original article

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# Insulin-like growth factor receptor 1 (IGF1R) expression and survival in surgically resected non-small-cell lung cancer (NSCLC) patients

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**Background:** The purpose of this study is to investigate the prognostic role of insulin-like growth factor receptor 1 (IGF1R) expression in surgically resected non-small-cell lung cancer (NSCLC).

**Patient characteristics and methods:** This retrospective study was conducted in 369 stage I–II–IIIA, surgically resected, NSCLC patients. Patients exposed to anti-epidermal growth factor receptor (EGFR) agents were excluded. IGF1R expression was evaluated by immunohistochemistry in tissue microarray sections.

**Results:** A positive IGF1R expression (score ≥ 100) was observed in 282 cases (76.4%) and was significantly associated with squamous cell histology ($P = 0.04$) and with grade III differentiation ($P = 0.02$). No difference in survival was observed between the positive and negative group when score 100 was used as cut-off for discriminating a positive versus a negative IGF1R result (52 versus 48 months, $P = 0.99$) or when median value of IGF1R expression was used (45 versus 55 months, $P = 0.36$). No difference in survival was observed between IGF1R-positive and -negative patients in a subgroup of stage I–II adenocarcinoma ($n = 137$) with known EGFR mutation and copy number status.

**Conclusions:** IGF1R expression does not represent a prognostic factor in resected NSCLC patients. Patients with squamous cell carcinoma overexpress IGF1R more frequently than patients with nonsquamous histology, justifying the different sensitivity to anti-IGF1R agents observed in clinical trials.

**Key words:** EGFR, IGF1R, non-small-cell lung cancer, prognosis

original article

## introduction

In 2008, non-small-cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths worldwide [1]. Prognosis for patients diagnosed with advanced NSCLC continues to be dismal and distant metastases develop in up to 70% of patients with early-stage disease, despite complete tumor resection, leading to a 5-year survival rate of ∼40% [2]. Recent discoveries in the field of lung cancer biology led to the clinical development of new drugs able to interfere with tumor cell proliferation. Among such agents, the mAb bevacizumab and drugs targeting the epidermal growth factor receptor (EGFR) demonstrated to significantly improve survival of NSCLC patients with advanced disease when used in combination with chemotherapy [3, 4] or as single agent [5].

The insulin-like growth factor receptor 1 (IGF1R) is a transmembrane heterotetrameric protein encoded by a gene located on chromosome 15q26.3 implicated in promoting oncogenic transformation, growth and survival of cancer cells [6–9]. IGF1R activation triggers a cascade of reactions involving two signal transduction pathways [10, 11]: one activates Ras, Raf and mitogen-activated protein kinase and the other involves phosphoinositol-3-kinase (PI3K). Agents targeting IGF1R demonstrated promising activity against metastatic NSCLC when used in combination with chemotherapy, particularly in patients with squamous cell histology [12]. Preclinical models showed that IGF1R expression could be implicated in acquired resistance to anti-EGFR strategies [13, 14]. Chakravarti et al. [13] demonstrated that IGF1R can compensate for loss of EGFR function in primary glioma cell lines. In breast and prostate cancer cells, Jones et al. [14] showed that increased signaling via the IGF1R pathway leads to acquired resistance to the EGFR tyrosine kinase inhibitor gefitinib. In two previous studies, we

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evaluated whether IGF1R expression and gene copy number affected response to gefitinib or cetuximab in NSCLC and colorectal cancer, respectively [15, 16]. Although both studies demonstrate no association of IGF1R gene copy number or protein expression with response to anti-EGFR agents, patients overexpressing IGF1R had significantly longer survival than individuals lacking the protein. These findings raised the question whether IGF1R expression represented a prognostic rather than a favorable predictive factor for survival in NSCLC and colorectal cancer patients exposed to anti-EGFR drugs. The prognostic role of IGF1R has been previously investigated in human malignancies including NSCLC, leading to conflicting results [17–19]. In NSCLC, a previous study showed a nonsignificant shorter survival for IGF1R-overexpressing patients compared with individuals with low or absent IGF1R expression [19], indicating that IGF1R expression represents a negative prognostic factor.

