Kidney Cancer

Proposal for Reclassification of the TNM Staging System in Patients with Locally Advanced (pT3–4) Renal Cell Carcinoma According to the Cancer-Related Outcome

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Abstract

Objectives: The optimal stratification of locally advanced renal cell carcinoma (RCC) is controversial, with the prognostic relevance of ipsilateral adrenal gland invasion and cranial extension of vena cava thrombosis being the most debatable issues. We evaluated the prognosis of patients with locally advanced RCC and identified a new model to stratify their outcome.

Materials and methods: We analyzed the data of 227 patients who had undergone partial or radical nephrectomy for pT3–4 RCC at two academic centers between 1986 and 2002. The log-rank test and Cox proportional hazards model were used for univariate and multivariate analysis, respectively.

Results: At a median follow-up of 29 mo, we censored 108 (47.6%) cancer-related deaths. On univariate analysis, the 2002 T stage was not statistically significant. According to cancer-related outcome, we identified three subgroups of patients with different prognoses: pT3a(n): tumors with perirenal fat invasion or renal vein thrombosis or thrombosis within the vena cava below the diaphragm; pT3b(n): tumors with renal vein thrombosis or thrombosis within the vena cava below the diaphragm and concomitant perirenal fat invasion; pT4(n): adrenal gland or Gerota fascia invasion or thrombosis within the vena cava above the diaphragm. The three subgroups had significantly different prognoses. The new reclassification was an independent predictive variable on multivariate analysis, as well as the pathologic lymph node stage.

Conclusions: The 2002 version of TNM of locally advanced RCC did not stratify patient outcome. The present study suggests the possibility of reclassifying pT3–4 RCC into three categories capable of predicting cancer-specific survival, regardless of all other prognostic factors.

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1. Introduction

The pathologic stage is the most important prognostic factor in renal cell carcinoma (RCC), since the TNM staging system is the most widely used to classify the local extension of the primary tumor (T), locoregional lymph node involvement (N), and the presence of metastasis (M) [1,2].

Locally advanced RCCs are classified as pT3 and pT4. The former group includes tumors invading perirenal fat and/or ipsilateral adrenal gland (pT3a), as well as those presenting with renal thrombosis within the renal vein or the vena cava below the diaphragm (pT3b) or above the diaphragm (pT3c). Tumors extending beyond the Gerota fascia are classified as pT4 [3]. Despite updates and proposals for change, the optimal stratification of RCC patients in the context of the TNM staging system is still controversial [2]. The prognostic relevance of ipsilateral adrenal gland invasion [4,5], renal sinus fat invasion [6], and the cranial extension of vena cava thrombosis [7,8] are the most debatable issues. The most recently published studies on prognostic factors underscored the need for a further revision of the latest version of the TNM staging system for RCC. According to Gospodarowicz [9], the main steps in the TNM review process include the development of unambiguous criteria for information and recording data to consider changes in the classification, as well as the formation of expert panels with experts from all over the world [9].

With the aim of contributing to the update of the TNM staging system for locally advanced RCC, Thompson et al. [10] recently published a proposal of reclassification of patients with pT3–4 RCC into five different subgroups: pT3aN (thrombus level 0 without fat invasion); pT3bN (fat invasion only); pT3cN (thrombus level 0 with fat invasion or thrombus levels I–III without fat invasion); pT3dN (thrombus levels I–III with fat invasion or thrombus level IV); pT4 (extension beyond the Gerota fascia). To date, this reclassification from the Mayo Clinic is the most important proposal for TNM modification, but external validation is still lacking.

The objectives of the present study is to assess the cancer-specific survival of patients with locally advanced RCC, and to identify an appropriate clinical and statistical model to stratify their cancer-related outcome.

2. Material and methods

We analyzed the data of 984 patients who had undergone partial or radical nephrectomy for RCC at the departments of urology of Padua and Verona universities between 1986 and 2002. We extracted from the databases of the participant centers the clinical records of 227 (23%) patients with pT3–4 RCC. Of 227 patients, 129 (56.8%) had been treated at the Department of Urology, University of Verona, and 98 (43.2%) at the Department of Urology, University of Padua.

