Nongenital Cancers Metastatic to the Ovary :Our Experience

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Abstract :

Aim : This study was conducted to analyze the incidence, pre-operative and peri-operative clinicopathologic features, patient outcome and prognostic factors in cancers metastasising to ovary. Clinical, serological or radiological factors which would help in pre-operative detection of metastatic ovarian tumours were also analyzed. **Material and Methods :** It is a retrospective study in which records of 700 patients presenting with ovarian malignancies were reviewed. Primary ovarian tumors, tumor metastases from gynaecological tract and lymphomas were excluded from this study. **Results :** A total of 73 cases were identified and followed up. Primary tumor sites were gastric 26% (19/ 73) breast, 23%(17/73), appendix 15% (11/73), colorectal region 15%(11/73) and one case each for lung, thyroid, bladder, anal canal and gall bladder. Metastatic tumors with unknown primary tumors originating from gastrointestinal tract were 13%(10/73). The prevalence of ovarian metastases was 10.4% of ovarian tumors in our study. The median overall survival after ovarian metastasectomy for all patients was 10.67 months. No patient with synchronous or metachronous ovarian metastases survived for more than 5 years. **Conclusion :** Management of tumors metastasising to ovaries is challenging, as it requires detailed pre-operative planning and involvement of surgical oncologists for optimal surgery. However, most of the metastases were detected only during surgery or after a histological diagnosis. Radiological pre-operative detection rate was < than 10%. There is currently no optimal or curative treatment strategy for these tumors. The significant factors in increasing survival were the optimal surgery for both the primary tumor and the metastases and adjuvant chemotherapy.

Key words: Breast, Gastrointestinal tract, Metastasis, Ovary.

Introduction :

A malignant ovarian mass encountered clinically can be a metastatic lesion, the most common sites of origin being the colon, breast and stomach. [1] The identification of the primary tumor pre-operatively is required to avoid inappropriate treatment and sub-optimal outcome. [1,2] Only a few studies are available which have described the secondary ovarian tumors from non-genital sites. We hereby describe our experience of 73 patients with ovarian metastases from non-genital sites at our institute.

Material and Methods:

Records of 700 patients with diagnosed ovarian

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cancers who were treated at our institute between 1st November 2009 to 31st October 2013 were reviewed. These patients also included those who were operated outside our institute but had come for follow-up at any time during their course of treatment. Efforts were made to contact the patients who were lost to follow up by writing to them or calling them. Ovarian metastases confirmed by histological and immunologic stains were included in the study. Metastatic tumor from lymphomas and other genital tract i.e., uterus, cervix and fallopian tube were excluded from the study. A search for primary tumor, if not known, was done with pathological or clinical confirmation of the primary tumor. However, the primary tumor remained undiagnosed in 13.7% of cases.   73 patients with histologically or immunologically confirmed metastatic ovarian cancer were selected for this study.

Patient information including age, presenting complaints, menopausal status, parity, blood group, weight, serum Ca-125, serum Carcinoembryonic

antigen(CEA), site of primary malignancy, interval between the diagnosis of primary and secondary tumor, tumor size, laterality, consistency (solid,cystic), type of surgery (optimal, sub-optimal, palliative, biopsy) chemotherapy, follow-up and months of survival were recorded. Pre-operative diagnostic imaging findings in diagnosing origin of primary malignancy were also analyzed.

We also analyzed the clinical effects of cytoreductive surgery in treating metastatic ovarian cancer. Surgery was considered optimal when total abdominal hysterectomy with unilateral or bilateral salpingo-oophorectomy with pelvic lymph node dissection, omentectomy along with excision of primary tumor was done with residual tumor < 2 cm. Surgery was considered sub-optimal if residual tumor was >2 cm or incomplete removal of ovaries or primary tumor could be done. The other two groups comprised of palliative surgery and only biopsy groups. All data for all the patients was not available, so results were calculated as percentages of the total available data. Loss of follow-up for more than 6 months was evaluated as loss of survival. Statistical analysis was done by univariate analysis(Kaplan -Meier) method. Multivariate analysis using Cox Regression (Hazard Ratio) was done using all the significant factors.

We analyzed the

1) Effects of known primary/ primary diagnosed peri-operatively and undiagnosed primary in terms of survival.

2) Effect of optimal versus sub-optimal, palliative or no surgery in survival.

3) Effect of adjuvant chemotherapy in prolonging survival.

4) Correlation of age, parity, menopausal status, blood group and weight in survival and pre-operative diagnosis of metastasis.

