Does the assessment of tumor markers in the context of the last negative conclusions still have any impact in ovarian cancer?

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Summary:

The incidence of ovarian cancer is very high in Europe and there is still a lot of encertainaity about the best screening method today. The regular use of ultrasound investigation and CA125 testing is not established as a screening, so the greatest number of patients diagnosed with this tumor has a locally advanced disease. Their prognosis is unfavourable even with the treatment by chemotherapy. We describe the role of main factors associated with the primary tumor (staging, grading, histological type) and it´s treatment (surgery type and the influence of residual tumor, type and regimen of chemotherapy and inclusion of radiation therapy in the primary treatment) for disease-free and overall survival. We also confirmed that tumor markers (CA125 incl.) used in screening, during treatment measuring response to chemotherapy and for folow-up as an early predictor of disease recurrence have low specificity and sensitivity to be used today. They have role of a prognostic factor – at least some of them – unfortunately with no impact on survival even when palliative chemotherapy can start immediately when the markers are rising, about 5 months earlier then clinical progression can be diagnosed. Monitoring of tumor markers is at that point not useful and because of poor prognosis of relapsed cancer not meaningful and can not be recomended. It is necessary to look for another markers.

Methods:

In our retrospective single center study we included all consecutive patients treated for a primary ovarian cancer between 1. January 1997 and 30. June 2003 with a median follow up of more than 4 years. 37% of them was alive on last March, 2010. Median age was 56,2 (17,3 – 87,9) years. Patients treated for a relapsed disease undergoing primary surgery previously and with a secondary tumors (e.g. metastatic gastric or lung carcinoma in the ovary) were excluded, so the total number of women included in this study was 263. We focused on the influence of the histology and side involvement, extent of surgery and residual tumor, use of different chemotherapy regiment and primary radiation therapy done at that time for the prognosis of patients with ovarian cancer. For the statistical analyse we used survival curves according to Kaplan-Meier method, for a time-dependent recurrence as a covariate the Cox model with the proportional hazards assumption. Tumor markers were measured initialy at the time of diagnosis and during treatment and follow-up and we tried to identify their progression and remission values.

Results:

As expected only women with T1N0M0 tumors are the good prognostic group. The risk of recurrence (associated with the DFS) as far as the risk of cancer related death (evaluated as an OS) in other patiens with larger tumors (T2, T3), positive lymph nodes (N1) or metastatic disease (M1) have about 3,5-fold higher risks for each of this factors. The risk of reccurence is 4-fold higher and risk of death 4,2-fold higher for patients with stage II., III. and IV. disease in comparison with the stage I.; 2,2-fold higher, resp. 3,1-fold higher risks for grade 2, 3 and 4 tumors in comparison with grade 1; and 1,8-fold higher, resp. 2,0-fold higher risks for patients aged more then 60 years in comparison with the population under 60 years of age. The same situation was seen in patients with non-radical surgery (at least total abdominal hysterectomy, bilateral salpingoophorectomy, omentectomy, appendectomy ± lymphadenectomy needed) with 2,2-fold higher risk of recurrence and 2,4-fold higher risk of

death in comparison with women undergoing radical surgery; and with residual tumor of any extent with 3,5-fold higher risks of poorer DFS and OS when compared with the R0 group. The paclitaxel-carboplatin regimen has been defined as a standard treatment of more advanced ovarian cancer, however no statistically significant diference in DFS and OS was associated with the combination of platinum derivate with cyclophosphamide ± adriamycin. Histological tumor type has also an impact on prognosis with the poorest outcome in patients with typical adenocarcinoma in comparison with e.g. endometrioid adenocarcinoma. To our knowledge there are not enough published data about the impact of ovarian cancer side involvement. The involvement of right ovary seems to be a protective factor with the risk of recurrence (cancer death, resp.) beeing 1,7-fold higher (1,3-fold higher, resp.) when the left ovary is involved and 1,6-fold (1,7-fold higher resp.) in bilateral tumors.

According to the last published recommendations not to use tumor markers (mainly CA125) we also focused on this topic. Only preoperative value of CA125 has some kind of prognostic significance with better outcome in patiens with cut-off levels < 280. It has no impact during the next course of the disease; the survival is the same even in the group of early treated (following the raise of CA125) patiens as far as when the next line of chemotherapy was delayed at the time of clinicaly confirmed recurrence or symptoms. Similar prognostic was associated with CA72-4. However, none of markers measured have a predictive value and even the most common CA125 has no impact on prognosis when it ´s rise was detected early. Posttreatment markers monitoring is not helpful and could not be reccomended. We confirmed simile results already Publisher.

Discussion:

The main prognostic factor is a complete tumor resection, so the radical surgery should be performed. It seems not to be important what type of chemotherapy regimen is used in the primary treatment. Probably there is no a standard one today and even the platinum monotherapy can be used with a similar results as it was shown in previously published studies. Even when the number of patients undergoing primary radiotherapy was small in our study, a positive impact of this treatment method on prognosis was clearly seen. By inclusion of more radiated patients the statistical significance should be more pronounced. This will be explained by extanding the study population in our next analyses. Unfortunatelly, the most common histological tumor type; tumor classification T2,3, N1 and M1; G 2,3,4 and stage II., II. and IV. are associated with the poorest prognosis. Probably, earlier surgery due to the symptoms similar to acute or chronic appendicitis could explain the protective influence of this side involvement on prognosis when the risk of recurrence and death are halved against left-sided or bilateral tumors.

Conclusion:

Surgery and probably radiation therapy have a greatest impact on DFS and OS in women with ovarian cancer. The practice changing debate should be started about the re-introduction of radiation therapy in the primary treatment of this disease. The role of chemotherapy is surprisingly very limited because the survival rates of patients treated with monotherapy, dublet or triple combination of cytotoxic drugs is very unfavourable with the median DFS and OS not excceding 4,5 years. The assessment of tumor markers, predominantly CA125 was done too with establishing it´s role. Good prognostic group are only T1N0M0 patients who do not need chemotherapy. The use of tumor markers (CA125) have some role prior surgery only with no impact within the next course of the disease. We need to identify new markers, mainly for screening to find more ovarian cancer patiens with an early stage and better prognosis. Maybe HE4 could be one of them?