariate hazard ratio for incremental change of GPS; NR, not reported.
Table 5
Studies (n = 11) of the prognostic value of the GPS/mGPS, in patients with inoperable cancer (n > 2000).

<table>
<thead>
<tr>
<th>Study</th>
<th>Centre</th>
<th>Tumour site</th>
<th>n</th>
<th>HR (p-value)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forrest et al.</td>
<td>Glasgow, UK</td>
<td>Lung (NSCLC)</td>
<td>109</td>
<td>1.7 (&lt;0.001)</td>
<td>GPS predicted survival independent of ECOG-ps/stage/treatment</td>
</tr>
<tr>
<td>Al Murri et al.</td>
<td>Glasgow, UK</td>
<td>Breast</td>
<td>96</td>
<td>2.3 (&lt;0.001)</td>
<td>GPS predicted survival independent of stage/treatment</td>
</tr>
<tr>
<td>Crumley et al.</td>
<td>Glasgow, UK</td>
<td>Gastro-oesophageal</td>
<td>258</td>
<td>1.5 (&lt;0.001)</td>
<td>GPS predicted survival independent of stage/treatment</td>
</tr>
<tr>
<td>Glen et al.</td>
<td>Glasgow, UK</td>
<td>Pancreas</td>
<td>187</td>
<td>1.7 (&lt;0.001)</td>
<td>GPS predicted survival independent of stage</td>
</tr>
<tr>
<td>Read et al.</td>
<td>Sydney, Australia</td>
<td>Colorectal</td>
<td>84</td>
<td>2.3 (&lt;0.05)</td>
<td>GPS independent of stage/treatment</td>
</tr>
<tr>
<td>Ramsey et al.</td>
<td>Glasgow, UK</td>
<td>Renal</td>
<td>119</td>
<td>2.4 (&lt;0.001)</td>
<td>GPS predicted survival independent of scoring systems</td>
</tr>
<tr>
<td>Sharma et al.</td>
<td>Sydney, Australia</td>
<td>Ovarian</td>
<td>154</td>
<td>1.7 (&lt;0.01)</td>
<td>GPS independent of stage/treatment</td>
</tr>
<tr>
<td>Pinato et al.</td>
<td>London, UK</td>
<td>Lung (mesothelioma)</td>
<td>171</td>
<td>2.6 (&lt;0.001)</td>
<td>mGPS predicted survival independent of NLR and EPS</td>
</tr>
<tr>
<td>Leung et al.</td>
<td>Glasgow, UK</td>
<td>Lung (NSCLC)</td>
<td>261</td>
<td>1.7 (&lt;0.001)</td>
<td>mGPS predicted survival independent of ECOG-ps/stage/treatment</td>
</tr>
<tr>
<td>Pinato et al.</td>
<td>London, UK</td>
<td>Hepatocellular</td>
<td>578</td>
<td>2.7 (&lt;0.01)</td>
<td>GPS predicted survival in training and validation datasets</td>
</tr>
<tr>
<td>Partridge et al.</td>
<td>Edinburgh, UK</td>
<td>5 sites</td>
<td>102</td>
<td>2.7 (&lt;0.01)</td>
<td>mGPS predicted survival independent of tumour site in palliative care</td>
</tr>
</tbody>
</table>

HR, multivariate hazard ratio for incremental change of GPS; NR, not reported; NLR, neutrophil lymphocyte ratio; EPS, European organisation for the research and treatment of cancer Prognostic Score.
Table 6
Studies ($n = 15$) of associations with the GPS/mGPS in patients with cancer ($n > 2000$).

<table>
<thead>
<tr>
<th>Study</th>
<th>Centre</th>
<th>Tumour site</th>
<th>$n$</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al.</td>
<td>Glasgow, UK</td>
<td>Lung and colorectal</td>
<td>50</td>
<td>GPS associated with weight loss, poor performance status and biochemical disturbance</td>
</tr>
<tr>
<td>K-Korpacka</td>
<td>Wroclaw, Poland</td>
<td>Gastro-oesophageal</td>
<td>96</td>
<td>GPS associated with weight loss, transferrin, IL-1, IL-6, IL-8, TNF, VEGF-A and midkine concentrations</td>
</tr>
<tr>
<td>Leung et al.</td>
<td>Glasgow, UK</td>
<td>Colorectal</td>
<td>106</td>
<td>mGPS associated with plasma retinol, lutein, lycopene, alpha and beta carotene</td>
</tr>
<tr>
<td>Kerem et al.</td>
<td>Ankara, Turkey</td>
<td>Gastric</td>
<td>60</td>
<td>GPS associated with weight loss, ghrelin, resistin, adiponectin and leptin</td>
</tr>
<tr>
<td>Fujisawa et al.</td>
<td>Tokyo, Japan</td>
<td>Hepatocellular</td>
<td>66</td>
<td>GPS associated with blood transfusion and post-operative complications</td>
</tr>
<tr>
<td>Meek et al.</td>
<td>Glasgow, UK</td>
<td>Lung (NSCLC)</td>
<td>56</td>
<td>mGPS associated with haemoglobin and IGFBP-3</td>
</tr>
<tr>
<td>Skipworth et al.</td>
<td>Edinburgh, UK</td>
<td>Gastro-oesophageal</td>
<td>293</td>
<td>mGPS associated with weight loss, dietary intake, MAMC and KPS</td>
</tr>
<tr>
<td>Shimoda et al.</td>
<td>Tochigi, Japan</td>
<td>Pancreas (unresectable)</td>
<td>83</td>
<td>GPS associated with responses to treatment</td>
</tr>
<tr>
<td>Diakowska et al.</td>
<td>Wroclaw, Poland</td>
<td>Gastro-oesophageal</td>
<td>135</td>
<td>GPS associated with cachexia in cancer and controls</td>
</tr>
<tr>
<td>Giannouli et al.</td>
<td>Heraklion, Greece</td>
<td>Lung (metastatic)</td>
<td>122</td>
<td>GPS associated with MNA, anxiety, depression and survival</td>
</tr>
<tr>
<td>Blomberg et al.</td>
<td>Stockholm, Sweden</td>
<td>ENT and non-cancer</td>
<td>484</td>
<td>Combination of C-reactive protein and albumin associated with mortality following PEG</td>
</tr>
<tr>
<td>Richards et al.</td>
<td>Glasgow, UK</td>
<td>Colorectal</td>
<td>343</td>
<td>mGPS associated with tumour necrosis</td>
</tr>
<tr>
<td>Naito et al.</td>
<td>Shizuoka, Japan</td>
<td>Gastro-oesophageal</td>
<td>47</td>
<td>GPS associated with clinical responses to oxycodone</td>
</tr>
<tr>
<td>Leung et al.</td>
<td>Glasgow, UK</td>
<td>Colorectal</td>
<td>108</td>
<td>mGPS associated with plasma B6</td>
</tr>
<tr>
<td>Richards et al.</td>
<td>Glasgow, UK</td>
<td>Colorectal</td>
<td>174</td>
<td>mGPS associated with skeletal muscle index</td>
</tr>
</tbody>
</table>

NSCLC, non-small cell lung cancer; MNA, mini-nutritional assessment; IGFBP-3, insulin like growth factor binding protein-3.
Prognostic Factors in Patients with Advanced Cancer: A Comparison of Clinicopathological Factors and the Development of an Inflammation-Based Prognostic System

Barry J. Laird¹,⁶, Stein Kaasa¹,³, Donald C. McMillan⁷, Marie T. Fallon⁶, Marianne J. Hjemstad¹,⁵, Peter Fayers¹, and Pal Klepstad¹,⁴,²

Clin Cancer Res; 19(19); 5456–64. ©2013 AACR.
Glasgow prognostic score

Biomarkers

CRP and albumin were used as biomarkers of the inflammatory response and were taken by venous blood sampling at entry points to both studies. The limit of detection of CRP was less than 5mg/L, all samples (CRP and albumin) were analyzed at a central laboratory. The mGPS was calculated as follows:

- CRP $\leq$ 10mg/L = 0
- CRP > 10mg/L = 1
- CRP > 10mg/L and albumin < 35g/L = 2
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test sample (n = 1825)</th>
<th>Validation sample (n = 631)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (≤65/65–74/≥74 years)</td>
<td>1,014/509/302 (56/28/16)</td>
<td>368/148/115 (58/24/18)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>931/894 (51/49)</td>
<td>237/294 (53/47)</td>
</tr>
<tr>
<td>Countrya</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>109 (6)</td>
<td>61 (10)</td>
</tr>
<tr>
<td>Germany</td>
<td>248 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Denmark</td>
<td>12 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Australia</td>
<td>0 (0)</td>
<td>11 (2)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>284 (16)</td>
<td>52 (18)</td>
</tr>
<tr>
<td>Iceland</td>
<td>150 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Austria</td>
<td>0 (0)</td>
<td>80 (13)</td>
</tr>
<tr>
<td>Italy</td>
<td>348 (19)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Norway</td>
<td>541 (30)</td>
<td>426 (68)</td>
</tr>
<tr>
<td>Sweden</td>
<td>133 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Canada</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Primary cancer site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>244 (13)</td>
<td>88 (14)</td>
</tr>
<tr>
<td>Urological</td>
<td>124 (7)</td>
<td>43 (7)</td>
</tr>
<tr>
<td>Gynaecologic</td>
<td>138 (8)</td>
<td>14 (2)</td>
</tr>
<tr>
<td>Prostate</td>
<td>223 (12)</td>
<td>69 (11)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>387 (21)</td>
<td>183 (29)</td>
</tr>
<tr>
<td>Haematologic</td>
<td>107 (6)</td>
<td>23 (4)</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>90 (5)</td>
<td>15 (2)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>310 (17)</td>
<td>117 (19)</td>
</tr>
<tr>
<td>Others</td>
<td>202 (11)</td>
<td>79 (13)</td>
</tr>
<tr>
<td>Place of care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient</td>
<td>1,510 (83)</td>
<td>437 (69)</td>
</tr>
<tr>
<td>Outpatient</td>
<td>315 (17)</td>
<td>194 (31)</td>
</tr>
</tbody>
</table>

aWhere n = 0, study not recruiting in that country.
### Table 2. The relationship between clinicopathological factors and survival in patients with advanced cancer—test sample (*n* = 1,825) and validation sample (*n* = 631)

<table>
<thead>
<tr>
<th></th>
<th>Test sample</th>
<th>Validation sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Univariate^b^</td>
</tr>
<tr>
<td></td>
<td><em>N</em></td>
<td><strong>HR (95% CI)</strong></td>
</tr>
<tr>
<td>Age (≤65/65–74/≥74)</td>
<td>1,014/509/302</td>
<td>1.13 (1.05–1.21)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>931/894</td>
<td>0.93 (0.82–1.06)</td>
</tr>
<tr>
<td>Symptoms (EORTC QLQ-C30)^a^</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive function</td>
<td>1,529</td>
<td>0.96 (0.93–0.98)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1,528</td>
<td>1.04 (1.02–1.06)</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>1,531</td>
<td>1.02 (1.01–1.04)</td>
</tr>
<tr>
<td>Quality of life</td>
<td>1,513</td>
<td>0.94 (0.92–0.97)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>1,533</td>
<td>0.89 (0.87–0.91)</td>
</tr>
<tr>
<td>Role functioning</td>
<td>1,525</td>
<td>0.93 (0.91–0.96)</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>1,528</td>
<td>0.98 (0.96–1.01)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>1,524</td>
<td>0.99 (0.97–1.01)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1,531</td>
<td>1.05 (1.03–1.07)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>1,537</td>
<td>1.01 (0.99–1.03)</td>
</tr>
<tr>
<td>Pain</td>
<td>1,535</td>
<td>1.01 (0.99–1.03)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1,530</td>
<td>0.98 (0.98–1.01)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1,524</td>
<td>1.00 (0.98–1.01)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1,521</td>
<td>0.99 (0.97–1.01)</td>
</tr>
<tr>
<td><strong>BMI (&lt;20/≥20)^c^</strong></td>
<td>376/1403</td>
<td>0.84 (0.74–0.95)</td>
</tr>
<tr>
<td>Performance status (ECOG grouping)^d^</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1 (ECOG 2)</td>
<td>713</td>
<td>1.21 (1.05–1.40)</td>
</tr>
<tr>
<td>P2 (ECOG 3)</td>
<td>549</td>
<td>1.98 (1.71–2.29)</td>
</tr>
<tr>
<td>P3 (ECOG 4)</td>
<td>179</td>
<td>3.61 (2.97–4.39)</td>
</tr>
<tr>
<td>mGPS^d^</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1 (mGPS 1)</td>
<td>544</td>
<td>1.55 (1.32–1.84)</td>
</tr>
<tr>
<td>G2 (mGPS 2)</td>
<td>1,004</td>
<td>2.01 (1.71–2.35)</td>
</tr>
</tbody>
</table>

^a^EORTC QLQ-C30 scores available on approximately 1,500 patients in test sample.

^b^HR expressed as per 10 unit change.

^c^BMI available on 1,779 patients in test sample.

^d^Using indicator variables.
Figure 1. Kaplan–Meier curves examining the relationship between mGPS and survival, and performance status (ECOG grouping) and survival. Test sample ($n = 1,825$). Both mGPS and performance status predict survival $P < 0.001$. 

mGPS (0, 1, 2 from top to bottom).  
Log-rank $P < 0.001$

PS (ECOG grouping 0-1, 2, 3, 4 from top to bottom).  
Log-rank $P < 0.001$
Figure 2. Kaplan-Meier curves examining the relationship between mGPS and survival, and performance status (ECOG grouping) and survival. Validation sample (n = 631). Both mGPS and performance status predict survival P < 0.001.

mGPS Grouping (0, 1, 2 – from top to bottom). Log-rank P < 0.001

ECOG Grouping (0-1, 2, 3, 4 – from top to bottom). Log-rank P < 0.001
A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study