The conflicting available data and the growing interest on anti-IGF1R agents support the present study aimed to investigate the prognostic significance of IGF1R expression in NSCLC.

## patient characteristics and methods

### cohort

The present study was conducted retrospectively in a cohort of early-stage (I–IIIA) NSCLC patients who received radical resection of a primary NSCLC at the Istituto Clinico Humanitas IRCCS, Rozzano, Italy, from 2000 to 2004. Selection criteria included availability of tumor tissue from primary lung cancer, pathologically confirmed stage I, II or IIIA and survival data. In order to avoid any confounding effect of postsurgery chemotherapy, we restricted our observation to patients who received surgery before adjuvant chemotherapy became a standard approach. Moreover, patients exposed to anti-EGFR agents at relapse were excluded. The study was approved by the local ethics committee and was conducted in accordance with ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice, whichever represented the greater protection to the individuals.

### tissue microarray, antibody and immunohistochemistry

Paraffin-embedded tumor specimens were used to construct a tissue microarray with 600-um diameter cores. Each patient was represented by three tissue cores. An adhesive-coated tape system (Instrumedics, Hackensack, NJ) was used for sectioning the tumor array blocks at 4 μm. Sections were stained with antibodies against IGF1R (Novus Biologicals, Littleton, CO) according to the manufacturers' recommended protocols. Immunohistochemical (IHC) staining was carried out at the Pathology Department of the Bellaria Hospital and slides were interpreted independently by three observers at the University of Colorado Cancer Center (WAF, GF and RSW) who were blinded to all patient information. Images were obtained by using the digitizing pathology system APERIO (Aperio Technology Inc., Vista, CA).

A semiquantitative approach was used to generate a score for each tissue core. The percentage of positive cells per core (from 0% to 100%) was multiplied by the dominant intensity pattern of staining, considering 1 as negative or trace, 2 as weak, 3 as moderate and 4 as strong. Therefore, the overall score ranged from 0 to 400. When heterogeneous results were detected among the three tested cores, the mean value was used to represent the patient in the statistical analyses. Based on our previously published classification [15, 16], an IGF1R protein expression below 100 qualified the patient as negative (IGF1R−), while a score ≥100 qualified the sample as positive (IGF1R+). Analysis was also carried out using median value as the cut-off.

### statistical analyses

The objective of the study was to assess whether IGF1R expression affected survival of surgically resected NSCLC patients. Overall survival (OS), calculated from the time of diagnosis to patient death or last contact, was evaluated using Kaplan–Meier method [20] and hazard ratio was calculated by using the Cox proportional hazards regression model. Associations with clinical characteristics were compared by $\chi^2$ test. OS for the groups with negative and positive biomarker was compared using the log-rank test. Statistical significance was set at $<0.05$ for each analysis. All statistical analyses were carried out using R package.

## results

### patient characteristics

A total of 369 surgically resected NSCLC patients were included in the present analysis. As shown in Table 1, the majority of patients were male (85.6%), former (52.0%) or current (36.0%) smokers, with moderately or poorly differentiated tumors (grade II and III). The median age was 66.7 years. All patients received radical surgery, with evidence of pathological stage I in 43.1%, stage II in 26.0% and stage III in 30.9%. Patients with stage III disease and pathological evidence of N2 disease ($N = 85$) received postoperative mediastinal radiotherapy. With a median follow-up of 60 months, a total of 185 patients died and median survival was 50 months. As expected, median survival was longer in stage I–II than in stage III (not reached

