

Letters

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Survival of Advanced Ovarian Cancer Patients with Microscopic Partial Response After Surgery and First-line Chemotherapy

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MOST WOMEN with advanced ovarian cancer have persistent or recurrent disease and die of cancer; the overall survival rate at 5 years is less than 10% [1]. Survival is influenced by several factors including the response to first-line chemotherapy, with patients with a complete response after first-line therapy surviving longer [2]. The survival prognosis of women with microscopic disease after first-line chemotherapy is not well defined. We report here 3-year survival rates of women with microscopic disease after first-line chemotherapy.

Between 1982 and 1993, we observed a total of 40 women with stage III ovarian carcinoma who had a microscopic partial response (MPR) to surgery and first-line chemotherapy. The criterion for MPR was the largest residual tumour nodule, after primary surgery and chemotherapy, being <1 cm in diameter. The histology was serous in 28 cases (70%), endometrioid in 6 (15%), clear cell in 2 (5%), mucinous in 2 (5%), undifferentiated in 1 (2.5%) and mixed in 1 (2.5%). 2 patients (5%) had grade 1 tumour, 15 (37.5%) grade 2 and 23 (57.5%) grade 3. Patients' characteristics and 3-year survival rates according to various factors are shown in Table 1.

All patients underwent debulking surgery at first diagnosis. Residual tumour was ≥ 2 cm in 24 (60%) cases and <2 cm in 16 (40%) cases. All received first-line chemotherapy; 19 (47.5%) were treated with a single agent (cisplatin or carboplatin), and 21 (52.5%) with a combination, based on cisplatin plus cyclophosphamide for 16 (40%) patients or doxorubicin for 5 (12.5%) patients. The response was documented with laparotomy or laparoscopy, multiple biopsies and pelvic and abdominal cytologic washing. At second look, 23 (57.5%) women had microscopic disease diffuse in the abdomen, 16 (40%) unifocal disease (15 on the pelvic side, one on diaphragm), and one

Table 1. Patients' characteristics and survival rates for advanced ovarian cancer according to various prognostic factors, Milan, Italy, 1982–1993

	No. of patients	No. of deaths	3-year cumulative survival (%)
Total	40	15	63
Age (years)			
25–54	20	7	73
55–74	20	8	55
Residual tumour after primary surgery (cm)			
≥ 2	24	10	50
<2	16	5	78
Response to first-line chemotherapy			
Multifocal microscopic disease	23	12	60
Unifocal microscopic disease/positive cytology	17	3	72

(2.5%) had only positive washing. After second look, 24 patients (60%) received local therapy: 11 cases with MOV18 (monoclonal ovarian 18) (27.5%), 4 (10%) with T lymphocytes, 9 (22.5%) with radiotherapy. Two women (5%) received systemic hormone therapy, and 14 (35%) were given chemotherapy only at progression; of these, 10 cases received monotherapy (carboplatin, paclitaxel, epirubicin or ifosfamide) and 4 cases received polychemotherapy (doxorubicin, etoposide or cyclophosphamide plus platinum). No patient was lost to follow-up and the present analysis is based on data collected up to December 1993. The median follow-up was 25 months (range 1–131). Three-year cumulative survival was computed using an actuarial method and differences in survival were tested using the usual log-rank test.

Of 40 women, 15 (37.5%) died of cancer, 9 (22.5%) had disease and 16 (40%) were alive with no evidence of disease. The 3-year cumulative survival rate from second look was 63% (Figure 1).

Younger patients and those with residual tumour <2 cm after surgery had longer survival: patients aged 25–54 years had a 3-

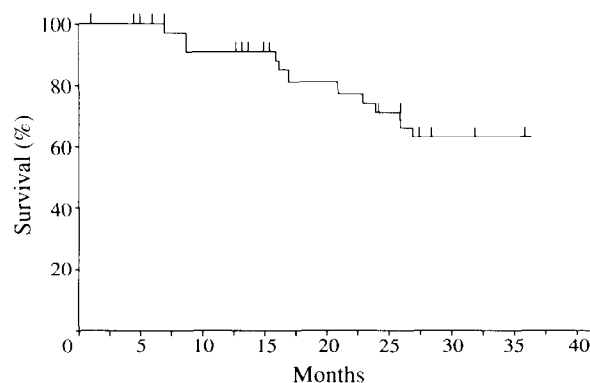


Figure 1. Three-year cumulative survival of 40 ovarian cancer cases, with microscopic partial response after surgery and first-line chemotherapy (vertical lines indicate censored patients). Milan, Italy, 1982–1993.