Michael J. Proctor a,*, David S. Morrison d, Dinesh Talwar b, Steven M. Balmer b, Colin D. Fletcher b, Denis St.J. O’Reilly b, Alan K. Foulis c, Paul G. Horgan a, Donald C. McMillan a
Introduction: Components of the systemic inflammatory response, combined to form inflammation-based prognostic scores (modified Glasgow Prognostic Score (mGPS), Neutrophil Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR), Prognostic Index (PI), Prognostic Nutritional Index (PNI)) have been associated with cancer specific survival. The aim of the present study was to compare the prognostic value of these scores.
<table>
<thead>
<tr>
<th>The modified Glasgow Prognostic Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein $\leq 10$ mg/l and albumin $\geq 35$ g/l</td>
<td>0</td>
</tr>
<tr>
<td>C-reactive protein $\leq 10$ mg/l and albumin $&lt; 35$ g/l</td>
<td>0</td>
</tr>
<tr>
<td>C-reactive protein $&gt; 10$ mg/l</td>
<td>1</td>
</tr>
<tr>
<td>C-reactive protein $&gt; 10$ mg/l and albumin $&lt; 35$ g/l</td>
<td>2</td>
</tr>
<tr>
<td><strong>Neutrophil Lymphocyte Ratio</strong></td>
<td></td>
</tr>
<tr>
<td>Neutrophil count:lymphocyte count $&lt; 5:1$</td>
<td>0</td>
</tr>
<tr>
<td>Neutrophil count:lymphocyte count $\geq 5:1$</td>
<td>1</td>
</tr>
<tr>
<td><strong>Platelet Lymphocyte Ratio</strong></td>
<td></td>
</tr>
<tr>
<td>Platelet count:lymphocyte count $&lt; 150:1$</td>
<td>0</td>
</tr>
<tr>
<td>Platelet count:lymphocyte count $150-300:1$</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count:lymphocyte count $&gt; 300:1$</td>
<td>2</td>
</tr>
<tr>
<td><strong>Prognostic Index</strong></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein $\leq 10$ mg/l and white cell count $\leq 11 \times 10^9$/l</td>
<td>0</td>
</tr>
<tr>
<td>C-reactive protein $\leq 10$ mg/l and white cell count $&gt; 11 \times 10^9$/l</td>
<td>1</td>
</tr>
<tr>
<td>C-reactive protein $&gt; 10$ mg/l and white cell count $\leq 11 \times 10^9$/l</td>
<td>1</td>
</tr>
<tr>
<td>C-reactive protein $&gt; 10$ mg/l and white cell count $&gt; 11 \times 10^9$/l</td>
<td>2</td>
</tr>
<tr>
<td><strong>Prognostic Nutritional Index</strong></td>
<td></td>
</tr>
<tr>
<td>Albumin (g/L) + $5 \times$ total lymphocyte count $\times 10^9$/l $\geq 45$</td>
<td>0</td>
</tr>
<tr>
<td>Albumin (g/L) + $5 \times$ total lymphocyte count $\times 10^9$/l $&lt; 45$</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Patients n = 8759 (%)</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>≤65 years</td>
<td>4237 (48)</td>
</tr>
<tr>
<td>65–74 years</td>
<td>2620 (30)</td>
</tr>
<tr>
<td>≥75 years</td>
<td>1902 (22)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4115 (47)</td>
</tr>
<tr>
<td>Female</td>
<td>4644 (53)</td>
</tr>
<tr>
<td><strong>SIMD 2006</strong></td>
<td></td>
</tr>
<tr>
<td>1 (least deprived)</td>
<td>1278 (15)</td>
</tr>
<tr>
<td>2</td>
<td>1138 (13)</td>
</tr>
<tr>
<td>3</td>
<td>1391 (16)</td>
</tr>
<tr>
<td>4</td>
<td>1786 (20)</td>
</tr>
<tr>
<td>5 (most deprived)</td>
<td>3166 (36)</td>
</tr>
<tr>
<td><strong>Tumour site</strong></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>1853 (21)</td>
</tr>
<tr>
<td>Bladder</td>
<td>437 (5)</td>
</tr>
<tr>
<td>Gynaecological</td>
<td>460 (5)</td>
</tr>
<tr>
<td>Prostate</td>
<td>456 (5)</td>
</tr>
<tr>
<td>Gastroesophageal</td>
<td>874 (10)</td>
</tr>
<tr>
<td>Haematological</td>
<td>817 (10)</td>
</tr>
<tr>
<td>Renal</td>
<td>400 (5)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>996 (11)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>555 (7)</td>
</tr>
<tr>
<td>Hepatopancreaticobiliary</td>
<td>474 (5)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1437 (16)</td>
</tr>
<tr>
<td><strong>Inflammation based prognostic scores</strong></td>
<td></td>
</tr>
<tr>
<td>mGPS</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>2436 (28)</td>
</tr>
<tr>
<td>2</td>
<td>2650 (30)</td>
</tr>
<tr>
<td>NLR</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>3608 (41)</td>
</tr>
<tr>
<td>PLR</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>3522 (40)</td>
</tr>
<tr>
<td>2</td>
<td>2505 (29)</td>
</tr>
<tr>
<td>PI</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>3460 (40)</td>
</tr>
<tr>
<td>2</td>
<td>2215 (25)</td>
</tr>
<tr>
<td>PNI</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>4417 (50)</td>
</tr>
</tbody>
</table>
Fig. 1 – The relationship between the mGPS (0-top, small dash line; 1-middle, large dash line; 2-bottom, solid line), NLR (0-top, large dash line; 1-bottom, solid line), PLR (0-top, small dash line; 1-middle, large dash line; 2-bottom, solid line), PI (0-top, small dash line; 1-middle, large dash line; 2-bottom, solid line), PNI (0-top, large dash line; 1-bottom, solid line) and cancer specific survival in all patients (all p<0.001).
Table 3 - The relationship between inflammation-based prognostic scores and survival. Adjusted for age, sex, deprivation and stratified by tumour site.

<table>
<thead>
<tr>
<th></th>
<th>Overall survival</th>
<th>Cancer specific survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>p-Value</td>
</tr>
<tr>
<td><strong>All patients (n = 8759)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGPS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>1.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>2.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NLR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>1.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PLR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>1.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>1.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>2.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>2.87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PNI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>2.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Patients sampled within two months following cancer diagnosis (n = 4674)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGPS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>1.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>2.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NLR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>1.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PLR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>1.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>1.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>1.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>2.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PNI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>1.98</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 4 – The relationship between inflammation-based prognostic scores and survival in colorectal cancer patients sampled within two months following cancer diagnosis. Adjusted for age, sex, deprivation and Dukes stage.

<table>
<thead>
<tr>
<th>n = 374</th>
<th>Overall survival</th>
<th>Cancer specific survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>p-Value</td>
</tr>
<tr>
<td>mGPS</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.81</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2.30</td>
</tr>
<tr>
<td>NLR</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.27</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.16</td>
</tr>
<tr>
<td>PLR</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.16</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.13</td>
</tr>
<tr>
<td>PI</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.69</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2.83</td>
</tr>
<tr>
<td>PNI</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.33</td>
</tr>
</tbody>
</table>
In summary, the results of the present study show that systemic inflammation-based scores mGPS, NLR, PLR, PI and PNI have prognostic value in a variety of cancers. However, in terms of differentiating good from poor prognostic groups in a variety of tumour sites and the existing validated literature, the mGPS is superior. A measurement of systemic inflammation, in particular the mGPS, should be included in the routine assessment of all patients with cancer.
The predictive value of pre-treatment inflammatory markers in advanced non-small-cell lung cancer

G. Kasymjanova MD, * N. MacDonald MD, †
J.S. Agulnik MD, *‡ V. Cohen MD, † C. Pepe MD, *‡
H. Kreisman MD, *‡ R. Sharma MD, *
and D. Small MD *‡
<table>
<thead>
<tr>
<th>PI</th>
<th>C-Reactive protein</th>
<th>White blood cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>≤10 mg/L</td>
<td>≤11x10⁹</td>
</tr>
<tr>
<td>1</td>
<td>≤10 mg/L</td>
<td>&gt;11x10⁹</td>
</tr>
<tr>
<td>1</td>
<td>&gt;10 mg/L</td>
<td>≤11x10⁹</td>
</tr>
<tr>
<td>2</td>
<td>&gt;10 mg/L</td>
<td>&gt;11x10⁹</td>
</tr>
</tbody>
</table>

**Definition of the prognostic index (PI)**
**TABLE II  Clinical characteristics of the study patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>71</td>
</tr>
<tr>
<td>Female</td>
<td>63</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>40</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>65</td>
</tr>
<tr>
<td>Never-smoker</td>
<td>29</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>116</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Tumour type</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>96</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>13</td>
</tr>
<tr>
<td>Other</td>
<td>25</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>IV (pleural effusion)</td>
<td>15</td>
</tr>
<tr>
<td>IV</td>
<td>119</td>
</tr>
<tr>
<td>Chemotherapy type</td>
<td></td>
</tr>
<tr>
<td>Carboplatin–gemcitabine</td>
<td>71</td>
</tr>
<tr>
<td>Carboplatin–paclitaxel</td>
<td>46</td>
</tr>
<tr>
<td>Other platinum-based doublets</td>
<td>17</td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
</tr>
<tr>
<td>&lt;5%</td>
<td>86</td>
</tr>
<tr>
<td>≥5%</td>
<td>48</td>
</tr>
</tbody>
</table>

ECOG = Eastern Cooperative Oncology Group.

