Prognostic role of galectin-3 expression in patients with solid tumors: a meta-analysis of 36 eligible studies

Yi Wang†, Shiwei Liu†, Ye Tian†, Yamin Wang, Qijie Zhang, Xiang Zhou, Xianghu Meng* and Ninghong Song*

Abstract

Background: Galectin-3 as a β-galactoside-binding protein, has been found to be involved in tumor cell growth, anti-apoptosis, adhesion, angiogenesis, invasion, and distant metastases, indicating that it may play a pivotal role in cancer development and progression. However, their results remain debatable and inconclusive. Hence, this meta-analysis was performed to clarify the precise predictive value of galectin-3 in various cancers.

Methods: PubMed, Web of Science, Embase, Cochrane Library, CNKI and Wanfang databases were searched comprehensively for eligible studies up to July 15, 2018. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) of OS or DFS/PFS/RFS were calculated to demonstrate their associations.

Results: A total of 36 relevant studies were ultimately enrolled in this meta-analysis. Our results shed light on the significant association of elevated galectin-3 expression with reduced OS or DFS/RFS/PFS in overall cancer patients (pooled HR = 1.79, 95% CI 1.42–2.27, I² = 67.3%, p < 0.01; pooled HR = 1.57, 95% CI 1.04–2.37, I² = 67.1%, p = 0.001). In tumor type subgroup analysis, we found high expression of galectin-3 was correlated with shorter OS or DFS/RFS/PFS in colorectal cancer (pooled HR = 3.05, 95% CI 2.13–4.35, I² = 0.0%, p = 0.734; pooled HR = 2.49, 95% CI 1.82–3.41, I² = 0.0%, p = 0.738; respectively) and meanwhile it merely associated with reduced OS in ovarian cancer or non-small cell lung cancer (pooled HR = 2.24, 95% CI 1.38–3.64, I² = 0.0%, p = 0.910; pooled HR = 2.07, 95% CI 1.48–2.88, I² = 0.0%, p = 0.563; separately).

Conclusions: Taken together, our results suggested that galectin-3 played an oncogenic role in colorectal cancer, ovarian cancer and non-small cell lung cancer, indicating it could be a promising biomarker and a novel therapeutic target for them. Further studies were warranted to validate our findings.

Keywords: Prognostic role, Galectin-3, Cancer, Meta-analysis

Background

Galectins are a large family of widely distributed carbohydrate-binding proteins, characterized by their binding affinity for β-galactosides and conserved sequences in the binding site [1]. Meanwhile, galectins are often exhibited a high level of expression in cancer cells or cancer-associated stromal cells with the aggressiveness of tumors and the acquisition of the metastatic phenotype [2]. Because of their significant involvement in various biological functions and pathology, the role of galectins seems to be of importance [3]. Therein, galectin-3 also knew as LGALS3, L31, GAL3, MAC2, CBP35, GALBP and GALIG, belongs to the family of galectins [4]. In both extracellular and intracellular manners, galectin-3 exhibits its pleiotropic biological and molecular functions. Extracellularly, it has the ability to adjust microenvironment by means of interacting with the cell surface and extracellular matrix glycoproteins or glycolipids. Intracellularly, it was capable of modulating signaling pathways via interacting with cytoplasmic and nuclear proteins [5]. Up to now, a growing number of researches have...
suggested the involvement of galectin-3 in tumor progression and disease outcome [6–8]. Galectin-3 has been found to be differently expressed in various normal and malignant tissues. Previous studies indicated that down-regulation of galectin-3 was associated with loss of the transformed phenotypes in thyroid papillary carcinoma cells, but up-regulation of it could induce the transformed phenotype in normal thyroid follicular cell lines [9]. Accumulating data have demonstrated that different galectin-3 expression in tumor tissues was associated with unfavorable survival in cancer patients [10–14]. These studies concentrated on colorectal carcinoma, cervical carcinoma, breast cancers, gastric carcinoma, laryngeal squamous-cell carcinoma and so on. However, their results remained inconsistent. The discrepancies among these studies highlighted the importance of evaluating the prognostic significance of galectin-3 in multiple human malignant neoplasms.

Hence, this meta-analysis was conducted to clarify the relationship between galectin-3 expression and the prognosis of patients with carcinoma. Last but not least, it is the first time for us to shed light on their relationship and galectin-3 is anticipated to be a prognostic marker in clinical applications.

Materials and methods

Literature search strategy

We conducted a comprehensive search of online databases PubMed, EMBASE and Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI) and Wanfang database (Chinese) to identify relevant literature published before July 15, 2018. The search strategy was mainly consisted of the following keywords in combination with Medical Subject Headings (MeSH) terms and text words: (“cancer” or “carcinoma” or “neoplasm” or “tumor” or “tumour”) and (“galectin-3” or “GAL3” or “LGALS3” or “L31” or “MAC2” or “CBP35” or “GALBP” or “GALIG”). In addition, potentially eligible articles were identified via meticulously searching from the reference lists of relevant reviews and original literature.

Inclusion and exclusion criteria

The eligible studies needed to meet the following four inclusion criteria: (1) English or Chinese publications; (2) patients with carcinoma; (3) a relationship of galectin-3 expression with cancer prognosis; (4) sufficient data could be extracted. Additionally, the exclusion criteria included the following points: (1) non-English or non-Chinese research; (2) duplicates of the previous publication; (3) reviews or letters or case reports or comments or editorials; (4) unrelated to galectin-3 or human patients; (5) absence of key information.

Quality assessment

The following information should be extracted from included articles before being evaluated: (1) the study population and country; (2) the study design; (3) assay method to determine galectin-3 expression; (4) the prognosis or survival assessment; (5) the detected tumor and pathology information; (6) the cutoff point of galectin-3; and (7) the follow-up duration. In addition, Newcastle–Ottawa Scale (NOS), as one of the most useful scale to evaluate the quality of non-randomized studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm), was independently evaluated by two blind reviewers [15]. The criteria of quality assessment were as follows: (1) representativeness of the exposed cohort; (2) selection of the non-exposed cohort; (3) ascertainment of exposure; (4) outcome of interest not present at start of study; (5) control for important factor or additional factor; (6) assessment of outcome; (7) follow-up long enough for outcomes to occur; (8) adequacy of follow up of cohorts. Total quality score of NOS was ranged from 0 to 9, which was regarded as high quality with the final score > 6. Details were presented in Table 1.

Data extraction

All available data from the identified studies were extracted respectively by two reviewers (Y.W and SW.L). If any disagreement achieved, a third reviewer (Y.T) would join in and reached a consensus. Extracted data were recorded in a standardized form including following items: first author’s surname, publication year, patients’ median or mean age, nationality, dominant ethnicity, number of patients, investigating method, cutoff value, follow-up time, and hazard ratios (HRs) for prognostic outcomes (overall survival [OS] and disease/recurrence/progression-free survival [DFS/RFS/PFS]) along with their 95% CI and p-values. Data were extracted from Kaplan–Meier curves to extrapolate HRs with 95% CIs by using previously described methods, when it could not be directly obtained from each article [16, 17]. Details of the aforementioned data were displayed in Tables 2 and 3.