The following clinical and pathologic variables were evaluated: age, gender, mode of presentation, presence of synchronous metastases, pathologic tumor size (cm), local extension of the primary tumor, and regional lymph node involvement according to the 2002 TNM system [3], histologic subtype according to the Heidelberg classification [11], and nuclear grades according to the Fuhrman classification [12]. For each patient, invasions of the ipsilateral adrenal gland, perirenal fat, renal vein, and vena cava tumor thrombus, and the Gerota fascia were reported. We identified nine groups, including patients with the presence of (1) adrenal gland invasion, (2) perirenal fat invasion, (3) Gerota fascia invasion, (4) renal vein thrombosis, (5) thrombosis within vena cava below the diaphragm, (6) thrombosis within vena cava above the diaphragm, (7) renal vein thrombosis and perirenal fat invasion, (8) thrombosis within the vena cava below the diaphragm and perirenal fat invasion, and (9) thrombosis within the vena cava above the diaphragm and perirenal fat invasion. With regards to the mode of presentation, patients were divided into two groups. Those tumors diagnosed during abdominal imaging studies for signs and symptoms that were unrelated to RCC were classified as incidental. Flank pain, haematuria, flank mass, or systemic symptoms suggesting the presence of advanced-stage disease (weight loss, fever, paraneoplastic syndromes) identified the symptomatic patients. In patients with bilateral, synchronous, or metachronous RCC, only the initial mode of disease detection was used to distinguish incidental from symptomatic cases.

The presence of synchronous metastases was evaluated with abdominal computed tomography (CT) scans and chest x-rays. Bone scans and brain CT scans were obtained only when indicated by signs and symptoms.

Most of the patients did not undergo adjuvant therapy after surgery. The oncologic follow-up schedule included abdominal imaging twice a year (alternating ultrasound and CT scans) and chest x-rays once a year for the first 5 yr. Thereafter, abdominal imaging studies and chest x-rays were scheduled once a year. Data on survival were obtained from the clinical files at our center and, when necessary, from contacting patients’ general practitioners or relatives, or from a search of death records.

2.1. Statistical analysis

Continuous parametric variables were reported as the mean value ± SD and range. Continuous nonparametric variables were presented as the median values and interquartile ranges. The survival interval was defined as the time elapsed between surgery and the last clinical evaluation or death. Survival curves were estimated by using the Kaplan-Meier method. Patients who remained alive or who died of other causes were censored (disease-specific survival). The log-rank test was used for the comparison of survival curves and for univariate analysis. A Cox proportional hazards model was used for multivariate analysis.
In all statistical analyses, a two-sided p value < 0.05 was considered significant. All data were analyzed with the use of the Statistical Package for the Social Sciences software, version 12.0 (SPSS Inc, Chicago, IL).

### Results

Table 1 summarizes the clinical and pathologic characteristics of the 227 patients analyzed. Adrenal gland invasion was observed in 14 (6.2%) patients. Among the 213 patients without adrenal gland infiltration, 65 (30.5%) patients had only perirenal fat invasion, 7 (3.3%) patients had only Gerota fascia invasion, and 141 (66.2%) patients had venous tumor thrombus. Within this last subgroup, 54 patients had both perirenal fat and concomitant venous invasion (in 39 cases limited to the renal vein, in 11 and 4 cases up to the vena cava below and above the diaphragm, respectively). In contrast, 87 patients had neoplastic thrombosis only (Fig. 1).

The median follow-up of the patients was 29 mo (interquartile range: 12–67). At the follow-up, we censored 108 (47.6%) cancer-related deaths and 16 (7%) deaths unrelated to RCC. Twelve (5.3%) patients were alive with disease progression, while 91 (40.1%) were alive and disease-free. The median follow-up of the patients alive and disease-free was 40 mo (interquartile range: 24–76.5). The 5- and 10-yr cancer-specific survival probabilities were 50.7% and 38%.

