Drug Resistance-associated Markers P-Glycoprotein, Multidrug Resistance-associated Protein 1, Multidrug Resistance-associated Protein 2, and Lung Resistance Protein as Prognostic Factors in Ovarian Carcinoma

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ABSTRACT

Intrinsic and/or acquired resistance to chemotherapy is the major obstacle to overcome in the treatment of patients with ovarian carcinoma. The aim of the present study was to investigate the prognostic value of drug resistance-associated proteins P-glycoprotein (P-gp), multidrug resistance-associated protein 1 (MRP1), canalicular multispecific organic anion transporter (c-MOAT/MRP2), and lung resistance protein (LRP) in ovarian carcinoma. Expression of P-gp, MRP1, MRP2, and LRP was determined by immunohistochemistry of frozen tissue sections of 115 ovarian carcinoma patients and related to clinicopathological factors, response to chemotherapy, and progression-free survival. P-gp expression was observed in 20 of 115 (17%), MRP1 in 51 (44%), MRP2 in 19 (16%), and LRP in 85 (74%) tumors. Expression of MRP1 was related to MRP2 (P < 0.0001) and P-gp (P < 0.001) expression, whereas LRP expression was more frequently observed in patients with early stage (P < 0.001), lower grade (P < 0.05), and smaller residual tumor (P < 0.05). Early stage (P < 0.001), smaller residual tumor (P < 0.001), and lower differentiation grade (P < 0.05) were related to longer (progression-free) survival. P-gp, MRP1, MRP2, and LRP expression were neither related to response to first-line chemotherapy in 59 evaluable patients nor to progression-free survival in all patients. On multivariate analysis, only stage and residual tumor were independent prognostic factors for survival. In conclusion, in ovarian carcinoma, MRP1 expression is associated with MRP2 and P-gp expression, whereas LRP expression is associated with favorable clinicopathological characteristics. Assessment of P-gp, MRP1, MRP2, or LRP does not allow prediction of response to chemotherapy or survival in ovarian carcinoma.

INTRODUCTION

Ovarian carcinoma is the leading cause of death from gynecological malignancies in the Western world (1). Because the majority of patients are diagnosed in an advanced stage of disease, first-line treatment in general consists of surgical debulking, followed by paclitaxel and platinum-containing chemotherapy (2, 3). Meta-analysis has shown that the addition of doxorubicin to platinum-containing regimens in first-line treatment may further improve survival. (4) Despite a high initial response rate, however, most patients will relapse. Unfortunately, second-line chemotherapy with response rates of ~20% is seldom curative (5). These clinical data indicate that long-term prognosis in ovarian carcinoma depends on intrinsic and acquired resistance to chemotherapy. Insight into the cellular mechanisms responsible for drug resistance may lead to the development of more effective treatment schedules. In vitro studies have revealed that selection of cells for resistance to one type of anticancer drug may result in cross-resistance to other, structurally unrelated drugs including e.g., anthracyclines, epipodophyllotoxins, Vinca alkaloids, and taxanes (6). This phenomenon is called MDR. MDR has been related to several mechanisms, among which overexpression of membrane transporter proteins such as P-gp and MRP1. P-gp is a membrane glycoprotein, encoded by the MDRI gene, that acts as an ATP-driven drug efflux pump. Overexpression is associated with resistance to natural product drugs, including doxorubicin and taxanes (7, 8). In contrast to P-gp, the efflux of drugs by MRP1, another membrane transporter protein, appears to occur as glutathione conjugates and glucuronides (9). In vitro overexpression of MRP1 can confer resistance to a broad range of natural product drugs, including doxorubicin, but thus far, no obvious