Statistical analysis

Based on available data, the relationship between galectin-3 and multiple human malignant neoplasms was conducted by OS or DFS/RFS/PFS and the pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were utilized to evaluate their efficacy. The effect of heterogeneity was quantified via $I^2 = 100\% \times (Q − df)/Q$. If significant heterogeneity ($p < 0.1$ or $I^2 > 50\%$) existed, the random-effects model (DerSimonian–Laird method) would be applied; otherwise, a fixed-effects model
(Mantel–Haenszel method) would be utilized [18]. Moreover, in the case of significant heterogeneity, subgroup analysis was carried out by the type of malignant disease and dominant ethnicity to further minimize the influence. Sensitivity analysis was conducted to access the stability of results by deleting one single study each time to reflect the impact of the individual to overall. Publication bias was evaluated by the Begg’s funnel plot and Egger linear regression test with a funnel plot [19]. If \( p < 0.05 \), it indicated the existence of publication bias. All \( p \)-values were calculated using a two-sided test and \( p < 0.05 \) was considered statistically significant. Besides, all statistical data were conducted by Stata software (version 12.0; StataCorp LP, College Station, TX) and Microsoft Excel (V.2007, Microsoft Corporation, Redmond, WA, USA).

### Table 1 Newcastle–Ottawa quality assessments scale

| Studies   | Year | Quality indicators from Newcastle–Ottawa Scale | Scores |
|-----------|------|-----------------------------------------------|--------|
|           |      | 1 2 3 4 5 6 7 8                              |        |
| Chou [20] | 2018 | ★ – ★ ★ ★ ★ ★ – ★                          | 7      |
| Lu [10]   | 2017 | ★ ★ ★ ★ ★ ★ – ★                            | 8      |
| Huang [4] | 2017 | ★ ★ ★ ★ ★ – ★                               | 7      |
| Li [11]   | 2017 | ★ ★ – ★ ★ ★ – ★                            | 7      |
| Shimura [41]| 2017| ★ ★ ★ ★ – ★ ★ ★ – ★                      | 8      |
| Wang [49] | 2017 | ★ ★ ★ ★ ★ ★ – ★                            | 7      |
| Liu [37]  | 2017 | ★ ★ ★ ★ ★ – ★                              | 7      |
| Gopalan [21]| 2016| ★ ★ ★ ★ ★ ★ – ★                          | 8      |
| Ilmer [12]| 2016 | ★ ★ – ★ ★ ★ – ★                           | 7      |
| Yang [48]| 2016 | ★ ★ ★ ★ – ★ ★ ★ – ★                      | 8      |
| Tas [36]| 2016 | ★ – ★ ★ ★ ★ ★ – ★                          | 7      |
| Cheng [40]| 2015 | ★ ★ ★ ★ – ★ ★ ★ – ★                      | 7      |
| Lu [47]| 2015 | ★ ★ – ★ ★ ★ – ★                            | 8      |
| Jiang [22]| 2014 | ★ ★ ★ ★ – ★ ★ ★ – ★                      | 8      |
| Gomes [23]| 2014 | ★ – ★ ★ ★ – ★ ★ ★ – ★                    | 8      |
| Mu [44]| 2013 | ★ ★ ★ – ★ ★ ★ – ★                           | 7      |
| Wu [45]| 2013 | ★ ★ ★ ★ – ★ ★ ★ – ★                      | 7      |
| Liu [46]| 2013 | ★ – ★ ★ ★ – ★ ★ ★ – ★                    | 6      |
| Yamaki [24]| 2012| ★ ★ ★ ★ – ★ ★ ★ – ★                      | 8      |
| Yang [25]| 2012 | ★ – ★ ★ ★ – ★ ★ ★ – ★                    | 5      |
| Kim [26]| 2012 | ★ ★ ★ ★ – ★ ★ ★ – ★                           | 7      |
| Kosacka [38]| 2011| ★ ★ ★ – ★ ★ ★ – ★                      | 6      |
| Povegliano [27]| 2010| ★ ★ ★ ★ – ★ ★ ★ – ★                          | 7      |
| Canesin [42]| 2010| ★ – ★ ★ ★ – ★ ★ ★ – ★                    | 6      |
| Vereecken [43]| 2009| ★ ★ ★ – ★ ★ ★ – ★                          | 6      |
| Miranda [28]| 2009| ★ – ★ ★ ★ – ★ ★ ★ – ★                      | 6      |
| Szoke [29]| 2007 | ★ – ★ ★ ★ – ★ ★ ★ – ★                          | 5      |
| Kang [30]| 2007 | ★ ★ ★ – ★ ★ ★ – ★                           | 7      |
| Moisa [39]| 2007 | ★ ★ ★ – ★ ★ ★ – ★                           | 6      |
| Okada [13]| 2006 | ★ ★ ★ – ★ ★ ★ – ★                           | 7      |
| Plzak [31]| 2004 | ★ ★ ★ – ★ ★ ★ – ★                           | 5      |
| Piantelli [14]| 2002| ★ ★ ★ – ★ ★ ★ – ★                          | 8      |
| Brule [32]| 2000 | ★ ★ ★ – ★ ★ ★ – ★                           | 6      |
| Honjo [33]| 2001 | ★ ★ ★ – ★ ★ ★ – ★                           | 6      |
| Nakamura [34]| 1999| ★ ★ ★ – ★ ★ ★ – ★                          | 8      |
| Sanjuan [35]| 1997| ★ – ★ ★ ★ – ★ ★ ★ – ★                      | 4      |