On univariate analysis, the following variables turned out to be statistically significant: mode of presentation (log-rank p value = 0.01), pathologic tumor size (log-rank p value = 0.0001), tumor histologic subtype (log-rank p value = 0.0001), pathologic lymph nodes stage (log-rank p value < 0.0001), presence of metastases (log-rank p value < 0.0001), and Fuhrman nuclear grade (log-rank p value < 0.0001) (Table 2). In contrast, the pathologic stage

![Fig. 1 – Pathologic findings of the 227 patients according to the extension of the primary tumor.](image-url)
of the primary tumor did not achieve statistical significance (log-rank \( p \) value = 0.48) (Fig. 2).

Table 3 shows the cancer-specific survival probabilities for the nine subgroups of patients obtained by stratifying singularly all the pathologic features (log-rank \( p \) value < 0.0001). Statistical data concerning the presence of similar cancer-related outcomes among the subgroups as well as clinical considerations enabled us to cluster the nine subgroups into three categories, as follows: pT3a(n): presence of perirenal fat invasion or renal vein thrombosis or thrombosis within the vena cava below the diaphragm; pT3b(n): renal vein thrombosis or thrombosis within the vena cava below the diaphragm associated with perirenal fat invasion; pT4(n): adrenal gland invasion or Gerota fascia invasion or thrombosis within the vena cava above the diaphragm (Table 4). Comparing the cancer-specific survival probabilities among the three new categories, pT3a(n) patients had significantly higher survival than both pT3b(n) (log-rank \( p \) value = 0.0004) and pT4(n) patients (log-rank \( p \) value < 0.0001). Similarly, pT3b(n) patients had more favorable cancer-related outcome compared with pT4(n) cases (log-rank \( p \) value = 0.02) (Fig. 3).

On multivariate analysis, the new classification of the locally advanced RCC turned out to be an independent predictive variable (hazards ratio: 1.644; \( p \) = 0.01), alongside the presence of distant metastases (Table 5).

4. Discussion

Adrenal gland invasion, Gerota fascia invasion, and vena cava tumor thrombosis above the diaphragm were the pathologic features related to the worst cancer-related outcome. In addition, in the case of the concomitant presence of both perirenal fat invasion and venous thrombosis, the specific survival probabilities were significantly worse than those observed when the same pathologic features were present singularly. Our reclassification of locally advanced RCC within the three proposed categories is closely related to the patient’s outcome and is of easy clinical application.

The direct invasion of the ipsilateral adrenal gland is a feature that is rare but associated with an unfavorable outcome. In 2003, Han et al. [4] pointed out that the median cancer-specific survival
probability of patients with ipsilateral adrenal gland invasion was significantly worse than for those with tumor infiltrating only the perirenal fat (12.5 vs 36 mo, \( p < 0.001 \)) and similar to patients with pT4 RCC (11 mo). Consequently, the authors suggested that RCCs invading the adrenal gland should be assigned to the same category as those extending beyond the Gerota fascia. Similar data were recently provided by Thompson et al. [5], who reported that the 5-yr cancer-specific survival probabilities were 20.2\% in patients with cancer invading the ipsilateral adrenal gland, 53.9\% in patients with cancer invading only the perirenal fat, and 42.7\% in patients with pT3b RCC without concomitant adrenal gland involvement. Our proposal of reclassification of locally advanced RCC agrees with the literature data and with the findings of the Mayo Clinic, which indicated that patients with adrenal gland and Gerota fascia invasions should be staged similarly [10].

### Table 3 – Five- and 10-yr cancer-specific survival probabilities according to the local extension of the primary RCC tumor (log-rank \( p \) value <0.0001)