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2 The abbreviations used are: MDR, multidrug resistance; P-gp, P-glycoprotein; MRP, multidrug resistance-associated protein.
relation with resistance to taxanes has been reported (10). Recently, MRP2, the canalicular multispecific organic anion transporter (cMOAT), has been characterized and found to be overexpressed in a number of cisplatin-resistant cell lines (11, 12). Although in vitro data suggest that MRP2 might act as a drug efflux pump, there is no evidence yet for the involvement of MRP2 in clinical drug resistance (12–15). LRP, the major vault protein, is elevated in several non-P-gp tumor lines with an MDR phenotype (16). LRP is located at cytoplasmatic vaults, small subcellular structures that may be responsible for sequestration and subsequent exocytosis of drugs from the cell, but its exact role in drug resistance is unclear (17). In vitro, a relation with resistance to doxorubicin, cisplatin, and melphalan has been found (16). In a previous study, LRP overexpression was strongly related to poor response to chemotherapy and survival in higher stage ovarian carcinomas (18).

In the present study, the immunohistochemical expression of the drug resistance proteins P-gp, MRP1, MRP2, and LRP was determined in ovarian carcinomas and related to response to first-line chemotherapy and progression-free survival.

MATERIALS AND METHODS

Patients. All consecutive newly diagnosed patients with primary epithelial ovarian carcinoma, treated and evaluated at the Department of Gynecology, Gynecological Oncology, and Breast Cancer Unit, University of Turin, Italy, between June 1, 1991 and February 1, 1997 were included in this study. Patients were treated with cytoreductive surgery and staged according to the International Federation of Obstetrics and Gynaecology classification (19).

All patients with ovarian carcinoma stages I–IV were treated with chemotherapy containing at least cisplatin or carboplatin and/or, after 1996, paclitaxel, except those patients with ovarian carcinoma stages I–IIA, who were included in an European Organization for Research and Treatment of Cancer protocol ACTION (chemotherapy versus observation) and were randomized to the observation arm. In patients with evaluable tumor after first laparotomy (either by clinical or radiological examination), response to first-line chemotherapy was evaluated by clinical and/or radiological examination according to Gynecologic Oncology Group criteria in which a ≥50% reduction was considered a partial response, and complete disappearance of the disease either by clinical or radiological examination was considered a complete response (20). Stable disease was a steady state of response either less than a partial response or progression <25% maintained for at least 6 weeks duration. Progressive disease was defined as an increase of at least 25% or the appearance of any significant new lesions. Patients with incomplete response to first-line chemotherapy or recurrent tumors were treated with a variety of second-line chemotherapy protocols. After first-line treatment, all patients were followed up every 4 months for the first 2 years and every 6 months thereafter. The collection of tumor samples was approved by the medical ethical committee of the University Hospital of Turin. All patients gave informed consent.

Tumor Samples. Tumor samples were obtained during primary cytoreductive laparotomy, immediately frozen in liquid nitrogen, and stored at −80°C until further analysis. For histological classification, a part of each tumor was embedded in paraffin.

Histology. Primary tumors were classified according to the WHO classification using paraffin-embedded tissue (21). One section/cm tumor diameter was collected to get a good overall impression of the tumor histology. Tumors were graded into well (grade I), moderately (grade II), and poorly (grade III) differentiated, as described by Sobre et al. (22).

Antibodies. The monoclonal antibodies JSB-1 (diluted 1:20) for the detection of P-gp (no cross-reactivity with MRP1 and little cross-reactivity with MDR3 P-gp), MRPm6 (diluted 1:40) for the detection of MRP1 (no cross-reactivity with MDR1 or MDR3 P-gp), M3III-6 (diluted 1:60) for the detection of MRP2 (no cross-reactivity with DMR1 of MRP1 but recognizes the MRP3 fusion protein), and LRP-56 (diluted 1:400) for the detection of LRP (no known cross-reactivity with other drug resistance-associated proteins) were used. We produced all antibodies (R. S., G. L. S. and M. K.). They have been concentrated from culture supernatants, as described extensively elsewhere (23–26). Optimal dilution for immunostaining was obtained using the following tissue controls: colon tissue for P-gp; lung tissue for MRP1; liver tissue for MRP2; and lung tissue for LRP (14, 17). The optimal titer was defined as the dilution that gave clearly identifiable membrane or granular cytoplasmatic staining.