**Table 1.** Patient characteristics

| Characteristic | Total | % |
|---|---|---|
| Total | 369 | 100.0 |
| Median age (years; range) | 66.7 (37.4–85.1) | |
| Gender | | |
| Male | 316 | 85.6 |
| Female | 53 | 14.4 |
| Smoking history | | |
| Never | 30 | 8.2 |
| Former | 192 | 52.0 |
| Current | 133 | 36.0 |
| Unknown | 14 | 3.8 |
| Histology | | |
| Adenocarcinoma + bronchioloalveolar | 185 | 50.1 |
| Squamous cell carcinoma | 132 | 35.8 |
| Other[a] | 52 | 14.1 |
| Pathological stage | | |
| I | 159 | 43.1 |
| II | 96 | 26.0 |
| III | 114 | 30.9 |
| Grade | | |
| I | 27 | 7.3 |
| II | 205 | 55.5 |
| III | 125 | 33.9 |
| Not defined | 12 | 3.3 |

[a]Other histology included seven patients with large-cell carcinoma, 21 cases with neuroendocrine differentiation, eight undifferentiated NSCLC and 16 not specified NSCLC.
NSCLC, non-small-cell lung cancer.

versus 21 months, $P < 0.001$). No significant difference in survival was observed according to gender, smoking history, histology or grading.

## IGF1R results

Median IGF1R expression score was 133.3. A positive expression (score ≥ 100) was observed in 282 cases (76.4%), while 87 patients (23.6%) had very low or no IGF1R expression. Interestingly, a positive IGF1R score was significantly associated with squamous cell histology ($P = 0.04$) and with grade III differentiation ($P = 0.02$), with no significant association with any other clinical characteristic, including gender, histology, smoking status and stage, as presented in Table 2. As illustrated in Figure 1, no difference in survival was observed between the positive and negative group (52 versus 48 months, $P = 0.99$). Table 3 reports survival results in IGF1R-positive and -negative patients according to clinical characteristics, and no difference in survival was observed in any subgroup. In order to investigate whether a different cut-off could better discriminate populations with different survival outcome, we analyzed patient survival using the median IGF1R expression as cut-off value. As illustrated in Figure 2, median survival was no different in patients with IGF1R

**Table 2.** IGF1R expression and association with clinical characteristics

| Characteristic | IGF1R+ (*N*/%) | IGF1R− (*N*/%) | *P* value |
|---|---|---|---|
| All | 282/76.4 | 87/23.6 | |
| Female | 38/71.7 | 15/28.3 | 0.38 |
| Male | 244/77.2 | 72/22.8 | |
| Never smokers | 21/70.0 | 9/30.0 | 0.44 |
| Smokers (former + current) | 248/76.3 | 77/23.7 | |
| Squamous cell carcinoma | 109/82.6 | 23/17.4 | 0.04 |
| Other histology | 173/73.0 | 64/27.0 | |
| Grade I–II | 168/72.4 | 64/27.6 | 0.02 |
| Grade III | 104/83.2 | 21/16.8 | |
| Stage I–II | 198/77.7 | 57/22.3 | 0.41 |
| Stage III | 84/73.7 | 30/26.3 | |

IGF1R, insulin-like growth factor receptor 1.

**Table 3.** Survival in IGF1R-positive and -negative patients according to clinical characteristics

| Characteristic | IGF1R+ (*N*/months) | IGF1R− (*N*/months) | *P* value |
|---|---|---|---|
| All | 282/52 | 87/48 | 0.99 |
| Female | 38/42 | 15/NR | 0.51 |
| Male | 244/55 | 72/46 | 0.75 |
| Never smokers | 21/42 | 9/NR | 0.78 |
| Smokers (former + current) | 248/49 | 77/46 | 0.78 |
| Adenocarcinoma + bronchioloalveolar | 133/49 | 52/44 | 0.93 |
| Squamous cell carcinoma | 109/NR | 23/48 | 0.45 |
| Other histology | 40/21 | 12/30 | 0.21 |
| Grade I–II | 168/56 | 64/49 | 1.0 |
| Grade III | 104/38 | 21/27 | 0.70 |
| Stage I–II | 198/NR | 57/NR | 0.85 |
| Stage III | 84/21 | 30/24 | 0.53 |

IGF1R, insulin-like growth factor receptor 1; NR, not reached.

