Author's response to reviews

Title: Prognostic significance of multidrug-resistance protein (MDR-1) in renal clear cell carcinomas: a five years follow-up analysis.

Authors:

Chiara C Mignogna (chiara.mignogna@libero.it)
Stefania S Staibano (staibano@unina.it)
Vincenzo V Altieri (altieri@unina.it)
Gaetano G De Rosa (gaderosa@unina.it)
Giuseppe G Pannone (giuseppepannone@libero.it)
Angela A Santoro (angelasantoro1@hotmail.it)
Rosanna R Zamparese (rosannazamparese@libero.it)
Massimino M D'Armiento (giuseppepannone@virgilio.it)
Romualdo R Rocchetti (vangieson@libero.it)
Ernesto E Mezza (mezza@unina.it)
Mario M Nasti (mario.nasti@tin.it)
Viviana V Strazzullo (graziafanara@libero.it)
Vittorino V Montanaro (vincenzo.santoro.0@alice.it)
Massimo M Mascolo (mmascolo@libero.it)
Pantaleo P Bufo (p.bufo@unifg.it)

Version: 2 Date: 6 November 2006

Author's response to reviews:

Dear Editor,

We are very grateful for your precise and punctual revisions and for your lots of useful advice. By this cover letter, we want to provide point-by-point responses to your comments. Our paper has been written by observing and respecting the journal style. As regards language revisions and the English grammar, we have called for help a native English-speaking colleague. We have tried to perform major compulsory revisions, minor essential and discretionary ones, so obtaining a new revised and correctly formatted manuscript. In light of the reviewers’ comments, below, you can read a detailed description of all changes we have made since the previous version.

1. First of all, we have modified paper title and a few phrases in the abstract.
2. Major clearness has been made about study tumoral population. A previous survey was performed on an initial renal tumour population, represented by 30 RCCs (clear cell type), 3 RCCs (sarcomatoid type), 2 RCCs (cromophobe type), 1 RCC (papillary type) and 1 oncocytoma. This first research was directed to specify the most important prognostic factors in renal neoplastic pathology. By preliminary univariate analyses of the different histopathological, immune-histochemical and clinical parameters, we could identify MDR-1 as the only immune-histochemical factor and tumour stage as the sole histopathological parameter that were characterized by values that were close to statistical significance. To standardize our study population, we have selected only RCCs (clear cell type) for the further investigations and we have removed the other histotypes because, in the initial sample, they represented too small numerical fractions to be studied by statistical analysis. Successively, Cox multivariate regression analysis (MVA) has been used to confirm independent predictors of outcome among histopathological, immune-histochemical and clinical variables. Therefore, 30 RCCs (clear cell type) were employed in this following study only when a complete and long-term clinical follow-up was available.
3. Results and Discussion sections have been separated.
4. Clinic-pathological data, that were present at page 4 of the previous work, have been inserted in Results.
5. In the Discussion, we have added critical statement (new role of MDR-1 as prognostic factor in renal clear cell carcinoma) about our study and its possible limitations (small cohort of RCC patients, no variety of types of RCCs but only clear cell histotype).
6. We have created a new, more brief, Conclusions section.
7. For the IHC investigations, serial sections, conducted on our RCC samples, also included non-lesional areas, 5 cm distant from tumoral mass. Negative controls were performed on these sections (the non-lesional ones) and on other sections that comprised normal areas of removed kidneys for surgical
non-neoplastic renal diseases; while positive control was executed on sections obtained from a case of infiltrating breast cancer.

8. Tumour extent, that, in the course of our previous surveys, was defined by Robson system, in this study, has been revised and classified according to the 2002 TNM system (reported in references, too), for the statistical analyses.

9. RCC patients underwent open-surgery at the Department of Urology of the University "Federico II", Naples, Italy, from January 1993 to December 1996. All patients have been treated with radical open-nephrectomy, including resection of peri-nephric fat, Gerota's fascia, adrenal gland and regional lymph nodes.

10. Tables 1 and 2 have been revised, integrated and correctly formatted, in the content, in the label and in the caption, too.

11. In Table 2, moreover, years term substitutes for anni and the threshold tumour size has been fixed to 7 cm.

12. Figure 4 has been eliminated because of the small number of cases and events.

13. We have inserted other two tables in which results of Cox multivariate regression analysis have been summarized.

14. In reference 3, we have corrected the name of the first author (Stenzl and no more Stenzel).

15. Moreover, we have revised the literature, then we have added the titles of the publications that were missing. Other references have enriched the bibliography.

16. Tumour stages have been stated in Roman ordinal numbers.

17. Inter-rate reliability between the two investigators examining the immune-stained sections was assessed by the Cohen's K test, yielding K values higher than 0.70 in almost all instances.

18. At page 7 of the previous version (and at the same page in the revised manuscript), luminal surface term substitutes for inner surface of proximal tubule. We have also added a reference for this paragraph and concept.

19. Cox multivariate regression analysis has been done and added.

Please remember that, if you decide on acceptance our manuscript, a pro-forma invoice (as fax) can be addressed to:

Dr. Pio D'Errico
Fax: 0881 713032
Department of Surgical Sciences
University of Foggia
Foggia (ITALY)

In hopes that our new revised research article can be accepted and published and with our best regards,

Dr. Giuseppe Pannone
Via S Giacomo dei Capri 63/E - 80131 Napoli - Italy
Telephone and Fax: +39 081 5608495
E-mail: giuseppepannone@virgilio.it