Immunohistochemistry. Immunohistochemical staining was performed with the Multilink SuperSensitive StreptAvidin detection method (BioGenex Laboratories, San Ramon, CA). Briefly, cryostat sections, 4 μm thick, from each frozen tumor block were air dried and fixed in acetone at room temperature for 10 min. After washing in PBS (0.14 M NaCl, 2.7 mM KCl, 6.4 mM Na₂HPO₄, 1.5 mM KH₂PO₄, pH 7.4), sections were incubated with normal swine serum to block nonspecific background staining, followed by overnight incubation with the optimally diluted antibody. Sections were sequentially incubated, with intervening buffer washes, in biotinylated Multilink antibodies, streptavidin-horseradish peroxidase, and the chromogenic substrate 3-amino-9-ethylcarbazole and counterstained with hematoxylin.

As control tissues, colon was used for P-gp, lung for MRP1, liver for MRP2, and lung for LRP. P-gp in normal colon mucosa showed membranous and diffuse cytoplasmic staining. MRP1 immunostaining was strong granular cytoplasmic and membranous in bronchial epithelium, whereas MRP2 immunostaining was apical membranous in the hepatocytes lining the liver canaliculi. For LRP, strong granular cytoplasmic staining was observed in bronchial epithelium.

Scoring of Immunostaining Results. The evaluation of immunostaining results was scored by two investigators (A. S. and H. A.) without knowledge of the clinical data of the patients. Sections were scored as follows: −, no staining; ±, positive staining in <10% of tumor cells; +, positive staining in >10% of tumor cells; and ++, strong staining in most tumor cells. For statistical analysis, tumors scored as + or ++ were considered positive, and tumors scored as − or ± were considered negative. The pattern of immunostaining (membrane, cytoplasmic) was also recorded separately.

Statistics. Data analysis was performed using the SPSS statistical software package (SPSS, Inc., Chicago, IL). Relations
between clinicopathological characteristics and staining of P-gp, MRP1, MRP2, and LRP were determined using \( \chi^2 \) analysis. Differences in progression-free survival from the first laparotomy were analyzed using log-rank statistics. Multivariate analysis was performed with a Cox proportional hazards regression model, stepwise forward, including all of the factors that were significant in the univariate analysis. Only \( P < 0.05 \) were considered significant.

RESULTS

Patients. During the study period, 131 consecutive patients with primary epithelial ovarian carcinoma were included. Sixteen cases were excluded from the study because of insufficient frozen material. Two patients with stages III and IV disease who refused chemotherapy after surgery and one patient with stage III disease who was treated with melphalan monotherapy were excluded from survival analysis. Clinical and pathological characteristics at diagnosis are summarized in Table 1. Twelve patients with stage I \( (n = 11) \) or stage II \( (n = 1) \) carcinoma did not receive chemotherapy. Therefore, 100 patients were treated with chemotherapy, and regimens are summarized in Table 2. Fifty-nine patients with residual disease after primary laparotomy were evaluable for tumor response to first-line chemotherapy by clinical and/or radiological examination. Few second-look laparotomies were performed according to treatment protocols. Thirty-one of 59 patients had a complete clinical response (53.5%), 19 had a partial response (32%), 3 had stable disease (5%), and 5 had progressive disease (8.5%). Median progression-free survival for all patients \( (n = 112) \) included in the survival analysis was 18 months (range, 0–79). Median survival was 23 months (range, 3–79). Thirty-nine patients (35%) died of disease during or after first-line chemotherapy. Median follow-up of the patients who are presently alive is 25 months (12–79 months).