1. Representativeness of the exposed cohort; 2. Selection of the non-exposed cohort; 3. Ascertainment of exposure; 4. Outcome of interest not present at start of study; 5. Control for important factor or additional factor; 6. Assessment of outcome; 7. Follow-up long enough for outcomes to occur; 8. Adequacy of follow up of cohorts.
| First author | Publication year | Case nationality | Dominant ethnicity | Median or mean age | Study design | Malignant disease | Main type of pathology | Detected sample | Assay method | Survival analysis | Source of HR | Maximum months of follow-up |
|--------------|------------------|------------------|-------------------|-------------------|-------------|------------------|-------------------------|----------------|-------------|------------------|------------|--------------------------|
| Chou [20]    | 2018             | China            | Asian             | 50 R              | R           | Glioblastoma multiforme | Glioma         | Tissue           | ihc            | OS/PFS     | Reported                  | 207        |
| Lu [10]      | 2017             | China            | Asian             | 60 R              | R           | Colorectal cancer     | AdenoCa        | Tissue           | ihc            | OS         | SC                       | 40         |
| Huang [4]    | 2017             | China            | Asian             | 60 R              | R           | Colorectal cancer     | AdenoCa        | Tissue           | ihc            | OS         | Reported                  | 50         |
| Li [11]      | 2017             | China            | Asian             | 40 R              | R           | Cervical carcinoma    | SqCa           | Tissue           | ihc            | OS         | Reported                  | 78         |
| Shimura a [41] | 2017           | Japan            | Asian             | 55 R              | R           | Biliary cancer        | AdenoCa        | Serum ELISA      | OS             | Reported   | 69.9                     |
| Shimura b [41] | 2017             | Japan            | Asian             | 55 R              | R           | Pancreatic cancer     | AdenoCa        | Serum ELISA      | OS             | Reported   | 66                       |
| Wang [49]    | 2017             | China            | Asian             | NM R              | R           | Ovarian cancer        | SqCa           | Tissue           | ihc            | OS         | Reported                  | 72         |
| Liu [37]     | 2017             | China            | Asian             | 65.1 R            | R           | Colorectal cancer     | AdenoCa        | Tissue           | ihc            | OS         | SC                       | 60         |
| Gopalan [21] | 2016             | Australia        | Caucasian         | 60 R              | R           | Colorectal cancer     | AdenoCa        | Tissue           | ihc            | OS         | SC                       | 110        |
| Ilmer [12]   | 2016             | American         | Caucasian         | 47 R              | R           | Breast cancer         | AdenoCa        | Tissue           | ihc            | OS         | SC                       | 232        |
| Yang [48]    | 2016             | China            | Asian             | 66.8 R            | R           | Colorectal cancer     | AdenoCa        | Tissue           | ihc            |DFS         | Reported                  | 60         |
| Tas [36]     | 2016             | Turkey           | Caucasian         | 59.5 R            | R           | Gastric cancer        | AdenoCa        | Serum ELISA      | OS             | SC         | 97                       |
| Cheng [40]   | 2015             | China            | Asian             | 55.2 R            | R           | Gastric cancer        | AdenoCa        | Serum ELISA      | OS             | SC         | 60                       |
| Lu [47]      | 2015             | China            | Asian             | 51 R              | R           | Ovarian cancer        | SqCa           | Tissue           | ihc            | OS         | Reported                  | 77         |
| Jiang [22]   | 2014             | China            | Asian             | 50 R              | R           | Hepatocellular carcinoma | AdenoCa       | Tissue           | ihc            | OS         | Reported                  | 87         |
| Gomes [23]   | 2014             | Brazil           | Caucasian         | 50 R              | R           | Gastric cancer        | AdenoCa        | Tissue           | ihc            | OS         | SC                       | 55         |
| Mu [44]      | 2013             | China            | Asian             | 66 R              | R           | Gastric cancer        | AdenoCa        | Tissue           | ihc            | OS         | Reported                  | NM         |
| Wu [45]      | 2013             | China            | Asian             | 59.6 R            | R           | Non-small cell lung cancer | SqCa         | Tissue           | ihc            | OS         | Reported                  | 90         |
| Liu [46]     | 2013             | China            | Asian             | 57.1 R            | R           | Non-small cell lung cancer | SqCa         | Tissue           | ihc            | OS         | SC                       | 80         |
| Yamaki [24]  | 2012             | Japan            | Asian             | 53 R              | R           | Breast cancer         | AdenoCa        | Tissue           | ihc            | OS/PFS     | SC                       | 13         |
| Yang [25]    | 2012             | China            | Asian             | 45 R              | R           | Gallbladder carcinoma | AdenoCa        | Tissue           | ihc            | OS         | SC                       | 18         |
| Kim [26]     | 2012             | Korea            | Asian             | 60 R              | R           | Gastric cancer        | AdenoCa        | Tissue           | ihc            | OS         | Reported                  | 96         |
| Kosacka [38] | 2011             | Poland           | Caucasian         | 59.3 R            | R           | Non-small cell lung cancer | SqCa         | Tissue           | ihc            | OS         | SC                       | 24         |
| Povegliano [27] | 2010           | Brazil           | Caucasian         | 50 R              | R           | Colorectal cancer     | AdenoCa        | Tissue           | ihc            | OS         | SC                       | 83         |
| Cenesin [42] | 2010             | American         | Caucasian         | NM R              | R           | Bladder cancer        | SqCa           | Tissue           | ihc            | OS         | SC                       | 173        |
| Vereecken [43] | 2009            | American         | Caucasian         | 60 R              | R           | Melanoma              | NM            | Serum ELISA      | OS             | Reported   | 60                       |
| Miranda [28] | 2009             | Brazil           | Caucasian         | 59 R              | R           | Laryngeal carcinoma   | SqCa           | Tissue           | ihc            | DFS        | SC                       | 166        |
| Szoke [29]   | 2007             | German           | Caucasian         | 58.8 R            | R           | Non-small cell lung cancer | SqCa         | Tissue           | ihc            | OS         | SC                       | 127        |
| Kang [30]    | 2007             | Korea            | Asian             | 63 R              | R           | Esophageal cancer     | SqCa           | Tissue           | ihc            | OS         | SC                       | 108        |
| Moisa [39]   | 2007             | Germany          | Caucasian         | 56.8 R            | R           | Breast cancer         | AdenoCa        | Tissue           | ihc            | OS/DYS    | Reported                  | 185        |
| Okada [13]   | 2006             | Japan            | Asian             | 63.9 R            | R           | Gastric cancer        | AdenoCa        | Tissue           | ihc            | OS         | Reported                  | 72         |
Table 2 (continued)

| First author | Publication year | Case nationality | Dominant ethnicity | Median or mean age | Study design | Malignant disease | Main type of pathology | Detected sample | Assay method | Survival analysis | Source of HR | Maximum months of follow-up |
|--------------|------------------|------------------|--------------------|-------------------|--------------|-------------------|-----------------------|----------------|-------------|---------------------|-------------|---------------------------|
| Plzak [31]   | 2004             | Prague           | Caucasian          | 60 R              | Head and neck carcinoma | SqCa           | Tissue             | ihc             | OS           | SC                  | 60          |
| Piantelli [14] | 2002             | Rome             | Caucasian          | 60 R              | Laryngeal carcinoma | SqCa           | Tissue             | ihc             | OS/RFS       | SC                  | 90          |
| Brule [32]   | 2000             | Belgium          | Caucasian          | 65 R              | Prostate carcinomas  | AdenoCa        | Tissue             | ihc             | PFS          | SC                  | 86          |
| Honjo [33]   | 2001             | Japan            | Asian              | 60 R              | Tongue carcinoma    | SqCa           | Tissue             | ihc             | OS/DFS       | SC                  | 118         |
| Nakamura [34] | 1999             | Japan            | Asian              | NM R              | Colorectal cancer   | AdenoCa        | Tissue             | ihc             | OS/DFS       | SC                  | 103         |
| Sanjuan [35] | 1997             | Spain            | Caucasian          | NM R              | Colorectal cancer   | AdenoCa        | Tissue             | ihc             | OS/RFS       | SC                  | 96          |