*FIGURE 1  Cohort organization chart. NSCLC = non-small-cell lung cancer; RT = radiotherapy; SC = supportive care; CRP = C-reactive protein.*
**TABLE III** Clinical difference among the prognostic index (PI) groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients by PI group (n)</th>
<th>p Value (Spearman correlation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (N=46)</td>
<td>1 (N=80)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>30</td>
<td>34</td>
</tr>
<tr>
<td>≥65</td>
<td>16</td>
<td>26</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker or ex-smoker</td>
<td>30</td>
<td>13</td>
</tr>
<tr>
<td>Never-smoker</td>
<td>16</td>
<td>47</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>43</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Male</td>
<td>18</td>
<td>34</td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5%</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>≥5%</td>
<td>10</td>
<td>23</td>
</tr>
</tbody>
</table>

**TABLE V** Factors affecting rate of progression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.26</td>
<td>0.002</td>
</tr>
<tr>
<td>Age</td>
<td>0.47</td>
<td>0.09</td>
</tr>
<tr>
<td>Sex</td>
<td>1.37</td>
<td>0.45</td>
</tr>
<tr>
<td>Weight loss</td>
<td>1.11</td>
<td>0.81</td>
</tr>
<tr>
<td>Smoking status</td>
<td>0.61</td>
<td>0.30</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>2.58</td>
<td>0.09</td>
</tr>
<tr>
<td>Prognostic index</td>
<td>1.79</td>
<td>0.04</td>
</tr>
</tbody>
</table>

<sup>a</sup> y intercept.
ECOG = Eastern Cooperative Oncology Group.
FIGURE 2  Kaplan–Meier survival curves based on the prognostic index (PI).
Circulating levels of immune and inflammatory markers and long versus short survival in early-stage lung cancer

C. Bodelon\textsuperscript{1*}, M. Y. Polley\textsuperscript{2}, T. J. Kemp\textsuperscript{3}, A. C. Pesatori\textsuperscript{4}, L. M. McShane\textsuperscript{2}, N. E. Caporaso\textsuperscript{1}, A. Hildesheim\textsuperscript{1}, L. A. Pinto\textsuperscript{3} & M. T. Landi\textsuperscript{1}

\textsuperscript{1}Cancer Epidemiology and Genetics; \textsuperscript{2}Cancer Treatment and Diagnosis, National Cancer Institute, Rockville; \textsuperscript{3}HPV Immunology Laboratory, National Cancer Institute, SAIC, Frederick, USA; \textsuperscript{4}Department of Clinical Sciences and Community Health, Università degli Studi di Milano and Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
2100 lung cancer patients

651 patients with stage I (n=422) or II (n=209)*

540 patients with adenocarcinoma (n=323)
or squamous cell carcinoma (n=217)

2 subjects with no follow-up time were excluded

444 subjects surviving more than 156 weeks

Included 65% of non-smokers and a random selection of (past and current) smokers

160 subjects surviving more than 156 weeks

3 subjects excluded due to stage III in revised classification**

157 subjects surviving more than 156 weeks

94 subjects surviving less than 79 weeks

Included all non-smokers and a random selection of (past and current) smokers

89 subjects surviving less than 79 weeks

5 subjects excluded due to stage III in revised classification**

84 subjects surviving less than 79 weeks

*According to the 2004 World Health Organization classification of lung tumors (Travis et al., 2004).
**According to the revised staging by the American Joint Committee on Cancer (AJCC) (AJCC Cancer Staging Manual, 2010).

Figure 1. Flow diagram of study participants.
Table 1. Distribution of characteristics of lung cancer patients by survival status.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>LS (&gt;156 weeks)</th>
<th>SS (&lt;79 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 157)</td>
<td>(n = 84)</td>
<td></td>
</tr>
<tr>
<td>Median follow-up time (weeks), (IQR)</td>
<td>341.0 (289.4–389.1)</td>
<td>44.6 (20.6–61.3)</td>
</tr>
<tr>
<td>Age (years), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>56 (35.7)</td>
<td>20 (23.8)</td>
</tr>
<tr>
<td>65 to &lt;70</td>
<td>41 (26.1)</td>
<td>16 (19.0)</td>
</tr>
<tr>
<td>70 to &lt;75</td>
<td>44 (28.0)</td>
<td>20 (23.8)</td>
</tr>
<tr>
<td>≥75</td>
<td>16 (10.2)</td>
<td>28 (33.3)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>123 (78.3)</td>
<td>68 (81.0)</td>
</tr>
<tr>
<td>Females</td>
<td>34 (21.7)</td>
<td>16 (19.0)</td>
</tr>
<tr>
<td>Stage, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>43 (27.4)</td>
<td>16 (19.0)</td>
</tr>
<tr>
<td>IB</td>
<td>38 (24.2)</td>
<td>26 (31.0)</td>
</tr>
<tr>
<td>IIA</td>
<td>51 (32.5)</td>
<td>17 (20.2)</td>
</tr>
<tr>
<td>III</td>
<td>25 (15.9)</td>
<td>25 (29.8)</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>89 (56.7)</td>
<td>46 (54.8)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>68 (43.3)</td>
<td>38 (45.2)</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>22 (14.0)</td>
<td>5 (6.0)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>73 (46.5)</td>
<td>38 (45.2)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>62 (39.5)</td>
<td>41 (48.8)</td>
</tr>
<tr>
<td>COPD (self-reported), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>113 (75.8)</td>
<td>52 (71.2)</td>
</tr>
<tr>
<td>Yes</td>
<td>36 (24.2)</td>
<td>21 (28.8)</td>
</tr>
<tr>
<td>COPD (spirometer-based), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal or mild</td>
<td>81 (81.0)</td>
<td>28 (57.1)</td>
</tr>
<tr>
<td>Moderate or severe</td>
<td>19 (19.0)</td>
<td>21 (42.9)</td>
</tr>
<tr>
<td>Surgery, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5 (3.2)</td>
<td>13 (15.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>152 (96.8)</td>
<td>71 (84.5)</td>
</tr>
<tr>
<td>Chemotherapy treatment, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>111 (70.7)</td>
<td>55 (65.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>46 (29.3)</td>
<td>29 (34.5)</td>
</tr>
<tr>
<td>Radiation treatment, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>119 (76.3)</td>
<td>59 (72.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>37 (23.7)</td>
<td>23 (28.0)</td>
</tr>
</tbody>
</table>

Percentages might not add up to 100% because of rounding.
Patients treated according to standard practice at clinical site where they were seen; details of chemotherapy regimens not known.
LS, long survivors; SS, short survivors; IQR, interquartile range.
Table 2. Adjusted analysis for the associations between inflammatory circulating markers and survival status$^a$.