Immunohistochemistry. The results of immunohistochemistry are summarized in Table 1. Twenty (17%) of 115 tumor samples stained positive for P-gp. In six of these tumors, the staining pattern was both strong diffuse cytoplasmic as well as membranous in 10% of tumor cells (Fig. 1A). In the other 14 tumors, a weaker, more diffuse cytoplasmic staining (in 10% of tumor cells) was observed. MRP1 immunostaining was found in 51 tumor samples (44%) with predominantly diffuse, partly granular cytoplasmic staining in 10% of tumor cells. Staining intensity varied from low to moderate. In some tumors with strongest MRP1 staining, sporadic membranous staining was observed (Fig. 1B). Immunostaining for MRP2 was positive with a predominant diffuse cytoplasmatic pattern in

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical and pathological characteristics</th>
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<tr>
<td></td>
<td>All cases</td>
</tr>
<tr>
<td>All cases</td>
<td>115 (100)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;56</td>
<td>61 (53)</td>
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<tr>
<td>&gt;56</td>
<td>54 (47)</td>
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<tr>
<td>Stage</td>
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<tr>
<td>I/II</td>
<td>34 (30)</td>
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<tr>
<td>III/IV</td>
<td>81 (70)</td>
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<tr>
<td>Grade</td>
<td></td>
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<tr>
<td>I/II</td>
<td>47 (41)</td>
</tr>
<tr>
<td>III</td>
<td>68 (59)</td>
</tr>
<tr>
<td>Histotype</td>
<td>MA/CC</td>
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<tr>
<td>MA/CC</td>
<td>27 (23)</td>
</tr>
<tr>
<td>Others</td>
<td>88 (77)</td>
</tr>
<tr>
<td>Residual tumor</td>
<td>( \leq 2 \text{ cm} )</td>
</tr>
<tr>
<td>( \leq 2 \text{ cm} )</td>
<td>79 (69)</td>
</tr>
<tr>
<td>( &gt; 2 \text{ cm} )</td>
<td>36 (31)</td>
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</table>

* LRP immunostaining: stage I versus stage II: \( P < 0.05 \).
* Grade I/II versus grade III: \( P < 0.05 \).
* MA/CC, mucinous/clear cell.
* LRP immunostaining: MA/CC versus other histiotypes: \( P < 0.05 \).
* Residual tumor \( \leq 2 \text{ cm} \) versus \( > 2 \text{ cm} \): \( P < 0.05 \).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Chemotherapy regimens</th>
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<tr>
<td>MDR-related chemotherapy regimens*</td>
<td>No. of patients</td>
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<tr>
<td>Cisplatin/cyclophosphamide/doxorubicin</td>
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</tr>
<tr>
<td>Cisplatin/cyclophosphamide/epirubicin</td>
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<tr>
<td>Paclitaxel/carboplatin/epirubicin</td>
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<tr>
<td>Paclitaxel/cisplatin</td>
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</tr>
<tr>
<td>Paclitaxel/carboplatin</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
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</table>

* Each regimen included six cycles of chemotherapy.
>10% of tumor cells in 19 tumors (16%), whereas in 4 of these 19 positive tumors, both diffuse cytoplasmic as well as strong membranous staining was observed (Fig. 1C). MRP2 staining intensity was remarkably heterogeneous within the tumor samples. Most MRP2-positive tumors contained both negative as well as strong positive cells. For both MRP1 and MRP2, a weak diffuse cytoplasmic staining was also observed in fibrous stromal cells. LRP immunostaining was positive in 85 (74%) tumor samples with a granular cytoplasmic staining pattern without membranous staining (Fig. 1D). Staining intensity was mostly strong in nearly 100% of tumor cells and quite homogeneous throughout the tumors.

MRP1 immunostaining was related to MRP2 (P < 0.0001) and P-gp immunostaining (P < 0.001). However, tumor parts with strong MRP1 staining were not the same as the parts with strong staining for MRP2. There was no association between immunostaining for LRP and P-gp (P = 0.07), MRP1 (P = 0.06), or MRP2 (P = 0.2). Positive immunostaining for LRP was associated with favorable prognostic factors, including stage I/II tumors (P < 0.01), grade I/II tumors (P < 0.05), and residual tumor <2 cm after laparotomy (P < 0.05). No association was found between any other clinicopathological characteristic and immunostaining for P-gp, MRP1, MRP2, or LRP.