Results :

Out of the 700 cases of ovarian cancers analyzed, a total of 73 (10.4%) cases were identified as metastatic ovarian cancers. The commonest primaries were carcinoma stomach followed by carcinoma breast. The primary sites were grouped as

1) Stomach 26% (19/73)

2) Breast 23% (17/73)

3) Appendix 15% (11/73)

4) Colorectal 15% (11/73)

5) Unknown primary tumors originating from GIT 13% (10/73)

6) Others - one case each for lung, thyroid, bladder, anal canal and gall bladder which were grouped together as others.

The prevalence of ovarian metastases was 10.4% in our study. However, as all patients were not regular in follow up, exact data regarding their survival, recurrence or metastatic tumors are unavailable. The absence of a Centralized Cancer Registry increases the problem if the patient follows-up elsewhere. The clinical characteristics of the patients are summarized in Table-1

Out of the 73 patients, 23.2% had known primaries which were mostly cases of Carcinoma Breast. 9.5% (7/13) were diagnosed during imaging, 32.8% (24/73) during surgery ,20.8% were diagnosed by histopathological or immuno-histochemistry reports. 13.6% remained undiagnosed primaries from GIT.48/73 (65%) were post- menopausal.

In univariate analysis, known primary, post-menopausal status, previous chemotherapy, optimal surgery and post-operative chemotherapy were found significant in prolonging survival. However, in multivariate analysis using Cox -regression, pre-operative chemotherapy and menstrual status lost its significance (Table-2).

Table 1 : Clinical characteristics of patients

Parameters	Breast	Stomach	Appendix	Colorectal	Undiagnosed-GIT	Others
Number of patients	17/73(23%)	19/73(26%)	11/73(15%)	11/73(15%)	10/73(13%)	5/73(6.8%)
Age (in years)	33-56	22-55	35-79	18-70	22-60	37-55
Post-Menopausal	15/17(88%)	12/19(63%)	10/11(90%)	4/11(36%)	4/10(40%)	3/5(60%)
Known primary	15/17(88%)	1/19(5.2%)	0/11	0/11	0/10	1/5(20%)
Months of survival after diagnosis	2-48	2-16	3-19	1-15	2-8	6-19
Interval in months from primary (2-174 months)	2-174	36	NA	NA	NA	34
Previous Chemotherapy	15/17	3/19	1/11	3/11	1/10	0/5
Ca125 values	23-2107	11.4-1052	37.83-1168	22.7-1188	39-1165	68-443
CEA values	0.86-99	0.98-99.1	3.34-76.86	1.78-31.4	0.86-481.4	0.64-402.8
Weight in kg	45-78	35-81	30-75	43-70	50-87	55-90
Tumour size (cm)	8-14.5	5.1-17	5.2-16	6.5-16	5.8-15	9-16
Laterality	17/17	12/19	7/11	7/11	5/11	3/5
Gross (Solid-Cystic)	11/17	7/19	3/11	8/11	5/11	3/5
Ascites	8/17	12/19	9/11	4/11	5/10	2/5
Other Mets +ve	8/17	15/19	9/11	7/11	5/10	4/5
Optimal Surgery	13/17	5/19	7/11	6/11	5/10 (Residual disease < 2cm)	1/5
Post Operative chemo	16/17	17/19	11/11	9/11	6/10	5/5
Months of survival (months)	2-48	2-15	7-19	1-14	2-8	6-19

Table 2 : Univariate and Multivariate Analysis

Prognostic Variables	Univariate Analysis		Multivariate Analysis	
	ExpHR (95% CL)	P value	ExpHR (95% CL)	P value
Known Primary	5.59(2.81-11.12)	0.000	3.00(1.31-6.88)	0.009(significant)
Post-Menstrual	0.50(0.26-0.97)	0.042	0.64(0.31-1.30)	0.245
Previous Chemo	0.28(0.12-0.67)	0.004	0.57(0.230-1.42)	0,229
Surgery	2.73(1.70-4.38)	0.000	2.68(1.59-4.50)	0.000(significant)
Post Chemo	0.017(0.003-0.09)	0.000	0.02(0.004-0.184)	0.000(significant)

Survival in metastases to ovary is not related to age, size, laterality or tumor marker levels.

The mean size of tumors was 9.18 cm in tumors from known origin as compared to 11.5cm in tumors diagnosed later or undiagnosed. The maximum size of tumor was 17 cm. However, the size of the tumor did not affect pre-operative detection, optimal surgery or survival.

Ascites was present in 54.7% (40/73) of patients and tested positive for malignancy in 25% (10/40). The presence or absence of ascites did not affect detection, cyto-reduction or survival. The mean survival in patients with no ascites was 18.747 months, with ascites was 16.930 months and with ascites positive for cancer cells was 16.803 months, with no significance in survival (P=0.904).