<table>
<thead>
<tr>
<th>Local extension of the primary tumor</th>
<th>Cases</th>
<th>5-yr survival</th>
<th>10-yr survival</th>
<th>Median (mo)</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vena cava thrombosis below the diaphragm</td>
<td>10</td>
<td>100%</td>
<td></td>
<td>n.r.</td>
<td>–</td>
</tr>
<tr>
<td>Renal vein thrombosis</td>
<td>70</td>
<td>61.2%</td>
<td></td>
<td>n.r.</td>
<td>–</td>
</tr>
<tr>
<td>Perirenal fat invasion</td>
<td>65</td>
<td>58.6%</td>
<td></td>
<td>69</td>
<td>32–106</td>
</tr>
<tr>
<td>Renal vein thrombosis + perirenal fat invasion</td>
<td>39</td>
<td>43.3%</td>
<td></td>
<td>21</td>
<td>0–48</td>
</tr>
<tr>
<td>Vena cava thrombosis below the diaphragm + perirenal fat invasion</td>
<td>11</td>
<td>19.8%</td>
<td></td>
<td>36</td>
<td>24–48</td>
</tr>
<tr>
<td>Gerota fascia invasion</td>
<td>7</td>
<td>38.1%</td>
<td></td>
<td>20</td>
<td>4–36</td>
</tr>
<tr>
<td>Vena cava thrombosis above the diaphragm</td>
<td>7</td>
<td>14.2%</td>
<td></td>
<td>14</td>
<td>6–22</td>
</tr>
<tr>
<td>Adrenal gland invasion</td>
<td>14</td>
<td>13.3%</td>
<td></td>
<td>7</td>
<td>0–18</td>
</tr>
<tr>
<td>Vena cava thrombosis above the diaphragm + perirenal fat invasion</td>
<td>4</td>
<td>0%</td>
<td></td>
<td>6</td>
<td>0–14</td>
</tr>
</tbody>
</table>

CI: confidence interval; n.r.: not reached.
Another critical issue in the RCC staging system is the classification of tumor thrombosis within the renal vein and the vena cava. The literature data pointed out that cancer-specific survival was significantly higher in cases of renal vein thrombus, compared with vena cava thrombosis. In addition, in the latter subgroup of patients, the extension of the tumor thrombus below or above the diaphragm is a significant prognostic factor [7,8]. Moreover, patient outcome is significantly worse in the case of the

<table>
<thead>
<tr>
<th>Proposal of TNM modification</th>
<th>Definition</th>
<th>Cases</th>
<th>5-yr survival probability (%)</th>
<th>10-yr survival probability (%)</th>
<th>Log-rank p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT3a(n)</td>
<td>Presence of perirenal fat invasion or renal vein thrombosis or thrombosis within the vena cava below the diaphragm</td>
<td>145</td>
<td>61.7</td>
<td>44.76</td>
<td>pT3a(n) Vs pT3b(n): 0.0004 pT3a(n) Vs pT4(n): &lt;0.0001</td>
</tr>
<tr>
<td>pT3b(n)</td>
<td>Renal vein thrombosis or thrombosis within the vena cava below the diaphragm associated with perirenal fat invasion</td>
<td>50</td>
<td>39.4</td>
<td>29.5</td>
<td>pT3b(n) Vs pT4(n): 0.02</td>
</tr>
<tr>
<td>pT4(n)</td>
<td>Adrenal gland invasion or Gerota’s fascia invasion or thrombosis within the vena cava above the diaphragm</td>
<td>32</td>
<td>17.3</td>
<td>n.r.</td>
<td>–</td>
</tr>
</tbody>
</table>

n.r.: not reached.

Fig. 3 – Cancer-specific survival probability stratified according to our proposal for TNM modification. Log-rank p value <0.0001. Red plot: pT3a(n); blue plot: pT3b(n); orange plot: pT4(n). pT3a(n) patients had significantly higher survival than both pT3b(n) (log-rank p value = 0.0004) and pT4(n) patients (log-rank p value <0.0001). pT3b(n) patients had more favorable cancer-related outcome, compared with pT4(n) cases (log-rank p value = 0.02).
concomitant presence of tumor thrombosis and perirenal fat invasion [7,13]. In our study, the survival probabilities of patients with thrombus only within the renal vein or the vena cava below the diaphragm were similar and overlapped those reported for patients with only perirenal fat invasion. Similarly, Kim et al. [14] from the University of California, Los Angeles reported similar disease-specific survival probabilities for patients with thrombosis within the renal vein and the inferior vena cava below the diaphragm (3-yr disease-specific survival: 36% and 35%, respectively). In contrast with the reclassification proposed by the Mayo Clinic, the main difference was found in patients with only vena cava thrombosis below the diaphragm. Thompson et al. [10] suggested that those patients should be staged the same as those having renal vein tumor thrombus and concomitant perirenal fat invasion.