<table>
<thead>
<tr>
<th>Markers</th>
<th>Median LS</th>
<th>Median SS</th>
<th>P-value*</th>
<th>OR$^b$ (95% CI) Q2 versus Q1</th>
<th>OR$^b$ (95% CI) Q3 versus Q1</th>
<th>OR$^b$ (95% CI) Q4 versus Q1</th>
<th><em>P</em>$_{trend}$</th>
<th>Q-value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCL15</td>
<td>1957.03</td>
<td>2317.34</td>
<td>2.8 × 10$^{-4}$</td>
<td>2.60 (1.02–6.66)</td>
<td>3.82 (1.48–9.88)</td>
<td>4.93 (1.9–12.8)</td>
<td>7.4 × 10$^{-4}$</td>
<td>0.042</td>
</tr>
<tr>
<td>IL-8</td>
<td>7.30</td>
<td>9.77</td>
<td>0.002</td>
<td>0.62 (0.24–1.57)</td>
<td>1.41 (0.59–3.35)</td>
<td>3.05 (1.31–7.1)</td>
<td>0.002</td>
<td>0.064</td>
</tr>
<tr>
<td>CRP$^c$</td>
<td>25 256 000.00</td>
<td>66 605 000.00</td>
<td>0.007</td>
<td>0.98 (0.38–2.5)</td>
<td>2.72 (1.17–6.31)</td>
<td>3.08 (1.17–8.08)</td>
<td>0.004</td>
<td>0.071</td>
</tr>
<tr>
<td>IL-2Ra</td>
<td>3.20</td>
<td>6.25</td>
<td>0.020</td>
<td>–</td>
<td>1.12 (0.52–2.43)</td>
<td>2.58 (1.26–5.29)</td>
<td>0.023</td>
<td>0.249</td>
</tr>
<tr>
<td>TNF-a</td>
<td>8.56</td>
<td>9.44</td>
<td>0.007</td>
<td>1.72 (0.73–4.02)</td>
<td>1.27 (0.53–3.09)</td>
<td>2.92 (1.25–6.78)</td>
<td>0.029</td>
<td>0.249</td>
</tr>
<tr>
<td>IL-6</td>
<td>4.51</td>
<td>5.64</td>
<td>0.048</td>
<td>2.48 (0.95–6.47)</td>
<td>3.78 (1.45–9.83)</td>
<td>2.84 (1.08–7.43)</td>
<td>0.030</td>
<td>0.249</td>
</tr>
<tr>
<td>TRAIL</td>
<td>21.52</td>
<td>16.53</td>
<td>0.085</td>
<td>1.04 (0.46–2.34)</td>
<td>0.74 (0.32–1.71)</td>
<td>0.38 (0.15–0.95)</td>
<td>0.031</td>
<td>0.249</td>
</tr>
<tr>
<td>IL-6R</td>
<td>15 793.15</td>
<td>16 987.09</td>
<td>0.034</td>
<td>1.04 (0.43–2.48)</td>
<td>1.68 (0.72–3.93)</td>
<td>2.07 (0.91–4.75)</td>
<td>0.049</td>
<td>0.326</td>
</tr>
<tr>
<td>CXCL13</td>
<td>24.59</td>
<td>30.04</td>
<td>0.001</td>
<td>0.92 (0.39–2.21)</td>
<td>1.07 (0.46–2.53)</td>
<td>2.25 (0.97–5.24)</td>
<td>0.052</td>
<td>0.326</td>
</tr>
<tr>
<td>TNFRII</td>
<td>5369.65</td>
<td>6910.59</td>
<td>0.006</td>
<td>0.95 (0.38–2.36)</td>
<td>1.44 (0.6–3.49)</td>
<td>2.08 (0.86–5.05)</td>
<td>0.060</td>
<td>0.341</td>
</tr>
<tr>
<td>CCL19</td>
<td>59.72</td>
<td>67.90</td>
<td>0.031</td>
<td>1.14 (0.49–2.66)</td>
<td>1.21 (0.51–2.84)</td>
<td>2.02 (0.87–4.67)</td>
<td>0.109</td>
<td>0.566</td>
</tr>
<tr>
<td>G-CSF</td>
<td>89.84</td>
<td>101.34</td>
<td>0.219</td>
<td>1.07 (0.46–2.48)</td>
<td>1.08 (0.45–2.56)</td>
<td>1.89 (0.84–4.27)</td>
<td>0.136</td>
<td>0.645</td>
</tr>
<tr>
<td>TNFRI</td>
<td>1234.41</td>
<td>1377.58</td>
<td>0.009</td>
<td>2.01 (0.83–4.89)</td>
<td>1.64 (0.67–4.04)</td>
<td>2.13 (0.87–5.2)</td>
<td>0.167</td>
<td>0.700</td>
</tr>
<tr>
<td>EGFR</td>
<td>37 460.37</td>
<td>36 289.72</td>
<td>0.159</td>
<td>0.89 (0.4–1.97)</td>
<td>0.66 (0.29–1.5)</td>
<td>0.61 (0.26–1.41)</td>
<td>0.185</td>
<td>0.700</td>
</tr>
<tr>
<td>SAA$^e$</td>
<td>48 800 000.00</td>
<td>142 200 000.00</td>
<td>0.085</td>
<td>1.18 (0.47–2.98)</td>
<td>2.77 (1.16–6.63)</td>
<td>1.21 (0.43–3.42)</td>
<td>0.197</td>
<td>0.700</td>
</tr>
</tbody>
</table>

Markers ordered from the most significant association to the least significant according to *P*$_{trend}$.
LS, long survivors; SS, short survivors.
Mécanisme

Review

Inflammation Amplifier, a New Paradigm in Cancer Biology

Toru Atsumi, Rajeev Singh, Lavannya Sabharwal, Hidenori Bando, Jie Meng, Yasunobu Arima, Moe Yamada, Masaya Harada, Jing-Jing Jiang, Daisuke Kamimura, Hideki Ogura, Toshio Hirano, and Masaaki Murakami

Abstract

Tumor-associated inflammation can induce various molecules expressed from the tumors themselves or surrounding cells to create a microenvironment that potentially promotes cancer development. Inflammation, particularly chronic inflammation, is often linked to cancer development, even though its evolutionary role should impair nonself objects including tumors. The inflammation amplifier, a hyperinducer of chemokines in nonimmune cells, is the principal machinery for inflammation and is activated by the simultaneous stimulation of NF-κB and STAT3. We have redefined inflammation as local activation of the inflammation amplifier, which causes an accumulation of various immune cells followed by dysregulation of local homeostasis. Genes related to the inflammation amplifier have been genetically associated with various human inflammatory diseases. Here, we describe how cancer-associated genes, including interleukin (IL)-6, Ptgs2, ErbB1, Gas1, Serpine1, cMyc, and Vegf-α, are strongly enriched in genes related to the amplifier. The inflammation amplifier is activated by the stimulation of cytokines, such as TNF-α, IL-17, and IL-6, resulting in the subsequent expression of various target genes for chemokines and tumor-related genes like Bcl2L11, Cpne7, Fas, Hif1α, Il-1rap, and Sod2. Thus, we conclude that inflammation does indeed associate with the development of cancer. The identified genes associated with the inflammation amplifier may thus make potential therapeutic targets of cancers. Cancer Res; 74(1): 8–14. ©2013 AACR.
The five members of the NF-κB family of proteins: RelA (p65), RelB, c-Rel, NF-κB1 (p105), and NF-κB2 (p100). p105 and p100 are processed to their shorter forms p50 and p52, respectively. All members of the NF-κB family harbor an N-terminal Rel homology domain (RHD), which mediates DNA contact and homo- and heterodimerization. Three family members (RelA, RelB and c-Rel) contain C-terminal transactivation domains (TAs), which are essential for transcriptional activity.
The IκB family of proteins consists of four members: IκBα, IκBβ, IκBε and BCL-3. These proteins are characterized by the presence of ankyrin (ANK) repeats, which mediate binding of IκBs to the NF-κB family of proteins. Based on the presence of ankyrin repeats, p100 and p105 can also be included into the IκB family – as their DNA-binding RHD domain is covalently linked to an IκB-like inhibitory domain. In addition to the ANK repeats IκBα and IκBβ contain PEST domains, which are enriched in proline, glutamate, serine and threonine and are required for constitutive turnover. BCL-3 differs from other IκB family members by containing TA domains, which mediate transcriptional activity when BCL-3 is associated with NF-κB dimers that bind to DNA.
The three most important members of IκB kinase (IKK) complex: NF-κB Essential Modulator (NEMO or IKKγ), IκB kinase α, (IKKα or IKK1) and IκB kinase β (IKKβ or IKK2). Further abbreviations: leucin-zipper-like motif (LZ), death domain (DD), coiled-coil domain (CC), zinc-finger domain (ZF), helix-loop-helix domain (HLH), NEMO-binding domain (NBD). It is important to note that the total number of amino acids of protein as well as the start and end of some domains can differ between publications and databases.
**Signaling pathways activating NF-κB**

**Figure 2** The canonical, non-canonical and the atypical NF-κB signaling pathway. (A) In the canonical NF-κB signaling pathway, lipopolysaccharides (LPS), tumor necrosis factor α (TNFα) or interleukin-1 (IL-1) activate Toll-like receptors (TLRs), tumor necrosis factor receptor (TNFR) and interleukin-1 receptor (IL-1R), respectively. Through a variety of adapter proteins and signaling kinases this leads to an activation of IKKβ in the IKK complex, which can then phosphorylate IκBα on Serine residues S32 and S36. This phosphorylation is a prerequisite for its subsequent polyubiquitination, which in turn results in proteasomal degradation of IκBα. NF-κB homo- or heterodimers can then translocate to nucleus and activate target gene transcription. (B) In the non-canonical NF-κB signaling pathway, activation of B-cell activation factor (BAFFR), CD40, receptor activator for nuclear factor kappa B (RANK) or lymphotixin β-receptor (LTβR), leads to activation of IKKα by the NF-κB-inducing kinase (NIK). IKKα can then phosphorylate p100 on serine residues S866 and S870. This phosphorylation leads to polyubiquitination of p100 and its subsequent proteasomal processing to p52. p52-RelB heterodimers can then activate transcription of target genes. (C) In the atypical NF-κB signaling pathway, genotoxic stress leads to a translocation of NEMO to the nucleus where it is sumoylated and subsequently ubiquitinated. This process is mediated by the ataxia telangiectasia mutated (ATM) checkpoint kinase. NEMO and ATM can then return to the cytosol where they activate IKKβ.
Network of NF-κB interactors