*R* retrospective, *AdenoCa* adenocarcinoma, *SqCa* squamous carcinoma, *IHC* immunohistochemistry, *OS* overall survival, *DFS* disease-free survival, *PFS* progression-free survival, *RFS* recurrence-free survival, *SC* survival curve

*a* Data extracted from one study due to different malignant disease (biliary cancer and pancreatic cancer)
Table 3  HRs and 95% CIs of patient survival or cancer progression relating to galectin-3 expression in eligible studies

| First author Year | Malignant disease | Main type of pathology | Survival analysis | Cut off point | Case number | OS | DFS/RFS/PFS |
|-------------------|-------------------|------------------------|-------------------|--------------|-------------|----|-------------|
|                   |                   |                        |                   |              |             | HR (95% CI) | p-value     | HR (95% CI) | p-value     |
|                   |                   |                        | High expression   | Low expression|             |               |             |             |
|                   |                   |                        | OS/PFS            | IRS score ≥ 2 | 13.4 (0.59–3.03) | 0.478 | 0.181 (0.025–1.299) | 0.089 |
|                   |                   |                        | OS                | IRS score ≥ 2 | 1.88 (0.88–5.23) | 0.0086 | NM | NM |
|                   |                   |                        | OS                | IRS score ≥ 2 | 2.39 (1.12–4.75) | 0.015 | NM | NM |
|                   |                   |                        | OS                | IRS score ≥ 2 | 14.00 (1.75–112.31) | 0.013 | NM | NM |
|                   |                   |                        | OS                | IRS score ≥ 2 | 6.19 (1.18–32.36) | 0.031 | NM | NM |
|                   |                   |                        | OS                | IRS score ≥ 2 | 4.59 (1.17–17.68) | 0.028 | NM | NM |
|                   |                   |                        | OS                | IRS score ≥ 2 | 2.19 (1.17–4.02) | 0.014 | NM | NM |
|                   |                   |                        | OS                | IRS score ≥ 2 | 2.10 (1.05–4.17) | < 0.05 | NM | NM |
|                   |                   |                        | OS                | IRS score ≥ 2 | 4.00 (0.90–20.00) | 0.052 | NM | NM |
|                   |                   |                        | OS                | IRS score ≥ 2 | 0.69 (0.17–2.86) | 0.019 | NM | NM |
|                   |                   |                        | OS                | IRS score ≥ 2 | 0.79 (0.37–1.67) | 0.54 | NM | NM |
|                   |                   |                        | OS                | IRS score ≥ 2 | 1.63 (0.72–3.66) | 0.099 | NM | NM |
|                   |                   |                        | OS                | IRS score ≥ 2 | 2.32 (1.05–5.10) | 0.036 | NM | NM |
|                   |                   |                        | OS                | IRS score ≥ 2 | 7.51 (3.00–18.78) | < 0.01 | NM | NM |
|                   |                   |                        | OS                | IRS score ≥ 2 | 0.73 (0.27–1.98) | 0.798 | NM | NM |
|                   |                   |                        | OS                | IRS score ≥ 2 | 1.58 (1.11–2.86) | 0.013 | NM | NM |
|                   |                   |                        | OS                | IRS score ≥ 2 | 2.05 (1.05–1.97) | 0.015 | NM | NM |
|                   |                   |                        | OS                | IRS score ≥ 2 | 0.90 (0.15–5.35) | 0.041 | 0.46 (0.18–1.22) | 0.018 |
|                   |                   |                        | OS                | IRS score ≥ 2 | 1.68 (1.05–2.69) | 0.028 | NM | NM |
|                   |                   |                        | OS                | IRS score ≥ 2 | 0.80 (0.51–1.26) | 0.331 | NM | NM |
| First author | Year | Malignant disease          | Main type of pathology | Survival analysis | Cut off point | Case number | OS     | DFS/RFS/PFS | HR (95% CI) | p-value | HR (95% CI) | p-value |
|-------------|------|---------------------------|------------------------|-------------------|--------------|-------------|--------|-------------|-------------|---------|-------------|---------|
| Kosacka     | 2011 | Non-small cell lung cancer | SqCa                   | OS                | 10% of tumor cells stained | 18          | 29     | 1.24 (0.38–4.05) | 0.84         | NM      | NM          |         |
| Povegliano  | 2010 | Colorectal cancer         | AdenoCa                | OS                | 50% of tumor cells stained | 32          | 43     | 1.28 (0.01–138.79) | 0.056        | NM      | NM          |         |
| Canesin     | 2010 | Bladder cancer            | SqCa                   | OS                | 20% of tumor cells stained | 194         | 194    | 2.34 (1.81–3.02) | <0.001       | NM      | NM          |         |
| Vereecken   | 2009 | Melanoma                  | NM                     | OS                | ≥ 10.0 ng/ml        | NM          | NM     | 4.64 (2.17–9.91) | 0.0001       | NM      | NM          |         |
| Miranda     | 2009 | Laryngeal carcinoma       | SqCa                   | DFS               | 47             | 18     | NM     | 1.06 (0.44–2.60) | 0.5284       | NM      | NM          |         |
| Szoke       | 2007 | Non-small cell lung cancer | SqCa                   | OS                | 51             | 41     | NM     | 1.86 (1.09–3.15) | 0.003        | NM      | NM          |         |
| Kang        | 2007 | Esophageal cancer         | SqCa                   | OS                | IRS score ≥ 2 (range 0–4) | 18          | 44     | 0.98 (0.56–1.70) | 0.227        | NM      | NM          |         |
| Moisa       | 2007 | Breast cancer             | AdenoCa                | OS/DFS            | IRS score ≥ 2 (range 0–3) | 52          | 146    | 1.41 (1.16–3.89) | 0.013        | 1.65 (0.91–2.87) | 0.09   |
| Okada       | 2006 | Gastric cancer            | AdenoCa                | OS                | 60% of tumor cells stained | 60          | 55     | 0.26 (0.11–0.64) | 0.0031       | NM      | NM          |         |
| Plzak       | 2004 | Head and neck carcinoma   | SqCa                   | OS                | 50% of tumor cells stained | 23          | 30     | 0.30 (0.06–1.64) | 0.0024       | NM      | NM          |         |
| Piantelli   | 2002 | Laryngeal carcinoma       | SqCa                   | OS/RFS            | 5% of tumor cells stained | 42          | 31     | 0.54 (0.13–2.23) | 0.0001       | 0.49 (0.20–1.21) | 0.0013 |
| Brule       | 2000 | Prostate carcinomas       | AdenoCa                | PFS               | IRS score ≥ 1.5 (range 0–2) | 25          | 102    | NM     | 3.45 (1.49–7.95) | 0.044        |         |             |         |
| Honjo       | 2001 | Tongue carcinoma          | SqCa                   | OS/DFS            | 85% of tumor cells stained | 31          | 23     | 3.51 (1.32–9.37) | 0.012        | 2.30 (0.83–6.33) | 0.021  |
| Nakamura    | 1999 | Colorectal cancer         | AdenoCa                | OS/DFS            | 66.7% of tumor cells stained | 36          | 71     | 3.63 (1.88–7.01) | 0.014        | 2.65 (1.54–4.58) | 0.0224 |
| Sanjuan     | 1997 | Colorectal cancer         | AdenoCa                | OS/RFS            | 25% of tumor cells stained | 83          | 68     | 4.15 (2.01–8.55) | 0.0086       | 3.32 (1.67–6.60) | 0.01   |

AdenoCa, adenocarcinoma; SqCa, squamous carcinoma; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; RFS, recurrence-free survival; NM, not mentioned; IRS, immunoreactivity score; Hscore, the intensity and respective percentage cells that stain at each intensity were multiplied to reach a Hscore that ranged from 0 to 300; OS, overall survival; HR, hazard ratio; CI, confidence interval.