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year cumulative survival rate of 73% against 55% for those aged 55–74 years; patients with residual tumour <2 cm had 78% survival against 50% in those with residual tumour \geq 2 cm. These differences, however, were not significant (log rank test, respectively, $P = 0.3$ and 0.1), possibly due to the small numbers of patients. There was no difference in terms of survival according to type of response to first-line chemotherapy.

A study conducted by Copeland and associates in Texas, U.S.A., on 50 patients with microscopic persistent disease found similar results [3]. Patients with only microscopic evidence of disease have a good probability of extended survival, and small residual disease at initial surgery and young age may represent favourable prognostic factors.

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Different Detection Rates of *HER-2/NEU* Overexpression in Ovarian Carcinoma Using Two Different Commercially Available Detection Kits

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ALTHOUGH AN increasing number of reports seem to attribute a prognostic role to *HER-2/NEU* overexpression in human tumours, among which perhaps mammary carcinoma [1, 2] is the most notable, the role of this oncogene is far from being definitively established. A worrying feature when comparing many studies carried out on similar series of tumours, using basically the same detection techniques, is that they often yield contradictory and even totally opposite results. The rate of expression of the *HER-2/NEU* oncogene when using immunohistochemistry for detection particularly seems to vary widely from one group to another. This is especially true when we compare most studies performed on ovarian carcinoma, where variations in results are extreme, with expression rates ranging from 19 to 70% for similar series of tumours [3–5]. Recently, a well conducted methodological study was reported [6], where

exactly the same immunohistochemical technique was applied to the tumour samples, for which *HER-2/NEU* amplification had been previously characterised on fresh-frozen aliquots by means of molecular biology techniques. Multitumour blocks were prepared from paraffin-embedded portions of these tumours and cut on to the same glass slides, and immunohistochemistry was carried out only changing the primary antibodies. Twenty-eight antibodies against the *c-erb-B2* protein (21 monoclonal and seven polyclonal) were tested, and the results could not be more distressing: detection rates varied between 100 and 6%. The conclusion of this study was that the ability to detect *HER-2/NEU* overexpression is extremely variable, and that this could provide an important explanation to the different overexpression rates reported in the literature.

Through a finding that was elicited purely by chance (our laboratory had run out of stock of our usual immunohistochemistry kit, and some samples already processed were erroneously reprocessed using a theoretically identical kit from another manufacturer, with strikingly different results), we were compelled to carry out the present study, for internal quality control purposes.

Twenty-two paraffin-embedded ovarian carcinoma samples were studied by means of immunohistochemistry with the streptavidin–biotin–peroxidase technique, as previously reported by us for fresh-frozen tumour samples [7, 8], after previous deparaffination and rehydration of the slides, using the same monoclonal antibody (NCL-CB11, Novocastra, Newcastle, U.K.), but two commercially available immunohistochemistry kits from different manufacturers (kit A: LSAB streptavidin–biotin–peroxidase immunohistochemistry kit, Dako A/S, Denmark; kit B: Histostain-SP, Zymed, San Francisco, California, U.S.A.). The same positive control was used throughout the study, consisting of paraffin slides from a mammary carcinoma known to overexpress *HER-2/NEU* from a previous study carried out by us on fresh frozen tissue [8]. Although the positive control showed equally positive *HER-2/NEU* detection with either kit, and both with 1-h incubation at room temperature (which is the standard technique recommended by the manufacturer of the antibody), or with overnight incubation at 4°C (which is the technique preferred by us, Figure 1a, b, c), the results for the ovarian carcinoma test specimens were extremely different: 13/22 were clearly positive (59%) with characteristic membrane-bound reaction, using kit A overnight, while only four of 22 (18%) were positive using kit B under the same conditions, and two of 22 (9%) using kit B with the standard technique of 1-h incubation at room temperature (Figure 1d, e, f). It must be stressed once again that the positive control was positive in all three instances, and that the negative controls, carried out in parallel for each of the samples tested by omitting the primary antibody and incubating with blocking serum instead, were negative throughout, thus excluding a non-specific reaction from part of any of the kits.

The conclusions to be drawn from this study are that results of *HER-2/NEU* detection are indeed extremely variable, not only due to differences in the detection rate of different antibodies, such as reported by Press and associates for mammary carcinoma [6], but also using the same antibody, but theoretically equivalent detection kits from different manufacturers, as found here for ovarian carcinoma. In our experience, the range of variation is between 9 and 59%. What is worse is that a positive control from a tumour arising from another (human) organ (a common practice in immunohistochemistry) does not guarantee true negative results if no reaction is detected in the test tissues.

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