**Figure 4** Network of NF-κB interactors. Evidence view of the STRING database output depicting functional and physical interactors of the NF-κB proteins, RelA, Rel (c-Rel), RelB, NFKB1 and NFKB2 obtained from: http://string-db.org/. The five NF-κB proteins are highlighted in red.
L’inflammation dans le cancer bronchique
<table>
<thead>
<tr>
<th>Author</th>
<th>Study Size</th>
<th>Immune Cell Subtype Studied</th>
<th>TNM Stage</th>
<th>Histological Subtypes</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al.(^{48})</td>
<td>30</td>
<td>T lymphocytes, plasma cells, neutrophils,</td>
<td>III</td>
<td>Sq, Ad, LC</td>
<td>Increased stromal lymphocyte count associated with improved survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>macrophages</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tormanen-Napankangas et al.(^{62})</td>
<td>84</td>
<td>CD3(^+$) and CD8(^+$) T lymphocytes, B lymphocytes, macrophages</td>
<td>Not defined</td>
<td>Sq, Ad, LC</td>
<td>Increased intratumoral infiltration by CD3(^+$) and CD8(^+$) T lymphocytes and B lymphocytes associated with tumor cell apoptosis but not prognosis</td>
</tr>
<tr>
<td>Johnson et al.(^{64})</td>
<td>95</td>
<td>CD3(^+$) and CD8(^+$) T lymphocytes, B lymphocytes, NK cells, macrophages, Langerhans cells</td>
<td>I–III</td>
<td>Nonspecified NSCLC (97%), SCLC (3%)</td>
<td>Improved prognosis in subgroup with higher intratumoral infiltration of CD3(^+$) T lymphocytes and S100(^+$) Langerhans cells</td>
</tr>
<tr>
<td>Trojan et al.(^{65})</td>
<td>31</td>
<td>CD8(^+$) T lymphocytes</td>
<td>I–III</td>
<td>Sq, Ad, LC</td>
<td>No relationship between intratumoral lymphocyte infiltration and prognosis</td>
</tr>
<tr>
<td>Kawai et al.(^{66})</td>
<td>199</td>
<td>CD8(^+$) T lymphocytes, macrophages, mast cells</td>
<td>IV</td>
<td>Sq, Ad, undifferentiated NSCLC</td>
<td>Improved median survival times in patients with high intratumoral macrophages and CD8(^+$) T lymphocytes treated with adjuvant chemotherapy</td>
</tr>
<tr>
<td>Al-Shibli et al.(^{67})</td>
<td>335</td>
<td>CD4(^+$) and CD8(^+$) T lymphocytes, CD20(^+$) B lymphocytes</td>
<td>I–IIIA</td>
<td>Sq, Ad, LC</td>
<td>High intratumoral CD4(^+$) and CD8(^+$) lymphocyte numbers an independent prognostic factor</td>
</tr>
<tr>
<td>Hiraoka et al.(^{68})</td>
<td>109</td>
<td>CD4(^+$) and CD8(^+$) T lymphocytes</td>
<td>I–IIIA</td>
<td>Sq, Ad, LC, AS, carcinosarcoma(^{a})</td>
<td>High conjoint CD4(^+$) and CD8(^+$) T lymphocyte stromal infiltration a favorable prognostic factor</td>
</tr>
<tr>
<td>Study</td>
<td>Count</td>
<td>Cell Type</td>
<td>Stage</td>
<td>Histology</td>
<td>Comments</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------</td>
<td>------------------------------------</td>
<td>-------</td>
<td>-----------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Wakabayashi et al.⁶⁹</td>
<td>178</td>
<td>CD4⁺ and CD8⁺ T lymphocytes</td>
<td>I–IIIA</td>
<td>Sq, Ad</td>
<td>Higher CD8⁺ T lymphocyte intratumoral counts associated with shorter 5-yr survival. Increased intratumoral CD4⁺ T lymphocyte counts a favorable prognostic marker.</td>
</tr>
<tr>
<td>Petersen et al.⁸³</td>
<td>64</td>
<td>CD3⁺ and Foxp3⁺ T lymphocytes</td>
<td>I</td>
<td>Ad, Sq, “other”</td>
<td>Higher risk of disease recurrence with high intratumoral regulatory:total T-lymphocyte ratio.</td>
</tr>
<tr>
<td>Kerr et al.⁸⁹</td>
<td>95</td>
<td>CD3⁺ and CD8⁺ T lymphocytes, CD79⁺ B lymphocytes, NK cells, macrophages, Langerhans cells</td>
<td>I–III⁺</td>
<td>Sq, Ad, AS, LC, SCLC, Car</td>
<td>Increased CD3⁺ T lymphocytes, macrophages (in tumor islets only) and CD4:CD8 ratio in tumors showing histological appearances akin to regressing malignant melanoma.</td>
</tr>
<tr>
<td>Takanami et al.⁹⁰</td>
<td>150</td>
<td>NK cells</td>
<td>I–IIIA</td>
<td>Ad</td>
<td>NK cell infiltration (predominantly found in stromal regions) a prognostic factor in univariate analysis only.</td>
</tr>
<tr>
<td>Villegas et al.⁹¹</td>
<td>50</td>
<td>NK cells</td>
<td>I–IIIA</td>
<td>Sq</td>
<td>Low numbers of intratumoral NK cells associated with increased risk of death.</td>
</tr>
<tr>
<td>Welsh et al.⁴⁹</td>
<td>175</td>
<td>Macrophages, mast cells</td>
<td>I–IV</td>
<td>Ad, Sq, “other”</td>
<td>High tumor islet/stromal macrophage and tumor islet/stromal mast ratios independent favorable prognostic indicators.</td>
</tr>
<tr>
<td>Ohri et al.⁴⁰</td>
<td>40</td>
<td>Macrophages</td>
<td></td>
<td>Sq, Ad, LC, “other”</td>
<td>Tumor islets macrophages in patients with increased 5-yr survival predominantly show a cytotoxic M1 phenotype.</td>
</tr>
<tr>
<td>Kim et al.⁴⁰</td>
<td>144</td>
<td>Macrophages</td>
<td>I–IV</td>
<td>Sq, Ad, AS, LC</td>
<td>High tumor islet macrophage count independent predictor of improved 5-yr survival.</td>
</tr>
<tr>
<td>Takanami et al.⁴⁰³</td>
<td>113</td>
<td>Macrophages</td>
<td>I–IV</td>
<td>Ad</td>
<td>Greater macrophage infiltration associated with increased microvessel density and worse prognosis; macrophages predominantly identified in stroma.</td>
</tr>
<tr>
<td>Zeni et al.⁴⁰⁴</td>
<td>50</td>
<td>Macrophages</td>
<td>I–IV</td>
<td>Sq, Ad</td>
<td>Increased IL-10 expression by tumor islet macrophages associated with shorter survival.</td>
</tr>
<tr>
<td>Imada et al.¹²²</td>
<td>85</td>
<td>Mast cells</td>
<td>I</td>
<td>Sq, Ad</td>
<td>Stromal mast cells correlate with angiogenesis assessed by microvessel counts and poor outcome.</td>
</tr>
<tr>
<td>Tomita et al.¹²⁵</td>
<td>90</td>
<td>Mast cells</td>
<td>I–IV</td>
<td>Ad</td>
<td>Increased overall mast cell infiltration associated with improved 5-yr survival rates postsurgery.</td>
</tr>
</tbody>
</table>
Le système immunitaire dans le cancer bronchique

The Role of Tumor-Infiltrating Immune Cells and Chronic Inflammation at the Tumor Site on Cancer Development, Progression, and Prognosis