Both the Mayo Clinic’s and our proposals agree in identifying patients with concomitant perirenal fat invasion and venous thrombosis as those with the worst prognosis. Our data reconfirmed that patients with vena cava thrombus above the diaphragm, with or without adrenal fat invasion, had worse cancer-related outcomes than patients with tumor thrombosis below the diaphragm.

In the present study, the retrospective collection of the data did not allow us to assess the prognostic role of renal sinus fat invasion. The renal sinus contains a large number of veins and lymphatics. Tumor invasion into this compartment might permit a higher potential dissemination, compared with extension into perinephric fat, where veins and lymphatics are less abundant [2]. Recently, Thompson et al. [6] pointed out that tumors invading the renal sinus fat were more aggressive than those with perinephric fat involvement.

The TNM staging system is included in all the nomograms and algorithms predicting disease progression [15–17], overall survival [18], cancer-specific survival [18,19]. Integration of several clinical and pathologic variables increase the predictive power, compared with the single variables [20]. However, among all the included variables, the TNM staging system and, specifically, the pathologic stage of the primary tumor are the variables with the highest risk of misclassification; therefore, identification of the best staging system is still a relevant issue.

One limitation of our study is the size of the series, only 227 patients. The Mayo Clinic’s reclassification of locally advanced RCC was based on an analysis performed on 697 patients who had undergone radical nephrectomy from 1970 to 2000. Our study analyzed fewer patients, treated over a more limited period of time; thus, our series was more homogeneous. It is likely that some of the differences between the two reclassification proposals may be due to the different number of patients available in the analyzed subgroups. For this reason, the suggested reclassification proposals should be validated in larger, multicenter studies.

### 5. Conclusions

The current TNM staging system of locally advanced RCC cannot provide an appropriate stratification of the patients’ cancer-related outcomes. Consequently, a few authors recently suggested the need to define a new version of the TNM. The main reclassification proposal comes from the Mayo Clinic and suggests the subclassification of pT3–4 RCC into five subgroups with different outcomes. The data of the present study suggest the possibility of reclassifying locally advanced RCC into three categories capable of predicting cancer-specific survival, regardless of all other prognostic factors.

Ipsilateral adrenal gland infiltration, Gerota fascia invasion, and vena cava tumor thrombosis above the diaphragm were the pathologic features

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**Table 5 – Variables predictive of cancer-specific survival probability in patients with locally advanced RCC**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Categories</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of presentation</td>
<td>Incidental vs symptomatic</td>
<td>0.904</td>
<td>0.506–1.614</td>
<td>0.733</td>
</tr>
<tr>
<td>Pathologic tumor size</td>
<td>≤7.5 cm vs &gt;7.5 cm</td>
<td>1.233</td>
<td>0.687–2.214</td>
<td>0.482</td>
</tr>
<tr>
<td>Histologic subtype</td>
<td>Conventional vs papillary/</td>
<td>1.088</td>
<td>0.816–1.451</td>
<td>0.566</td>
</tr>
<tr>
<td></td>
<td>chromophobe vs collecting duct</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>unclassified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathologic stage of lymph nodes</td>
<td>pNo/Nx vs pN+</td>
<td>1.506</td>
<td>0.726–3.126</td>
<td>0.271</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Absent vs present</td>
<td>4.696</td>
<td>2.589–8.517</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fuhrman nuclear grade</td>
<td>G1–2 vs G3–4</td>
<td>1.219</td>
<td>0.910–1.632</td>
<td>0.184</td>
</tr>
<tr>
<td>Our proposal of TNM modification</td>
<td>pT3a vs pT3b vs pT4</td>
<td>1.644</td>
<td>1.127–2.398</td>
<td>0.01</td>
</tr>
</tbody>
</table>

CI: confidence interval; HR: hazards ratio.