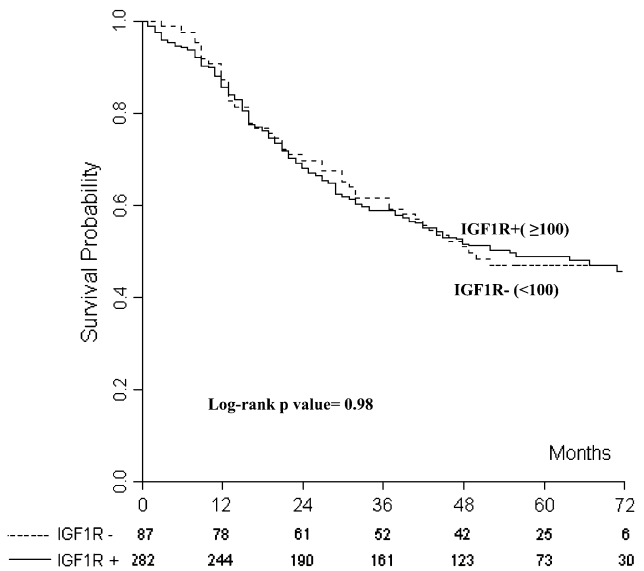


**Figure 1.** Survival in resected non-small-cell lung cancer with positive or negative IGF1R expression. In the study population, the 282 patients (76.4%) with positive IGF1R expression (score ≥ 100, IGF1R+) had a median survival of 52 months versus 48 months in the 87 patients (23.6%) with low or no IGF1R expression (<100, IGF1R−). The difference was not statistically significant (*P* value 0.98). IGF1R, insulin-like growth factor receptor 1.

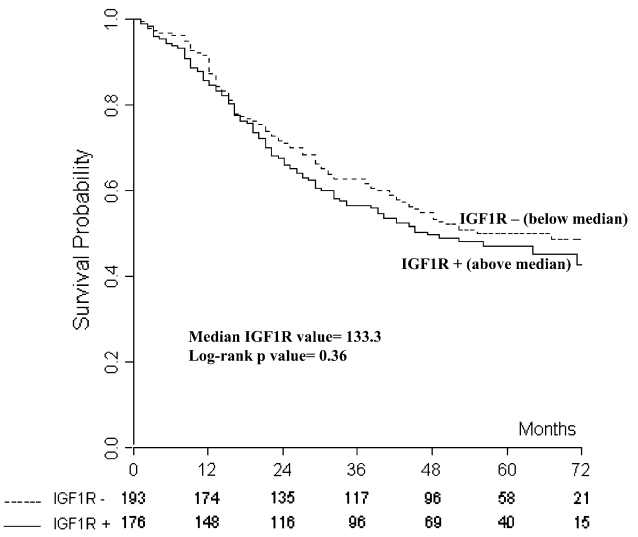


**Figure 2.** Survival of resected non-small-cell lung cancer with IGF1R expression above (IGF1R+) or below (IGF1R−) median value. Assuming as positive for IGF1R individuals with protein expression above the median score (>133.3) and as negative for patients with protein levels below the median score (≤133.3), median survival was 45 months in patients IGF1R+ and 55 months in IGF1R−. The difference was not statistically significant (*P* value 0.36). IGF1R, insulin-like growth factor receptor 1.

expression below or above the median value (55 versus 45 months, $P = 0.36$).

### IGF1R and EGFR

Because of the cross talk between IGF1R and EGFR and the potential implications of IGF1R in resistance to anti-EGFR agents [13, 14], we further investigated the role of IGF1R expression in a subgroup of 137 stage I–II adenocarcinoma patients with known *EGFR* status. All 137 patients were investigated for the presence of *EGFR* gene mutations and 111 were evaluated for *EGFR* copy number by FISH. *EGFR* resulted mutated (exon 19 or 21) in 12 cases (8.8%), and 47 patients (42.3%) resulted *EGFR* FISH positive defined according to criteria previously reported [21]. IGF1R expression was not associated with *EGFR* gene copy number ($P = 0.65$) or with the presence of *EGFR* mutations ($P = 0.23$). No difference in survival was observed in *EGFR* FISH-positive or -negative patients according to IGF1R expression, as well as in patients with or without *EGFR* mutations, as illustrated in Figure 3A–D.