Data extracted from one study due to different malignant disease (biliary cancer and pancreatic cancer).
Results
Summary of enrolled studies
The literature search yielded 1109 citations through online databases by means of previous search strategy. Amongst them, 970 records were excluded because of reviews, letters, case-reports, duplicates and so on, after screening the titles and abstracts. The full texts of the remaining 139 articles were evaluated by the reviewers. Among them, 103 potentially suitable studies were excluded because of lacking sufficient survival data (HRs and 95% CIs), not related to OS or DFS/RFS/PFS, absence of key information. Ultimately, 36 studies were considered to be eligible for this meta-analysis (Fig. 1) [4, 10–14, 20–49].

Detailed quality assessments of each eligible article were presented in Table 1 and the main characteristics of these 36 enrolled studies were summarized in Tables 2 and 3. Amongst them, 33 studies focused on OS and 11 articles investigated DFS or PFS or RFS. 15 of these records focused on Caucasian populations, which mainly came from European countries, and 22 focused on Asian populations. As for cancer type, malignant neoplasms assessed in this article included colorectal carcinoma, gastric carcinoma, breast cancer, laryngeal squamous cell carcinoma (LSCC), esophageal squamous cell carcinoma (ESCC), glioblastoma multiforme, cervical carcinoma, hepatocellular carcinoma, gallbladder carcinoma, non-small cell lung cancer, head and neck carcinoma, prostate carcinomas, tongue carcinoma, biliary cancer, pancreatic cancer, ovarian cancer, bladder cancer and melanoma. Besides, all these aforementioned studies were retrospective.

OS associated with galectin-3 expression
A total of 33 eligible studies were enrolled to evaluate the role of elevated galectin-3 expression in multiple
human malignant neoplasms by OS, within a random-effects model. Our results did indicate that high galectin-3 expression was significantly associated with unfavorable OS in overall cancer patients (pooled HR = 1.79, 95% CI 1.42–2.27, \( I^2 = 67.3\), \( p < 0.01\); Fig. 2a). In the subgroup analysis of specific cancer type, we found high expression of galectin-3 correlated with reduced OS in colorectal cancer, ovarian cancer and non-small cell lung cancer (pooled HR = 3.05, 95% CI 2.13–4.35, \( I^2 = 0.0\), \( p = 0.734\); pooled HR = 2.24, 95% CI 1.38–3.64, \( I^2 = 0.0\), \( p = 0.910\); pooled HR = 2.07, 95% CI 1.48–2.88, \( I^2 = 0.0\), \( p = 0.563\); respectively) (Fig. 2b). Furthermore, in terms of dominant ethnicity subgroup analysis, both the Asian and Caucasian ethnicity were statistically significant (pooled HR = 1.95, 95% CI 1.43–2.66, \( I^2 = 70.1\), \( p < 0.01\); pooled HR = 1.58, 95% CI 1.07–2.33, \( I^2 = 63.7\), \( p = 0.001\); separately) (Fig. 2c). Besides, no matter galectin-3 in the tissue or in the plasma, its elevated expression was associated with reduced OS (pooled HR = 1.72, 95% CI 1.34–2.20, \( I^2 = 67.6\), \( p < 0.01\); pooled HR = 2.49, 95% CI 1.10–5.63, \( I^2 = 71.3\), \( p = 0.008\); respectively) (Fig. 2d).
DFS/RFS/PFS associated with galectin-3 expression

A total of 11 original studies were included to evaluate the role of elevated galectin-3 expression in patients with various solid tumors by DFS/RFS/PFS, within a random-effects model. Our results successfully identified the significant association of high galectin-3 expression with reduced DFS/RFS/PFS in overall cancer patients (pooled HR = 1.57, 95% CI 1.04–2.37, $I^2 = 67.1\%$, $p = 0.001$; Fig. 3a). In the subgroup analysis of specific cancer type, we found that high expression of galectin-3 was correlated with shorter DFS/RFS/PFS in colorectal cancer (pooled HR = 2.49, 95% CI 1.82–3.41, $I^2 = 0.0\%$, $p = 0.738$; Fig. 3b). However, in terms of dominant ethnicity subgroup analysis, both the Asian and Caucasian ethnicity were not statistically significant (Fig. 3c).

Sensitivity analyses

In order to determine the robustness and the stability of our results, sensitivity analysis was conducted to access the stability of results by deleting one single study each time, to reflect the impact of the individual to overall. Our results indicated that no single study significantly influenced the pooled OR and 95% CIs. Namely, our results are comparatively reliable and stable (Fig. 4).

Publication bias

The combined application of Begg’s and Egger’s test was utilized to evaluate the publication bias and meanwhile the funnel plots were displayed in Fig. 5. In the pooled analysis of OS or DFS/RFS/PFS, the $p$ values of Begg’s test and the $p$ values of Egger’s test were all above 0.05, indicating no publication bias in this study.

Discussion

Up to now, elaborate efforts have been made to establish reliable and convincing evidence to detect promising biomarkers for patients with solid tumors. Galectins, as a family of animal carbohydrate-binding proteins, which had the ability to agglutinate cells, were considered to be potential biomarkers of cancer prognosis given their unique structure and functions into consideration [50, 51]. Over the past years, galectins have been implicated in the development of cancer, the pathogenesis of heart failure and ventricular remodeling, infectious processes, and inflammatory processes [52]. Amongst them, due to its differential expression between cancer and normal tissues, galectin-3 was regarded as one important member of galectins family. However, the definite role of galectin-3 in various human malignant neoplasms remained inconsistent. Hence, this meta-analysis was conducted to clarify this question.

It was the first time for us to shed light on the association between elevated galectin-3 expression and the prognosis of patients with solid tumors. Meanwhile, our results were the systematic evaluation of the prognostic outcomes (OS or DFS/RFS/PFS) in a larger population. Our results did suggest that galectin-3 play an oncogenic role in overall cancer patients. Moreover, we found that high expression of galectin-3 was correlated with shorter OS or DFS/RFS/PFS in colorectal cancer and meanwhile it merely associated with reduced OS in ovarian cancer or non-small cell lung cancer, indicating that it could be a promising biomarker and a novel therapeutic target for them. Furthermore, in subgroup analyses of dominant ethnicity, we observed that both the Asian and Caucasian ethnicity were statistically significant for OS, suggesting that the detection of high galectin-3 expression in these patients might be useful for prognosis prediction. Besides, the outcomes of us shed light on that no matter galectin-3 in the tissue or in the plasma, its role remained stable, indicating it could be a promising biomarker and a novel therapeutic target. Meanwhile, according to the results of sensitivity analyses and publication bias, no single study significantly influenced the pooled OR and 95% CIs and no obvious publication bias was detected in this meta-analysis, indicating the robustness and the stability of our results.