Relation between Immunostaining for P-gp, MRP1, MRP2, and LRP and Response to First-Line Chemotherapy.
No relation could be established between response to first-line chemotherapy and immunostaining for P-gp, MRP1, MRP2, or LRP. When comparing patients with tumors positive for different combinations of P-gp, MRP1, MRP2, or LRP, no subgroup could be identified with a higher chance of poor therapy outcome.

Patients in our study were treated with a variety of drug regimens, all of which were platinum based (Table 2). In 25 patients treated with regimens containing MDR-related drugs, e.g., paclitaxel, doxorubicin, or epirubicin, no relation between response and positive immunostaining for P-gp and/or MRP1 and/or MRP2 and/or LRP was found (Table 3). Positive immunostaining for MRP2 and/or LRP did not predict therapy outcome for 34 patients who were treated with regimens containing non-MDR-related drugs (Table 4).

Survival Analysis. Univariate analysis of the log-rank curve of the prognostic impact of clinical, histopathological, and immunohistochemical parameters on progression-free and overall survival for all 112 patients included in the survival analysis identified the following significant factors: stage (P < 0.001), residual tumor after first laparotomy (P < 0.001), and tumor grade (P < 0.05). Immunostaining for P-gp, MRP1, MRP2, or LRP had neither predictive value for progression-free or overall survival.
survival in all patients nor in stage III/IV patients (Fig. 2). No combination of drug resistance-related proteins in individual tumors could predict progression-free or overall survival. Multivariate analysis revealed stage (P < 0.001) and residual tumor after first laparotomy (P < 0.001) as independent prognostic factors for overall survival.

DISCUSSION

Our study shows that drug resistance-related proteins (P-gp, MRP1, MRP2, and LRP) are frequently expressed in ovarian carcinoma. P-gp expression was observed in 17% of tumors. We and others reported previously a wide range of P-gp immunostaining in ovarian carcinomas (7–62%; Refs. 18 and 27–30). This wide range in P-gp expression can be attributed to the use of different methodologies for P-gp detection in the different studies (different antibodies, frozen or paraffin-embedded tissue, and/or different visualization systems). In the present study, no relation was established between P-gp expression and response to chemotherapy and/or survival, which is in agreement with the majority of earlier studies (18, 27–29, 31). However, as only a minority of tumors is P-gp positive (17%), it is important to note that this study lacks the statistical power to detect survival differences <20%. Furthermore, it may be speculated that immunohistochemical detection of P-gp expression lacks sufficient sensitivity to detect all clinically relevant P-gp levels. In vitro studies have shown that even very low levels of P-gp can effectively transport paclitaxel out of the cell (32). Using a more sensitive RT-PCR assay, Kavallaris et al. (33) found MDR1 gene expression (RNA) in 36% of 53 patients with ovarian carcinoma, which was associated with a shorter progression-free survival. Our present study is the first to analyze the prognostic role of P-gp in ovarian cancer patients primarily treated with paclitaxel-containing chemotherapy and does not reveal any prognostic impact of P-gp expression in this (sub)group of patients. However, the number of patients treated with paclitaxel in our study is rather small (n = 22). Therefore, it is possible that in a larger group of ovarian cancer patients primarily treated with paclitaxel, P-gp expression may have some prognostic impact.

MRP1 is overexpressed in many non-Pgp MDR cell lines (34, 35). In the present study, immunostaining for MRP1 was observed in 45% of ovarian carcinomas, whereas in a previous study by Izquierdo et al. (18) in 68% of 57 stage III and IV ovarian carcinomas. Although elevated MRP1 mRNA levels have been reported in several human cancers, the role of MRP1 in clinical drug resistance is not fully defined (36). Neither our present nor previous study showed a relation with response to chemotherapy or survival (16). Using RT-PCR, Kavallaris et al. (33) detected moderate MRP1 expression in all ovarian carcinomas and high MRP1 expression in 43% of ovarian carcinomas without relation to progression-free survival. In vitro and clinical data thus far do not point to a relation for MRP1 with response to platinum- and/or paclitaxel-containing chemotherapy. Because of the small number of patients also treated with doxorubicin, our study lacks the power to detect a possible additional role for MRP1 in resistance to chemotherapy in patients treated with this compound.