Emphasis on Non-small Cell Lung Cancer

Roy M. Bremnes, MD, PhD,*† Khalid Al-Shibli, MD, PhD,‡§ Tom Donnem, MD, PhD,*† Rafael Sirera, PhD,‖ Samer Al-Saad, MD, PhD,†‖ Sigve Andersen, MD,*† Helge Stenvold, MD,*† Carlos Camps, MD, PhD,# and Lill-Tove Busund, MD, PhD‡‖

(J Thorac Oncol. 2011;6: 824–833)
FIGURE 2. Integration of immunoediting and oncogenesis during cancer progression. Oncogenesis leads to transformed cells, which are attacked by immune cells due to neoantigen presentation. This immune surveillance imposes a selection for transformed cells that acquire tactics to escape control. Their genetic instability facilitates evolution of strategies for immune evasion or suppression, which may tilt the tumor microenvironment from hostile to supportive for the transformed cells. At one point, a state of equilibrium may be achieved, corresponding to a clinically occult dormant disease. Further iteration of evasion mechanisms may ultimately drive immune suppression beyond the local microenvironment, accomplishing immune escape and in this manner licensing invasive and metastatic behavior. Adapted from Oncogene.30
FIGURE 1. Schematic presentation of the interplay between innate and adaptive immunity. NK T cells and γδ T cells play their roles in the crossroad between the innate and adaptive immune system. The crosstalk between these immune systems is mediated by complex interactions between cells of both immune subsets and their soluble factors. The innate immune system, i.e., the first line of immune defense, regulates adaptive immune responses by the production of cytokines, interactions between dendritic cells and lymphocytes, and activation of the complement system. The adaptive immune system modulates innate immune responses by cytokine and antibody production. Adapted from Cancer Immunol Immunother. DCs, dendritic cells; NK, natural killer; NT T cells, natural killer T cells.
<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Functions in the Tumor Microenvironment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAM</td>
<td>Classically activated macrophages (M1) contribute to tumor rejection, whereas alternatively activated macrophages (M2) promote angiogenesis and tissue remodeling. TAMs, sharing M2 characteristics, are tumor promoting and associated with poor prognosis.</td>
<td>55–57, 64–66</td>
</tr>
<tr>
<td>MDSC</td>
<td>Increased in almost all patients with cancer. Suppressive effect with respect to T cells.</td>
<td>28, 57, 58</td>
</tr>
<tr>
<td>MSC</td>
<td>Infiltrate different human cancers. In animal models, they increase cancer cell dissemination. Also found to be immunosuppressive, in part through inhibition of T-cell proliferation.</td>
<td>71–74</td>
</tr>
<tr>
<td>Mast cell</td>
<td>Important for generating and maintaining innate and adaptive immune responses. Increased numbers of mast cells correlate in some cases with poor prognosis. Have been implicated in angiogenic switch in animal models.</td>
<td>57, 60</td>
</tr>
<tr>
<td>TEM</td>
<td>Implicated in angiogenesis in animal models. Have been detected in human tumors and at low frequency in the peripheral blood of cancer patients.</td>
<td>57, 61, 62</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>Neutrophil levels are increased in patients with colon, gastric, and lung cancer. Increased neutrophil numbers are associated with poor prognosis in bronchoalveolar carcinoma. Neutrophils have been associated with angiogenesis and metastasis in animal models.</td>
<td>57, 87</td>
</tr>
<tr>
<td>NK cell</td>
<td>Effector lymphocytes of the innate immune system. Are cytotoxic to cancer cells. Important role in immunosurveillance of cancer.</td>
<td>13, 80, 81</td>
</tr>
<tr>
<td>NK T Cell</td>
<td>T cells cytotoxic to cancer cells and contribute to immunosurveillance of cancer. Type 2 NK T cells have been reported to down-regulate tumor immunosurveillance and suppress antitumor responses.</td>
<td>29, 84, 85</td>
</tr>
<tr>
<td>T helper cells</td>
<td>CD4+ T helper cells aid CD8+ T cells in tumor rejection.</td>
<td>2, 28, 87</td>
</tr>
<tr>
<td>Cytotoxic T cells</td>
<td>CTLs are effector cells of adaptive immunity and specifically recognize and destroy cancer cells.</td>
<td>2, 87, 90</td>
</tr>
<tr>
<td>Regulatory T cells</td>
<td>Treg cells are CD4+ lymphocytes, characterized by presenting the phenotype CD25+CD127-Foxp3+. Treg cells are a subset of T cells with the ability to suppress harmful immunological reactions to self- and foreign antigens and have also been attributed to polarize immunity away from an antitumor response, block CD8+ T cell activation and NK cell killing.</td>
<td>2, 28, 86, 88, 90, 106</td>
</tr>
<tr>
<td>B cell</td>
<td>B lymphocytes are essential mediators of the adaptive immune system, but in an animal model of squamous cell carcinoma, it was demonstrated to promote malignancy.</td>
<td>44, 87</td>
</tr>
</tbody>
</table>

**Notes:** CTL, CD8+ cytotoxic T cells; MDSC, myeloid-derived suppressor cells; MSC, mesenchymal stem cells; NK cells, natural killer cells; NK T cells, natural killer T lymphocytes; TAM, tumor-associated macrophage; TEM, TIE2-expressing monocyte; TIE2, angiopoietin receptor; Treg cells, regulatory T cells.
Abstract