Previous researches indicated that increased expression of galectin-3 often predicted unfavorable outcomes and the level of galectin-3 was positively correlated with invasion of depth, vessel invasion, lymph node metastasis, distant metastasis, and TNM stages of various cancers [26, 53]. Tao et al. [37] demonstrated that the positive expression of galectin-3 was associated with more malignant biological behavior of colorectal cancer and it could be used as a predictor of poor prognosis for patients. As for tongue carcinomas, Honjo showed that cytoplasmic galectin-3 expression increased during the progression from normal to cancerous states, whereas nuclear galectin-3 expression decreased during the progression from normal to cancerous states, indicating that enhanced expression of cytoplasmic galectin-3 could serve as a predictor of disease recurrence in these patients [33].

As for its relevant mechanisms, several studies found that galectin-3 was expressed in both cytosol and nucleus [10, 54]. Therein as an important regulator of the Wnt/β-catenin signaling pathway, galectin-3 could activate the epithelial–mesenchymal transition (EMT) in tumor cells to promote the invasion and metastasis of cancer [55, 56]. Furthermore, it could subsequently activate the Ras-mediated Akt signaling pathway to inhibit cell apoptosis by interacting with the activated GTP-bound K-Ras [57]. Besides, it could also modulate VEGF- and bFGF-mediated angiogenesis by binding its carbohydrate recognition domains (CRDs) to integrate αvβ3, and then promote the growth of new blood vessels [58].
**Fig. 3** Forest plots of DFS/RFS/PFS in association with galectin-3 in various cancers. **a** The overall group; **b** the subgroup analysis of cancer types; **c** the subgroup analysis of dominant ethnicity.

### a: Study ID and HR (95% CI) for overall group

| Study ID | HR (95% CI) | Weight |
|----------|-------------|--------|
| Chou (2018) | 0.18 (0.03, 1.36) | 3.17 |
| Liu (2017) | 2.10 (1.05, 4.17) | 1031 |
| Yang (2016) | 2.09 (1.06, 3.79) | 1089 |
| Yamaki (2012) | 0.46 (0.18, 1.22) | 8.16 |
| Miranda (2009) | 1.06 (0.44, 2.60) | 8.68 |
| Moise (2007) | 1.65 (0.91, 2.97) | 1131 |
| Pantell (2002) | 0.49 (0.20, 1.21) | 8.59 |
| Brule (2000) | 3.45 (1.48, 7.95) | 9.08 |
| Honjo (2001) | 2.30 (0.83, 6.33) | 7.73 |
| Nakamura (1999) | 2.65 (1.54, 4.58) | 1156 |
| Sanjuan (1997) | 3.32 (1.87, 6.00) | 1034 |
| **Overall** | 1.57 (1.04, 2.37) | 100.00 |

**NOTE:** Weights are from random-effects analysis.

### b: Study ID and HR (95% CI) for subgroup analysis of cancer types

| Study ID | HR (95% CI) | % Weight |
|----------|-------------|----------|
| Colorectal cancer | | |
| Liu (2017) | 2.10 (1.05, 4.17) | 10.31 |
| Yang (2016) | 2.09 (1.03, 3.79) | 10.69 |
| Nakamura (1999) | 2.65 (1.04, 6.80) | 11.56 |
| Subtotal | 3.22 (1.67, 6.27) | 10.34 |
| Subtotal (I-squared = 0.0%, p = 0.734) | | |
| Breast cancer | | |
| Yamaki (2012) | 0.46 (0.18, 1.22) | 8.16 |
| Moise (2007) | 1.65 (0.91, 2.97) | 11.31 |
| Subtotal | 0.87 (0.42, 2.05) | 19.46 |
| Laryngeal carcinoma | | |
| Miranda (2009) | 1.95 (0.44, 8.68) | 6.88 |
| Pantell (2002) | 0.49 (0.20, 1.21) | 8.69 |
| Subtotal (I-squared = 39.1%, p = 0.232) | | |
| Other cancer | | |
| Chou (2018) | 0.18 (0.03, 1.30) | 3.37 |
| Brule (2000) | 3.45 (1.48, 7.95) | 9.08 |
| Honjo (2001) | 2.30 (0.83, 6.33) | 7.73 |
| Subtotal (I-squared = 72.4%, p = 0.031) | | |
| **Overall** | 1.67 (1.04, 2.37) | 100.00 |

**NOTE:** Weights are from random-effects analyses.

### c: Study ID and HR (95% CI) for subgroup analysis of dominant ethnicity

| Study ID | HR (95% CI) | % Weight |
|----------|-------------|----------|
| Asian | | |
| Chou (2018) | 0.18 (0.03, 1.30) | 3.37 |
| Liu (2017) | 2.10 (1.05, 4.17) | 10.31 |
| Yang (2016) | 2.09 (1.03, 3.79) | 10.69 |
| Yamaki (2012) | 0.46 (0.18, 1.22) | 8.16 |
| Honjo (2001) | 2.30 (0.83, 6.33) | 7.73 |
| Nakamura (1999) | 2.65 (1.04, 6.80) | 11.56 |
| Subtotal (I-squared = 67.8%, p = 0.008) | | |
| Caucasian | | |
| Miranda (2009) | 1.95 (0.44, 8.68) | 6.88 |
| Moise (2007) | 1.65 (0.91, 2.97) | 11.31 |
| Pantell (2002) | 0.49 (0.20, 1.21) | 8.69 |
| Brule (2000) | 3.45 (1.48, 7.95) | 9.08 |
| Subtotal (I-squared = 73.0%, p = 0.005) | | |
| **Overall** | 1.67 (1.04, 2.37) | 100.00 |

**NOTE:** Weights are from random-effects analyses.
As for the effects on heterogeneity, subgroup analysis was a way to discover their potential sources and even decrease the huge heterogeneity. As presented by our results, we could easily find that there might be the existence of significant heterogeneity of elevated galectin-3 expression in the overall cancer patients. So we conducted a subgroup analysis based on the specific cancer types and found that most of their heterogeneity decreased significantly, even with no heterogeneity. However, subgroup analysis of dominant ethnicity was not associated with significant reduction of heterogeneity, indicating that the dominating source of heterogeneity might be the different cancer types.