Bilateral ovarian metastases was found in 69.86% (51/73) patients, with mean survival of 21.201 months. Patients with unilateral ovarian involvement had a mean survival of 11.36 months, thus unilateral or bilateral metastasis had no significance in survival (P= 0.126). Average weight was 56 kgs and there was no significant difference between different groups.

Serologically, serum Ca-125 was elevated in 95.5% (64/67)cases of all tumors. However, increased Ca-125 is a non-specific marker and is increased in primary ovarian tumors, it had no predictive value in differentiating primary and secondary ovarian cancer. It also had no predictive value during follow-up of these patients.

Serum CEA was elevated in 37.2% (22 / 59) cases and normal in 62% (37/ 59) cases. 9 patients had CEA values between 50-100 with highest being 402.8 in tumor of GIT with unknown primary. The values were unavailable in the rest. So raised CEA can raise suspicion and investigations to rule out another primary tumor can be done pre-operatively. However, normal CEA values did not have any significance in survival.

31.5%(23/73) cases had received chemotherapy after either primary surgery or pre-operatively as neo-adjuvant chemotherapy for present tumor and had mean survival of 28.43 months (95% CI- 20.514-36.349). The mean survival in non-treatment groups was 11.23months (95% CI 9.432-13.044). The median survival was 31 months for pre- treatment group and only 10 months for those who did not receive chemotherapy in past. The role of previous chemotherapy was statistically significant with P value <0.001.

87.6% received chemotherapy post-operatively with mean survival of 20 months (95% CI- 15.822- 25.324). The longest survival of 48 months was seen in a patient with metastasis from carcinoma breast. 15 patients were on regular follow up at the closure of study. The mean survival in non-treatment groups was 3 months (95% CI 1.975-4.025) with maximal survival documentation of 5 months. The median survival was 2 months (95% CI- 1.270- 2.370) for non-treatment group and 14 months (95% CI- 11.175- 16.25) for patients receiving chemotherapy. Post-operative chemotherapy was significant in survival with P value < 0.0001.

Mean survival was 24 months with optimal surgery as compared to 12.62 months with sub-optimal and 6.089 months in palliative surgery or in-operable cases.

Primary tumor site was a significant factor in survival. The overall mean survival in patients of metastatic ovarian tumors was 18.79 months with a median survival of 13 months. Patients with carcinoma breast as primary had better prognosis followed by carcinoma appendix in patients with ovarian metastasis. This was also because most of the patients were already treated for carcinoma breast and on regular or irregular follow-up with the institute allowing for early detection. (Figure-1)

Figure: 1 Primary Cancer Sites and Survival
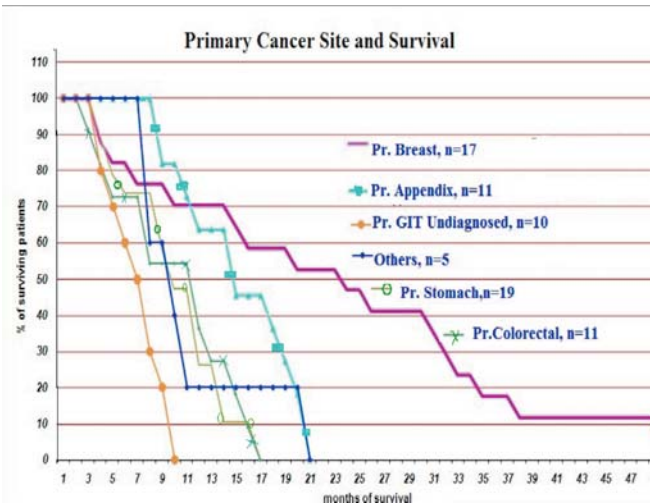
Also optimal surgery was performed in 76.47%(13/17) of carcinoma breast patients, 26.31%(5/19) in carcinoma stomach, 63.63% (7/11) in carcinoma appendix group, 54.54%(6/11) in colorectal group and in only 1 in other different malignancies. For the GIT tumors proven only by IHC, surgery was considered optimal in the 50% of patients who had residual disease <2cm. Thus, patients with optimum surgery fared better in months of survival.