## discussion

In the present study, the largest to our knowledge exploring the prognostic role of the IGF1R protein, we demonstrated that the survival outcome of early-stage, resected NSCLC patients is not different in individuals with low or high IGF1R expression.

There is an increasing interest on IGF1R in NSCLC. Several new drugs, including mAbs and tyrosine kinase inhibitors, are currently under evaluation in patients with advanced NSCLC. A recent phase II study randomly assigned 150 chemonaive NSCLC patients to the standard combination of carboplatin plus paclitaxel versus the same regimen plus CP-751,871, an anti-IGF1R mAb [12]. The study showed a significant improvement in response rate favoring the experimental arm, with an impressive 78% response rate in patients with squamous histology. The higher expression of the IGF1R protein in patients with squamous cell carcinoma compared with nonsquamous histology observed in the present report, as well as in a previous study [22], provides the biological background for the highest sensitivity to anti-IGF1R agents observed in clinical trials in this patient population.

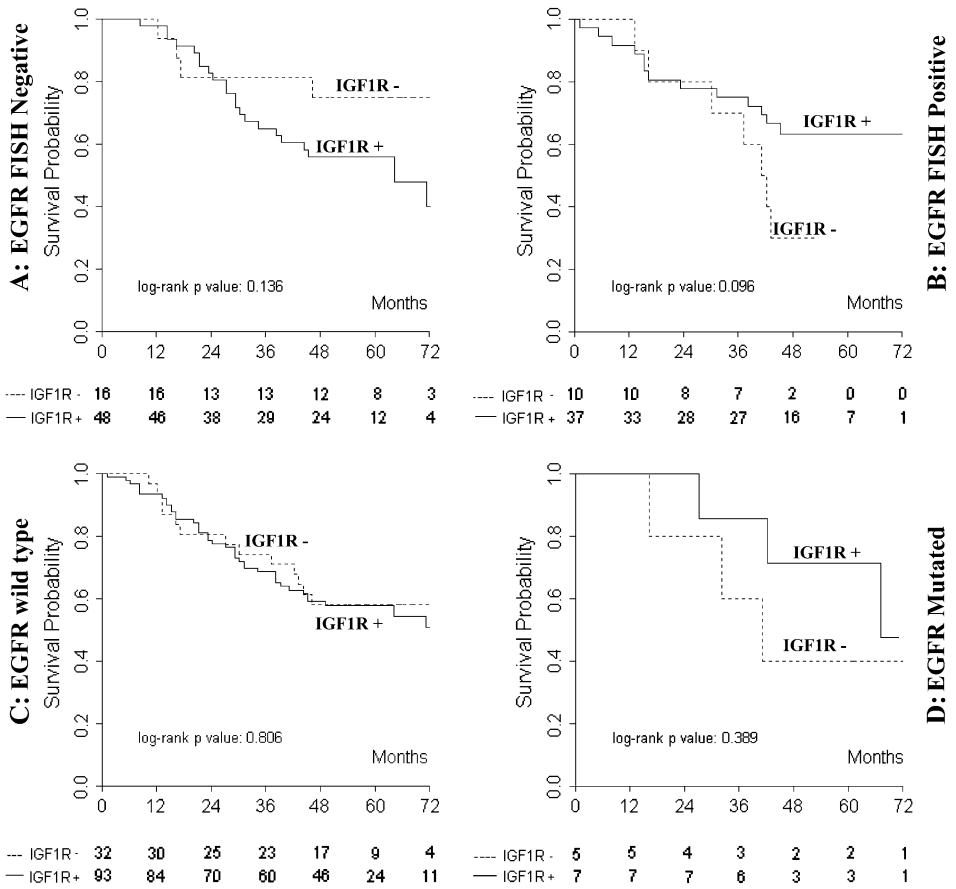


**Figure 3.** IGF1R expression and survival according to EGFR gene copy number and mutation. The panel shows patient survival in IGF1R+ (score ≥ 100) and IGF1R− (score < 100) according to presence of EGFR mutations and according to EGFR gene copy number. (A) In EGFR FISH− patients ($n = 64$, 57.7%), the difference in survival between IGF1R+ ($n = 48$) and IGF1R− ($n = 16$) was not significant (45 months versus not reached, $P$ value 0.14). (B) Among EGFR FISH+ patients ($n = 47$, 42.3%), median survival was not reached in IGF1R+ ($n = 37$) and was 41 months in IGF1R− ($n = 10$). The difference was not statistically significant ($P$ value 0.10). (C) Among EGFR wild-type patients ($n = 125$), 93 were IGF1R+ and 32 IGF1R−. Median survival was 71 months in IGF1R+ versus not reached in IGF1R−. The difference was not statistically significant ($P$ value 0.81). (D) In the small subgroup of patients with EGFR mutations ($n = 12$), median survival was 42 months in the seven patients IGF1R+ and 32 months in the five IGF1R− patients. The difference was not statistically significant ($P$ value 0.39). IGF1R, insulin-like growth factor receptor 1; EGFR, epidermal growth factor receptor.