Sometimes, galectin-3 combined with another biomarker was often utilized simultaneously in prognostic outcome analyses, showing it might not be an independent factor affecting the prognosis of cancer patients. As indicated by Li et al. [11] the expressions of ezrin and galectin-3 were correlated with the development of cervical cancer, and over-expressions of those proteins were indicative of poor prognosis in patients with cervical cancer. Galectin-3 associated with cyclin D1 expression was also studied in non-small cell lung cancer. As a result,
In summary, it was the first time for us to shed light on the prognostic role of elevated galectin-3 expression in various cancers. Our results did suggest that galectin-3 played an oncogenic role in colorectal cancer, ovarian cancer and non-small cell lung cancer, indicating that it could be a promising biomarker for predicting the prognosis of patients with malignant neoplasms, and the biological functions of galectin-3 were of great research value of the subject. Due to the aforementioned limitations, larger samples of more strictly designed studies were required to provide more high-quality data to elaborate their associations.

Conclusions

In summary, it was the first time for us to shed light on the prognostic role of elevated galectin-3 expression in various cancers. Our results did suggest that galectin-3 played an oncogenic role in colorectal cancer, ovarian cancer and non-small cell lung cancer, indicating that it could be a promising biomarker for predicting the prognosis of patients with malignant neoplasms, and the biological functions of galectin-3 were of great research value of the subject. Due to the aforementioned limitations, larger samples of more strictly designed studies were required to provide more high-quality data to elaborate their associations.

Authors’ contributions

NH5, XHM: protocol/project development; QJZ, XZ: data collection or management; YMW, YT: data analysis; YW, SWL: manuscript writing/editing. All authors read and approved the final manuscript.

Acknowledgements

We would like to thank the researchers and study participants for their contributions.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

All the data (pooled hazard ratios with 95% confidence intervals of OS or DFS/PFS/RFS) used to support the findings of this study are included within the article. Please contact author for data requests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

Funding

This article was funded by Medical key talent of Jiangsu Province: ZDRCA2016009 and the National Natural Science Foundation of China (Grant Number: 81871151; 81801438).

Publisher’s Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 22 June 2018 Accepted: 27 October 2018

Published online: 03 November 2018

References

1. Ding R, Miller MC, Griffin RJ, Mayo KH. Galectins as molecular targets for therapeutic intervention. Int J Mol Sci. 2018;19(3):905.
2. Chung LY, Tang SJ, Wu YC, Sun GH, Liu HY, Sun KH. Galectin-3 augments tumor initiating property and tumorigenicity of lung cancer through interaction with β-catenin. Oncotarget. 2015;6(7):4936–52.
3. Barondes SH, Castronovo V, Cooper DN, Cummings RD, Drickamer K, Feizi T, Gitt MA, Hibiayashi J, Hughes C, Kasai K, et al. Galectins: a family of animal beta-galactoside-binding lectins. Cell. 1994;76(4):597–8.
4. Huang Z, Ai Z, Li N, Xi H, Gao X, Wang F, Tan X, Liu H. Over expression of galectin-3 associates with short-term poor prognosis in stage II colon cancer. Cancer Biomark. 2016;17(4):445–55.
5. Liu FT, Rabinovich GA. Galectins as modulators of tumour progression. Nat Rev Cancer. 2005;5(1):29–41.
6. Knapp JS, Lokeshwar SD, Vogel UJ, Hennenlotter J, Schwentner C, Kramer MW, Stenzl A, Merseburger AS. Galectin-3 expression in prostate cancer and benign prostate tissues: correlation with biochemical recurrence. World J Urol. 2013;31(2):351–8.
7. Cheng CL, Hou HA, Lee MC, Liu CY, Jhuang JY, Lai YJ, Lin CW, Chen HY, Liu FT, Chou WC, et al. Higher bone marrow LGA.LS3 expression is an independent unfavorable prognostic factor for overall survival in patients with acute myeloid leukemia. Blood. 2013;121(16):3172–80.
8. Kramer MW, Kuczyk MA, Hennenlotter J, Serth J, Schilling D, Stenzl A, Merseburger AS. Decreased expression of galectin-3 predicts tumour recurrence in pTa bladder cancer. Oncol Rep. 2008;20(6):1403–8.
9. Yoshii T, Inohara H, Takenaka Y, Honjo Y, Akahani S, Nomura T, Raza A, Kubo T. Galectin-3 maintains the transformed phenotype of thyroid papillary carcinoma cells. Int J Oncol. 2001;18(4):787–92.
Galectin-3 is a poor prognostic marker in colorectal adenocarcinomas. Hum Pathol. 2016;53:105–13.

Williamson PR, Smith CT, Hutton JL, Marson AG. Aggregate data meta-analysis with time-to-event outcomes. Stat Med. 2002;21(22):3331–34.

Chou SY, Yen SL, Huang CC, Huang EY. Galectin-1 is a poor prognostic factor in patients with laryngeal squamous-cell carcinoma. J Clin Oncol. 2002;20(18):3850–6.

Stang A. Critical evaluation of the Newcastle–Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603–5.

Piantelli M, Iacobelli S, Gherisi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16.

Ilmer M, Mazurek N, Gilcrease MZ, Byrd JC, Woodward WA, Buchholz TA, Acklin K, Ramirez K, Hatley M, Alt E, et al. Low expression of galectin-3 is associated with poor survival in node-positive breast cancers and mesenchymal phenotype in breast cancer stem cells. Breast Cancer Res. 2016;18(1):97.

Okaa K, Shima T, Suehiro T, Mochiki E, Kuwano H. Reduced galectin-3 expression is an indicator of unfavorable prognosis in gastric cancer. Anticancer Res. 2006;26(2b):1369–76.

Piantelli M, Iacobelli S, Almadori G, Iezzi M, Tinari C, Cadoni G, Lauriola L, Ranelluti F.O. Lack of expression of galectin-3 is associated with a poor outcome in node-negative patients with laryngeal squamous-cell carcinoma. J Clin Oncol. 2002;20(18):3850–6.

Gabius HJ. Galectin-3—an emerging prognostic indicator in advanced head and neck carcinoma. Eur J Cancer (Oxford, England: 1990). 2004;40(15):2324–30.

van den Brule FA, Woltregny D, Liu FT, Castronovo V. Alteration of the cytoplasmic/nuclear expression pattern of galectin-3 correlates with prostate carcinoma progression. Int J Cancer. 2000;88(4):361–7.

Honjo Y, Inohara H, Akahani S, Yoshis T, Takenaka Y, Yoshida J, Hat- tori K, Tomiyama Y, Raz A, Kubo T. Expression of cytoplasmic galectin-3 as a prognostic marker in tongue carcinoma. Clin Cancer Res. 2000;6(12):4635–40.

Nakamura M, Inufusa H, Adachi T, Aga M, Kuriyomo M, Nakatani Y, Wakan T, Nakajima A, Hida JI, Miyake M, et al. Involvement of galectin-3 expression in colorectal cancer progression and metastasis. Int J Oncol. 1999;15(1):143–8.