Tumor-associated immune responses have polarized effects in regulating tumor growth. Although a clear association has been shown between the tumor immune response and clinical outcome in colorectal and ovarian cancers, the role of immune markers for stratifying prognosis in non–small cell lung cancer (NSCLC) is less defined. Herein, we review the prognostic significance of published immune markers in the tumor microenvironment and peripheral blood of NSCLC patients. To identify prognostic immune genes, we reviewed all published gene-profiling studies in NSCLC and delineated the significance of immune genes by doing subanalysis on the microarray database of the NIH Director’s Challenge study. This first comprehensive review of prognostic immune markers provides a foundation for further investigating immune responses in NSCLC. Clin Cancer Res; 17(16); 5247–56. ©2011 AACR.
<table>
<thead>
<tr>
<th>Role</th>
<th>Author</th>
<th>No. points</th>
<th>Stages</th>
<th>Observation and/or conclusion</th>
<th>Survival advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIL</td>
<td>Johnson et al. (7)</td>
<td>95</td>
<td>I, 54 (57%)</td>
<td>High CD3+ and S100+ in tumor correlated with longer OS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>II, 17 (18%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>III, 20 (21%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hiraoka et al. (9)</td>
<td>109</td>
<td>I, 67 (61%)</td>
<td>Concurrent high CD4+ and CD8+ in stroma correlated with longer survival</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>II-III, 42 (39%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kikuchi et al. (10)</td>
<td>161</td>
<td>I, 95 (59%)</td>
<td>HLA class I expression correlates with longer OS in stage I</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>II-IV, 66 (41%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ruffini et al. (15)</td>
<td>1,290</td>
<td>I, 714 (55%)</td>
<td>TIL (mostly CD8+) in tumor correlated with better OS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>II, 265 (21%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IIIA, 214 (17%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wakabayashi et al. (16)</td>
<td>178</td>
<td>I, 107 (60%)</td>
<td>High CD4+ in stroma correlated with longer OS</td>
<td>5-year OS 64% versus 43%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>II, 23 (13%)</td>
<td>High CD8+ in tumor correlated with shorter OS</td>
<td>5-year OS 47% versus 60%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IIIA, 48 (27%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Al-Shibli et al. (17)</td>
<td>335</td>
<td>I, 212 (63%)</td>
<td>High CD4+ in stroma correlated with longer DSS</td>
<td>5-year DSS 63% versus 42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>II, 91 (27%)</td>
<td>High CD8+ in stroma correlated with longer DSS</td>
<td>5-year DSS 75% versus 53%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IIIA, 32 (10%)</td>
<td></td>
<td>5-year DSS 61% versus 32%</td>
</tr>
<tr>
<td></td>
<td>Pelletier et al. (18)</td>
<td>113</td>
<td>I, 66 (58%)</td>
<td>Peritumoral CD20+ correlated with longer survival</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>II, 20 (18%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>III, 29 (26%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Stage Distribution</td>
<td>Findings</td>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
<td>--------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Ti-BALT Dieu-Nosjean et al. (19)</td>
<td>74</td>
<td>I, 62 (84%)</td>
<td>High mature DCs in tertiary lymphoid structures correlated with longer survival</td>
<td>4-year DFS 88% versus 51%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IIA, 12 (16%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treg Shimizu et al. (20)</td>
<td>100</td>
<td>I, 68 (68%)</td>
<td>High FoxP3+ correlated with shorter time to recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>II, 14 (14%)</td>
<td>COX-2 expression correlated with shorter time to recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>III, 18 (18%)</td>
<td>COX-2 expression correlated with FoxP3+ infiltration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petersen et al. (23)</td>
<td>64</td>
<td>I, 64</td>
<td>High proportion of FoxP3+ among TIL in tumor correlated with shorter DFS</td>
<td>Median DSS of 53 months, 63 months, and &gt;72 months for high, intermediate, and low risk group</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAM Chen et al. (25)</td>
<td>35</td>
<td>I, 14 (40%)</td>
<td>TAM in stroma correlated with shorter OS</td>
<td>Median OS 16 months versus 45 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>II, 4 (11%)</td>
<td>TAM-tumor interaction upregulated IL-8 mRNA expression</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>III, 17 (49%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role</td>
<td>Author</td>
<td>No. points</td>
<td>Stages</td>
<td>Observation and/or conclusion</td>
<td>Survival advantage</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------</td>
<td>------------</td>
<td>------------</td>
<td>---------------------------------------------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Zeni et al. (26)</td>
<td>47</td>
<td>I, 24 (51%)</td>
<td>IL-10 high TAMs associated with shorter OS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>II–IV, 23 (49%)</td>
<td>IL-10 high TAMs associated with advanced stage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ho et al. (27)</td>
<td>68</td>
<td>I, 24 (35%)</td>
<td>Increased high TREM-1 macrophages correlated with shorter DFS and OS</td>
<td>Median DFS 22 months versus not reached</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>II, 15 (22%)</td>
<td></td>
<td>Median OS 29 months versus not reached</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>III, 29 (43%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kim et al. (28)</td>
<td>144</td>
<td>I, 79 (55%)</td>
<td>TAM in tumor correlated with longer OS</td>
<td>5-year OS 64% versus 39%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>II, 25 (17%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>III, 38 (26%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Welsh et al. (29)</td>
<td>175</td>
<td>I, 79 (45%)</td>
<td></td>
<td>5-year OS of 53% versus 8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>II, 44 (25%)</td>
<td>High TAM in tumor correlated with longer OS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ohri et al. (32)</td>
<td>40</td>
<td>I, 26 (65%)</td>
<td>Increased M1 in long survivors</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>II, 8 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>III, 6 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ohtaki et al. (33)</td>
<td>170</td>
<td>IA, 95 (56%)</td>
<td>High stromal CD204+ (M2) associated with shorter survival</td>
<td>5-year OS of 61% versus 89%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IB–IIIA, 75 (44%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. Prognostic immune markers in NSCLC. T cells and B cells are associated with longer survival when found in the stroma along with Ti-BALT, which contains Lamp+ DCs. In contrast, FoxP3+ Tregs in the tumor are associated with shorter survival. Antitumor M1 macrophages are characterized by HLA-DR, INOS, MRP, and TNF-α. Protumor M2 macrophages express CD204. M2 expression of IL-8, IL-10, and TREM-1 (delineated by arrows) has been shown to correlate with shorter survival. Tumoral expression of COX-2 recruits FoxP3+ Treg cells, whereas expression of IL-10 and MCP-1 recruits M2 macrophages. In the peripheral blood, immune suppression is associated with poor clinical outcomes revealed by low total lymphocyte counts (TLC) and elevated NLRs.
Réponse immunitaire dans les cancers bronchopulmonaires

A.-P. Meert\(^1,2\), T. Berghmans\(^1\), C. Mascaux\(^1\), J.-P. Sculier\(^1\)

Résumé

Introduction: La réponse immunitaire antitumorale est essentiellement de type cellulaire et de nombreuses recherches sont conduites afin d’augmenter celle-ci, à voirie thérapeutique.

État des connaissances: Une activation du système immunitaire a été tapotée dans des études pilotes de cancer bronchique. Par contre, de nombreux essais ont montré un certain degré d’immunosuppression chez les patients porteurs d’une maladie cancéreuse avancée, principalement à tout traitement immuno-suppressif et, plus particulièrement, une abolition de leur immunité cellulaire. La présence d’un infiltrat lymphocytaire est un indicateur d’une réponse active de l’Hôte contre la tumeur. Pleurésie synchrone pathologique, l’existence d’auto-anticorps, cette année-ci, plus particulièrement en cas de cancer bronchique à petites cellules. D’autres anticorps, non associés à des syndromes pathologiques, ont été ainsi mis en évidence, principalement dirigés contre le gène suppresseur du tumour p53. L’immunothérapie active non spécifique (bacille de Calmette-Guerin, interféron, interleukines...) immunothérapie passives (anticorps monoclonaux) et l’immunothérapie adaptée sont étudiées depuis de nombreuses années avec des résultats peu satisfaisants. L’immunothérapie active spécifique (vacination antitumorale et thérapie génique) ont à l’heure actuelle la voie la plus étudiée.

Perspectives: L’ibadage corrigé des patients acceptant du bénéfice de traitements immunomodulateurs, la spécificité et l’efficacité des vecteurs, l’expression des gènes tumorigènes et le risque d’infection et de dissémination lors des essais cliniques sont des problèmes en cours d’investigation.

Conclusions: Des manipulations de la réponse immunitaire ont été et sont réalisées afin d’en améliorer l’efficacité. La vaccination anti-tumorale et la thérapie génique sont les voies les plus étudiées.

Mots-clés: Cancer bronchopulmonaire + Immunité + Immunothérapie + Vaccination + Anti-corps.
Fig. 1.
Schéma général de l’immunité antitumorale. Les lymphocytes T CD8 sont activés par la liaison de leur récepteur (RTC) avec le complexe molécule d’histocompatibilité (CMH) de classe 1 en association avec les peptides endogènes (par exemple tumoraux), préalablement endocytés par les cellules présentatrices d’antigène. Les lymphocytes T CD4 sont activés par la liaison de leur RTC avec le CMH de classe 2 en association avec les peptides exogènes et sécrètent ensuite des cytokines qui activent non seulement les lymphocytes B, mais également des cellules à potentiel cytolytique antitumoral (les macrophages, les lymphocytes T CD8 (CTL), les neutrophiles activés et les cellules « natural killer » (NK)). Un cinquième type d’acteur de la lyse tumorale, les lymphocytes activés « killer » ou LAK, sont activés par la sécrétion d’IL2 par les lymphocytes T CD8.
New Strategies in Lung Cancer: Translating Immunotherapy into Clinical Practice

Patrick M. Forde, Ronan J. Kelly, and Julie R. Brahmer

Abstract

Recent breakthroughs in translating the early development of immunomodulatory antibodies into the clinic, notably with the anti-cytotoxic T-lymphocyte antigen-4 antibody, ipilimumab, have led to durable benefits and prolonged survival for a subgroup of patients with advanced melanoma. Subsequent studies have shown that related immune checkpoint antibodies, specifically those targeting the programmed death-1 pathway, have activity in non-small cell lung cancer. Non-small cell lung cancer is the commonest cause of cancer death worldwide and this exciting avenue of clinical investigation carries with it great promise and new challenges. In this article, we discuss recent developments in lung cancer immunotherapy, reviewing recent findings from therapeutic vaccine studies and in particular we focus on the refinement of immunomodulation as a therapeutic strategy in this challenging disease. Clin Cancer Res; 20(5); 1067–73. ©2014 AACR.
Figure 1. Selected immune checkpoints for which modulating molecules are in late preclinical or clinical development. B7RP1, B7-related protein-1; ICOS, inducible T-cell costimulator; KIR, killer cell immunoglobulin-like receptor; LAG3, lymphocyte-activation gene 3; GAL9, galectin-9; TIM3, T-cell immunoglobulin domain and mucin domain 3; OX40L, OX40 ligand.