The search for new markers of chemoresistance recently identified MRP2 (c-MOAT). MRP2, a M190,000–200,000 membrane glycoprotein, has an amino acid identity of 49% with MRP1 (12). MRP2 has been shown to be a unidirectional ATP-driven export pump localized mainly in the canalicular membrane of hepatocytes (13). In vitro data suggest that MRP2 might act as an organic anion pump (15, 37). In contrast to MRP1, the expression of MRP2 was found to be elevated in a number of cell lines selected for cisplatin resistance (11, 12). Our study reports expression of MRP2 in 16% of ovarian carcinomas, whereas no further data exist on MRP2 expression in ovarian carcinomas. MRP2 expression did not predict response to chemotherapy and was not related to progression-free survival. This, however, does not preclude a role for MRP2 in drug resistance in ovarian carcinoma. In a study in rat hepatocytes, MRP2 was found to be strongly inducible with cisplatin, 2-acetylaminofluorene, and cycloheximide (38). In addition, an earlier study by our group showed that indeed expression of drug resistance-related proteins (P-gp) was induced by doxorubicin-containing chemotherapy in tumors obtained at second-look laparotomy (27). In fact, for all four presently studied drug resistance-related proteins, it may not be the expression in primary tumors but the induction by chemotherapy that determines response. It would therefore be interesting to study the expression and localization of MRP2 in tumor samples obtained shortly after chemotherapy or at relapse.

The present study confirms that strong cytoplasmic immunostaining for LRP is common in ovarian carcinomas, as was reported previously in a collaborative study by Izquierdo et al. (16). A new and striking observation is the relation of LRP immunostaining with favorable tumor characteristics and the lack of relation of LRP immunostaining with response to first-line chemotherapy or progression-free survival. This lack of correlation is in strong contrast to our
previous study in which LRP immunostaining was identified as the only independent prognostic factor for progression-free survival in 57 stage III/IV ovarian carcinoma patients (16). There is no obvious explanation for this apparent controversy. The relation of LRP immunostaining with favorable tumor characteristics in the present study is not found when stages III and IV patients are analyzed separately. In the present study, there is a trend toward an association between LRP immunostaining and small residual tumor after first laparotomy in stage III/IV, whereas in the study by Izquierdo et al. (18), exactly the opposite was observed. The study of Izquierdo et al. (18) comprised more stage IV, suboptimally debulked patients. At final evaluation time, in the present study 52% of stage III/IV patients are alive compared with only 33% of patients in the study of Izquierdo et al. (Ref. 18; 10 months longer median follow-up time). It can be speculated that the apparent differences between patient populations in the two studies are responsible for the conflicting results. When reviewing the literature, there is only one other report concerning the relation between LRP expression and response to chemotherapy in solid tumors. In this study, no relation between LRP expression and response to chemotherapy was observed in 40 patients with locally advanced breast cancer (39), whereas for hematological malignancies such as acute myeloid leukemia and multiple myeloma, several authors reported a relation between LRP expression and worse therapy outcome (40–43).

In conclusion, none of the tested drug resistance-related proteins alone or in combination can accurately predict therapy outcome or survival. Despite promising in vitro data, results from clinical studies are disappointing with regard to the clinical applicability of the determination of drug resistance-related pro-

Fig. 2 Progression-free survival according to resistance-associated protein expression in 112 patients with ovarian carcinoma stages I–IV. A, log-rank analysis of progression-free survival according to P-gp immunostaining; $P = $ not significant. B, log-rank analysis of progression-free survival according to MRP1 immunostaining; $P = $ not significant. C, log-rank analysis of progression-free survival according to MRP2 immunostaining; $P = $ not significant. D, log-rank analysis of progression-free survival according to LRP immunostaining; $P = $ not significant.
REFERENCES


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