The prognostic role of IGF1R expression in NSCLC has been previously investigated in three small retrospective studies [19, 22, 23], all using IHC for biomarker assessment. In the study conducted by Merrick et al., a total of 184 stage I–IV NSCLC were analyzed for IGF1R expression. Although patients with high IGF1R expression had shorter survival than individuals with low IGF1R levels, particularly in stage I, in the whole population the difference was not statistically significant [19]. The study conducted by Ludovini et al. [22] in 125 NSCLC patients reported no difference in survival between patients with negative or positive immunostaining. Finally, Korean investigators reported that IGF1R expression did not affect survival of 71 NSCLC patients with surgically resected stage I disease [23]. The main limitations of the above mentioned studies were the relatively small number of analyzed patients and the lack of data on anti-EGFR therapies eventually given to relapsing patients. When assessing IGF1R, the potential confounding effect of anti-EGFR strategies on patient survival could be a relevant issue since recent data indicated that individuals with high IGF1R expression benefited more from gefitinib [15, 24] or cetuximab [16] therapy. In our previous study, conducted in a small cohort of metastatic NSCLC patients treated with gefitinib, patients with high levels of IGF1R expression survived longer than individuals lacking protein expression [15]. More recently, Fidler et al. [24] showed improved efficacy with increased IGF1R expression in NSCLC patients treated with gefitinib. Why patients with high IGF1R expression should survive longer when treated with anti-EGFR agents is unclear and needs further investigation. In the present report, conducted in a large cohort of patients without the potential confounding effect of anti-EGFR strategies, we demonstrated that IGF1R expression levels have no impact on patient survival. No association with patient survival was observed irrespective of the adopted scoring system, with no linear association between IGF1R expression and duration of survival (data not shown). All together, these data, collected at the protein level using IHC staining, do not support a prognostic role for IGF1R.

In the present study, we did not investigate *Kras status* and the potential correlation with IGF1R expression. Although *Kras mutation* could be responsible for resistance to anti-IGF1R strategies, at present no data support this hypothesis.

In conclusion, this study demonstrated that IGF1R expression does not represent a prognostic factor in resected NSCLC patients. Patients with squamous cell carcinoma express IGF1R more frequently than patients with nonsquamous histology, justifying the different sensitivity to anti-IGF1R agents observed in clinical trials. Further studies should investigate the possible role of IGF1R as predictive factor for survival in individuals receiving anti-EGFR treatments.

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