Sanjuan X, Fernandez PL, Castells A, Castronovo V, van den Brule F, Liu FT, Cardesa A, Campo E. Differential expression of galectin-3 and galectin-1 in colorectal cancer progression. Gastroenterology. 1997;113(6):1906–15.

Tao F, Bilgin E, Tarteck D, Erturk K, Dunayridly D. Clinical significance of serum galectin-3 levels in gastric cancer patients. J Gastrointest Cancer. 2016;47(2):182–6.

Tao L, Jin L, Dechun L, Hongqiang Y, Changhua K, Guinun L. Galectin-3 expression in colorectal cancer and its correlation with clinical pathological characteristics and prognosis. Open Med (Warsaw, Poland). 2017;12:226–30.

Kim HC, et al. Low expression of Bax predicts poor prognosis in patients with locally advanced esophageal cancer treated with definitive chemoradiotherapy. Cardiothorac Surg. 2007;31(5):783–7.

Dersimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–88.

Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7129):629–34.

Gabius HJ. The role of microvascularization and growth/adhesion-regula-
tion and function of a large family of animal lectins. J Biol Chem. 1994;269(33):20807–10.

Tsiakaras P, Awada A, Suciu S, Castro G, Morandin R, Litynska A, Lienard E, Ezeddine K, Ghanem G, Heenen M. Evaluation of the prognostic significance of serum galectin-3 in American joint committee on cancer stage III and stage IV melanoma patients. Melanoma Res. 2009;19(5):316–20.

Mur XS, Wang SQ, Long B, Mou YF, Wu Y, Liao KY, Xu Y, Mo SJ, Ma B, Tang XL. The clinical significance of galectin-3 and P27 involved in treatment of elderly early gastric cancer with endoscopic submucosal dissection. Chin J Gerontol. 2014;19:5423–5.

Moisa A, Fritz P, Eck A, Wehner HD, Muelder T, Simon W, Gabius HJ. Growth/adhesion-regulatory tissue lectin galectin-3: stromal presence but not cytoplasmic/nuclear expression in tumor cells as a negative prognostic factor in breast cancer. Anticancer Res. 2007;27(4b):2131–9.

Cheng D, Liang B, Li Y. Serum galectin-3 as a potential marker for gastric cancer. Med Sci Monit. 2015;21:755–60.

Shimura T, Shibata M, Gonda K, Kofunato Y, Okada R, Hisigame T, Kimura T, Kenjo A, Kono K, Marubashi S. Significance of circulating galectin-3 in patients with pancreaticobiliary cancer. Anticancer Res. 2017;37(9):4979–86.

Canesin G, Gonzalez-Petamato P, Palou J, Uruttra M, Cordon-Cardo C, Sanchez-Carbayo M. Galectin-3 expression is associated with bladder cancer progression and clinical outcome. Tumour Biol. 2010;31(4):277–85.

Vereecken P, Awada A, Suciu S, Castro G, Morandin R, Litynska A, Lienard E, Ezeddine K, Ghanem G, Heenen M. Evaluation of the prognostic significance of serum galectin-3 in American joint committee on cancer stage III and stage IV melanoma patients. Melanoma Res. 2009;19(5):316–20.

Mu XS, Wang SQ, Long B, Mou YF, Wu Y, Liao KY, Xu Y, Mo SJ, Ma B, Tang XL. The clinical significance of galectin-3 and P27 involved in treatment of elderly early gastric cancer with endoscopic submucosal dissection. Chin J Gerontol. 2014;19:5423–5.

Wu SW, Yu L, Zhou L, Cheng ZN, Tao YS. Expression of Gal-3 and CD82/KAI1 proteins in non-small cell lung cancer and their clinical significance. Chin J Oncol. 2013;35(2):124–8.

Liu MY, Du B, Li CH, Zhao YB, Meng QW, Cai L. Expression and related factors of galectin-3 in non-small cell lung cancer. Chin J Lung Cancer. 2013;16(8):417–21.

Lu HW, Wang DY, Liu YY, Xu GC, Xie LL, Lin ZQ. Expression of galectin-3 and β-catenin in epithelial ovarian cancer and their clinical significance. J Sun Yat-sen Univ (Medial Sciences). 2015;36(6):883–8.

Yang XZ. Galectin-3 expression in colorectal cancer progression and metastasis. Int J Oncol. 2004;23(1):175–80.

Frazão T, Kayser K, Trajcom J, Kayser G, Furuk J, Tisslavis L, Baumhakel JD, Gabius HJ. The role of microvascularization and growth/adhesion-regula-
tory lectins in the prognosis of non-small cell lung cancer in stage II. Eur J Cardiothorac Surg. 2007;31(5):783–7. 35.

Argirou A, Chatzis P, Kontogiorgos K, Kalafatis M, Vrentzos G, Vrezakis S, Kontsali C, Kelepertzis A, et al. The expression of galectin-3 in gastric cancer correlates with the expression of Bcl-2 in lymph node metastases. Cancer Cell Int          (2018) 18:172

Pizlak J, Betka J, Smetana K Jr, Chovanec M, Kaltner H, Andre S, Kodet R, Gabius HJ. Galectin-3—an emerging prognostic indicator in advanced head and neck carcinoma. Eur J Cancer (Oxford, England: 1990). 2004;40(15):2324–30.

Bakshi M, Gonda K, Kofunato Y, Okada R, Hisigame T, Kimura T, Kenjo A, Kono K, Marubashi S. Significance of circulating galectin-3 in patients with pancreaticobiliary cancer. Anticancer Res. 2017;37(9):4979–86.

Canaresin G, Gonzalez-Petamato P, Palou J, Uruttra M, Cordon-Cardo C, Sanchez-Carbayo M. Galectin-3 expression is associated with bladder cancer progression and clinical outcome. Tumour Biol. 2010;31(4):277–85.
53. Zhou X, Jing J, Peng J, Mao W, Zheng Y, Wang D, Wang X, Liu Z, Zhang X. Expression and clinical significance of galectin-3 in osteosarcoma. Gene. 2014;546(2):403–7.
54. Rubio D, Garcia S, De la Cueva T, Paz MF, Lloyd AC, Bernad A, Garcia-Castro J. Human mesenchymal stem cell transformation is associated with a mesenchymal–epithelial transition. Exp Cell Res. 2008;314(4):691–8.
55. Thiery JP. Epithelial–mesenchymal transitions in tumour progression. Nat Rev Cancer. 2002;2(6):442–54.
56. Steinestel K, Eder S, Schrader AJ, Steinestel J. Clinical significance of epithelial–mesenchymal transition. Clin Transl Med. 2014;3:17.
57. Elad-Sfadia G, Haklai R, Balan E, Kloog Y. Galectin-3 augments K-Ras activation and triggers a Ras signal that attenuates ERK but not phosphoinositide 3-kinase activity. J Biol Chem. 2004;279(33):34922–30.
58. Markowska AI, Liu FT, Panjwani N. Galectin-3 is an important mediator of VEGF- and bFGF-mediated angiogenic response. J Exp Med. 2010;207(9):1981–93.