The Median survival of patients was only 5.48 months with unknown primary as compared to 13.53 months in primary tumors diagnosed during investigations, surgery or by HPE/IHC. However patients with known primary tumors showed a median survival of 32.73 months. (Figure-2)

Figure 2: Known Primary Site and Survival
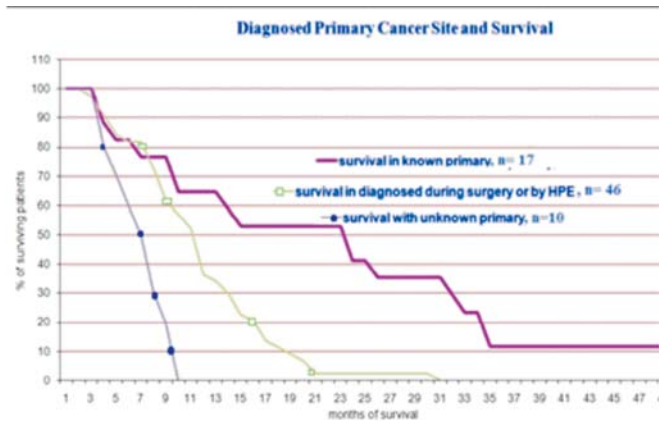
The hazard to survival was 1.76 times per category in case of unknown primary, 1.61 times if the surgery was sub-optimal instead of optimal. Post-operative compliance to chemotherapy reduced hazard to survival by 75%. (Figure 3,4)

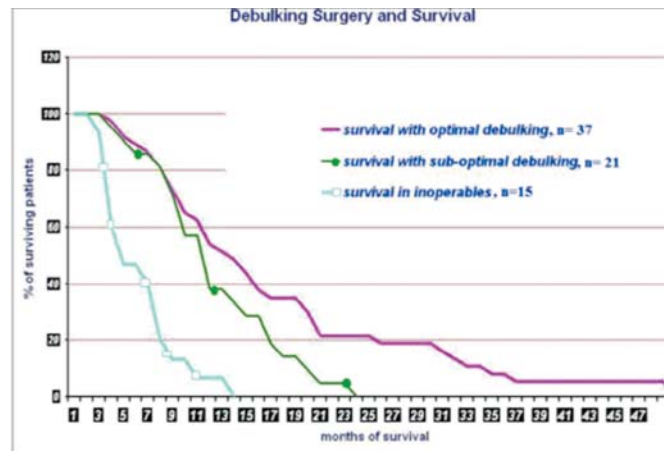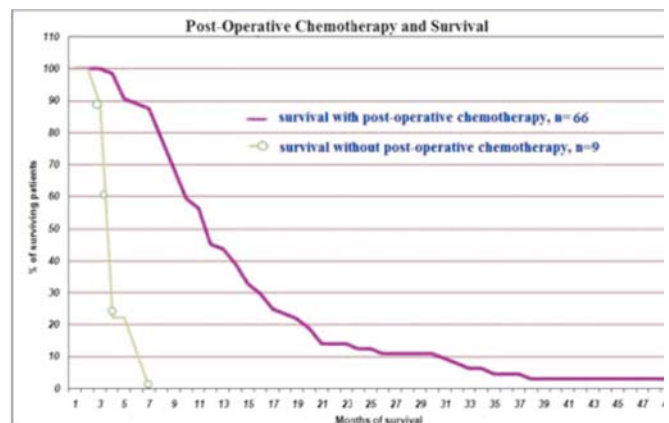**Figure 3 : Debulking Surgery and Survival**

Figure 4 : Post –operative Chemotherapy

During the 4 years of study, only 13(17%) patients were on regular follow up, 17 (23%)patients were lost to follow up and 43(58%) had expired.

In patients with metastasis from carcinoma breast, 70% (12/17) had survived at the end of 1 year, 47%(8/17) at the end of 2 years and only 2 patients survived at the end of 3 and 4 years. However, despite optimal surgery and multiple chemotherapies, they had widespread bone metastasis and multiple complications during the last year of their survival.

In metastasis from stomach cancer, only 10%(2/19) patients survived after 12 months and 52%(10/19) expired within first 8 months. Although 10%(2) patients survived for 15 months, they presented with ascites and recurrent intestinal obstruction in their last months of life.

8/11(72%) of patients having metastasis from carcinoma appendix survived during the first year but none of them survived at the end of 24 months.

In metastasis from GIT (colorectal), only 27%(3/11) patients survived at the end of 12 months whereas none of the patients survived up to 1 year in patients in whom primary tumor site remained undiagnosed.

However 68%(50/73) patients survived at the end of 6 months only 34%(25/73) patients survived at the end of first year.

Discussion :

The prevalence of ovarian metastases was 10.4% in our study as compared to global 1.7 – 13.6%.[1,3,4,5,6,7] As our Institute is a Centre for Cancer patients, so overall detection rate is higher as many patients were already in our follow up for some other cancer.