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associated with the worst prognosis. The concomitant presence of perirenal fat invasion and venous thrombosis identifies a subgroup of patients with poorer outcomes, compared with patients in whom the same pathologic features were present singularly. Multicenter studies are needed to assess and validate the prognostic importance of our proposal for redefining the TNM staging system for locally advanced RCCs.

**References**


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**Editorial Comment**

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The UICC TNM staging system is a universally accepted system assessing the tumor, lymph nodes and metastases in human solid tumors. The advantages are that the system provides standardized information on the anatomical extent of the tumor and also provides prognostic information. It is well-recognized that the system is not perfect. Thus, revisions are made every 5 years in parallel to the developments in diagnostic imaging, tumor markers and treatment.

Although the TNM classification provides some prognostic information, individual patients in the same stage group have completely different outcome. The reasons for this difference are multifold, including clinical, histological, molecular and therapeutic factors. This observation prompted many more sophisticated integrated staging systems to be developed in order to predict oncological outcome for renal cell carcinoma (RCC). Currently,
three major prognostic nomograms challenge the prognostic capability of the TNM system. These are the UISS of University of California at Los Angeles, the Kattan nomogram of Memorial Sloan-Kettering Cancer Center and the SSIGN score of Mayo Clinic [1–3]. The real challenge here is: can the predictive accuracy of the TNM system be improved based on the cancer-related outcome information of large series?

Dr. Ficarra and colleagues must be congratulated for their efforts in proposing a reclassification system for locally advanced RCC [4]. Based on the retrospective analysis of 227 patients with locally advanced RCC from 2 institutions with a median follow up of 29 months, the authors are proposing a revision of the TNM system. The major limitation of the study is the relatively few patients in some subgroups. The involvement of the ipsilateral adrenal gland is a poor prognosticator, and like others, they propose this to be changed in the new system [4]. Although their attempt is worthwhile, many factors may have an impact on their analysis. Despite being a retrospective series, a re-evaluation of pathology specimens might have had a tremendous impact. Microscopically important factors such as renal sinus fat invasion, microvascular invasion, necrosis, sarcomatoid differentiation and others could have been assessed and included in the analysis.

It is an established fact that surgery plays the major role on the oncological outcome. Thus residual disease after surgery has to be known and taken into account in the multivariate analysis. Likewise, performance status is another factor for inclusion in multivariate analysis.

The widely used TNM staging system is a limited, anatomical staging system. It is inadequate to expect an anatomical staging to reflect the biological complexity of RCC. On the other hand, any staging system should stratify the patients into more clinically meaningful groups. The incorporation of histological, genetic and molecular factors will most likely cause the development of a better staging system in the near future, which will guide the urologist for the treatment selection and provide more accurate prognostication.

References


Editorial Comment

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The paper by Ficarra et al. reassesses the controversial issue of the accuracy of the current TNM classification within T3–T4 tumours. As mentioned by the authors, concordant reports have suggested that T3 tumours with adrenal invasion should be reclassified as T4 tumours [1,2]. Additionally, it is obvious that fat invasion (perinephric or renal sinus), renal vein invasion, inferior vena cava invasion, tumour size, Fuhrman grade, performance status, and symptoms all are important prognostic variables in this setting, justifying previous attempts to reclassify these tumours [3,4]. The real question is how to integrate all these key prognostic variables within the TNM classification.

Two types of results are provided by the authors in this interesting paper. The first one is not debatable. The 2002 TNM classification is not able to stratify accurately T3–T4 tumours in the study population and the authors are providing new evidence supporting the need for a TNM modification in this setting. The second one is a proposal for a new T3–T4 classification. The general concept is correct because it is likely that combining independent prognostic variables is better than taking variables alone. However, the limitation of the proposed system is the size of the study sample; it is obvious that such a classification should be validated in larger series. The number of prognostic variables that are available reflects the biologic complexity of the disease. In the near future, it is likely that prognostic nomograms derived from large multicentre series, integrating all indepen-
dent prognostic variables and assigning a score to each variable, will be more accurate than the TNM system for predicting outcome. Finally, further prognostication strategies should integrate both clinical and molecular variables for providing the best prognostic information and allowing individual therapeutic and follow-up strategies [5].

References