The overall increase in the incidence of ovarian metastases is also due to progress in diagnostic criteria for distinguishing primary and metastatic ovarian tumors in case of mucinous adenocarcinoma due to increased skill of pathologists as well as introduction of immunologic markers like CD7 and CD20. [1, 7] Also, many cases were detected outside pre or post-operatively and later on referred to our centre, thus making the over-all percentage higher.

The most common primary cancer site in other studies were breast followed by colon and then stomach. [1,2] Moore et al and Ulbright et al reported colon as the most common site resulting in metastatic tumor to ovary followed by appendix and breast . [3, 5] In our study, the commonest site was stomach followed by breast and colon. This maybe because our south east Asian region and East Asian region has greater incidence of gastric cancer as compared to the Western World. [7]

The survival of patients with cancers metastatic to ovary remains very poor. Other studies also show an overall poor prognosis. [1] Recent studies have shown an overall 5-year survival of 18.5% with 11% from GI origin tumors and 26-44% in metastasis from breast (non-GI) cancers. [1, 8] These trends were similar to as observed in our study.

The increased survival in tumors originating from breast may be due to either early detection or possible optimal surgery. Also, previous history of breast cancer preceded detection of metastasis in 86-88% in other studies which is similar to our pre-operative detection rate of 88.2%. [1, 4] Better prognosis in carcinoma breast with disseminated primary disease giving rise to ovarian metastasis can also be explained by the availability of newer therapies. [1]

Some studies have also reported no 5-year survivors amongst patients with primary stomach as seen in our study. [6] This may be due to inoperability of these tumors. [6]

A recent study on Krunkenberg tumours from stomach has reported overall survival range from 4 up to 70 months with optimal surgery and newer chemotherapeutic agents unlike previous studies in which median survival ranged from 9 to 11 months. [9,12] Our study showed a maximum survival of 15 months. Unknown primary with no gastro-intestinal surgeries had the worst prognosis in most studies except a few studies showing 32% five year survival rate. [1]Better prognosis with optimal debulking surgery is reported by many studies. [4,6,7] However, prognosis was worse with debulking surgery in a study in Sweden perhaps due to presence of extensive disease and a prior worse prognosis. [1]

Menopausal status has been reported to be a prognostic factor in some studies but other authors and our study did not find it to be significant. [6, 10]Petru et al reported unilateral metastasis from colonic cancer to be significant in survival. [6] However, he reported no significant differences in breast and gastric cancer. Li et al reported no significance of laterality, size of ovarian

metastases, presence of local invasion, serum Ca-125 and CEA levels similar to our study. [10]Detection of GI-origin tumor at the time of surgery indicates that these patients could have been more thoroughly investigated. [1] However, even with thorough pre-operative work up, the diagnosis and management of ovarian metastases from extra-genital sites is challenging in up to 50% of cases. [10] Antila et al concluded that primary and secondary ovarian malignancy could not be distinguished by age, parity and menopausal status. [11] Higher CEA levels, smaller (62-89 mm) and more often solid tumors were seen in metastatic tumors as compared to primary in his study. [11] The patients in our study mostly presented at a later stage with large solid-cystic masses.

The mechanism of ovarian metastasis has largely been discussed in the literatures. Commonly described routes of metastases for metastastic ovarian tumors arising from extragenital primary cancer include direct invasion and surface implantation. Other possible routes for gastric cancer to disseminate to ovary may include lymphatic drainage via the receptaculum chili to the urogenital lymph vessel trunks and hematogenous spread from gastrointestinal tract tumors . [13] The lymphatic dissemination and transcoelomic spread are also proposed to be important mechanisms due to the high incidences of synchronized involvement of peritoneum and lymph nodes in colorectal cancer . [14]

This study had certain limitations. The role of nutritional status, financial support, and regular follow-up are major factors in outcome and survival of these patients but has not been included in the study due to practical limitations. It was also seen that use of newer drugs in chemotherapy prolonged survival and outcome in the patients who were enrolled later.

Staging of the primary tumor could not be taken into account due to unknown primaries. As all the patients were not operated at Cancer Institute's with trained surgical oncologists, the extent of operability at the time of primary surgery would have varied. Histological grade of tumor could not be taken into consideration due to limited data availability.

Conclusion :

Management of tumors metastasising to ovaries is challenging, as it requires detailed pre-operative planning and involvement of surgical oncologists for optimal surgery. However, most of the metastases were detected only during surgery or after a histological diagnosis. Radiological pre-operative detection rate was < than 10%. There is currently no optimal or curative treatment strategy for these tumors. The significant factors in increasing survival were the optimal surgery for both the primary tumor and the metastases and adjuvant chemotherapy.

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