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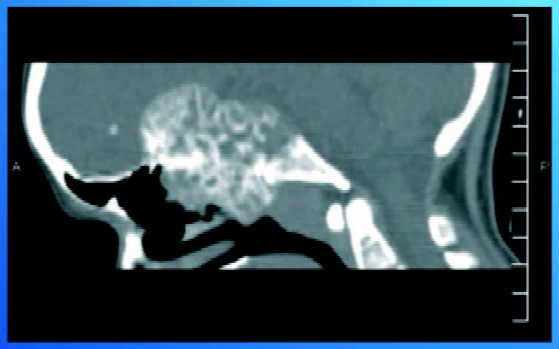

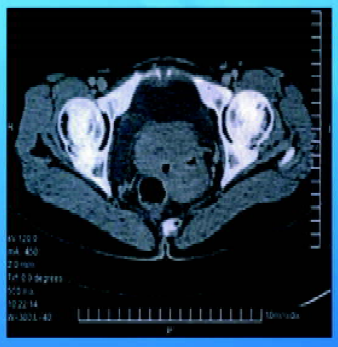

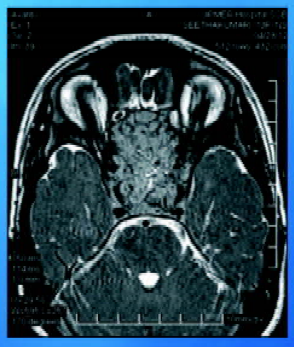

Editor-In-Chief
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Acknowledgements

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The Journal

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EDITORIAL

It is with a lot of trepidation I write this, though it is a great honour and pleasure to write the first editorial of a new journal "JIPMER Journal of Cancer", which you hold in your hands. This marks a significant milestone in the history of Regional Cancer Center at JIPMER which started with humble beginnings and rose to an important tertiary cancer care center in this part of the country.

The start of new journal is always an exciting event. I have witnessed the hard work and commitment required to make this journal happen. You might wonder as to the need for another journal when there are a number of journals already available and a lot of information is available to us through electronic information. Most of us practice our profession with a lot of limitations in terms of adequate / up-to date laboratory investigations, pathological typing, X-ray, CT, MRI, Nuclear medicine studies and modern facilities for management. Many of us work hard and when we try to report our experience and get these published we face a high rejection rate. Most of us also receive comments like our work perhaps is more suitable for local readers; the standard of care apparently isn't up to the standard of big centers in the developed countries. It is with these factors in mind we present this journal to all practitioners of oncology in our country to present their experience and be heard / read. I hope this journal will assimilate all the needs of oncologists and prove popular. It should stimulate most of you to write your experiences and express your views.

The journal will be published initially twice a year and we would like to see its frequency increase and become a leading journal in the field of oncology. The papers submitted will be subjected to strict reviewing procedures before publication.

The journal has three sections viz.: review articles to be written by experienced oncologists, original articles relating to work done, interesting case reports and images. One can also send in their opinions through comments and letters to the editors.

Several esteemed colleagues have been inducted into the editorial board, which of course will be expanded to represent all aspects of cancer and its management. I hope all of you will read this new journal and also send in your views to share with colleagues who are interested in cancer care. It is only with your support, this venture will become a success and compete with similar journals.

I wish to thank all my colleagues at Regional Cancer Center, JIPMER, Puducherry who have contributed immensely to bring out this new journal, which was not at all an easy and simple job. My special thanks to Dr. Shyama Prem who has committed herself for this job and to bring out this journal. I hope it will establish itself as a highly ranked journal in the field of cancer.

Dr. K.S. Reddy
Director
Regional Cancer Centre
JIPMER.

Review Article

Risk of cancer in women on hormone replacement therapy – an overview

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Abstract

Hormone replacement therapy (HRT) has been used extensively in postmenopausal women as a proven and effective therapy for the relief of menopausal symptoms and for prevention and treatment of osteoporosis. The two important cancers associated with HRT are breast cancer and endometrial cancer. Unopposed oestrogen therapy in post-menopausal women with intact uterus is associated with increased risk of endometrial carcinoma. There is an increased risk of invasive breast carcinoma in women who are on combined oestrogen and progestin regimen than on oestrogen alone. HRT increases the rate of recurrent breast cancer in breast cancer survivors. Tibolone was effective in relieving symptoms and the cancer recurrence rate in the Tibolone group was comparable to that of untreated controls. When HRT is indicated, it should be prescribed in the lowest possible dose or the shortest period to control symptoms. It is important to evaluate the risk benefit ratio of HRT and necessary modifications or alternative therapies should be advised to relieve the menopausal symptoms.

Keywords: Hormone replacement therapy, cancer

Introduction

Hormone replacement therapy has been used for treatment of menopausal symptoms for over 50 years. Unopposed oestrogen was used in postmenopausal women with an intact uterus which resulted in increased incidence of endometrial cancer and therefore was replaced by a combination of oestrogen and progestin. But recent trials have highlighted that risks outweigh the benefits with increased incidence of carcinoma breast and cardiovascular accidents. HRT has recently fallen out of favour and alternatives to HRT are being considered. The risks and benefits of hormone therapy to treat menopause related symptoms and prevent diseases such as osteoporosis in peri and postmenopausal women has always been a source of confusion.

HRT and Breast cancer risk

Several epidemiological studies most notably Women's Health Initiative (WHI) and

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Million Women's Study (MWS) reported several adverse effects among users of HRT including breast cancer.

WHI [1] was designed to study 16,608 women who were in the age group of 50 to 79 years at the time of enrolment. Cases of early menopause and premature ovarian failure were not included. It contained two arms - one arm included cases of surgical menopause on Conjugated Equine Oestrogen (CEE) and the other arm CEE and Medroxy Progesterone Acetate (MPA). It was designed to evaluate the long term benefits and risks, but not vasomotor symptoms. In the CEE / MPA group there was no increased risk of invasive breast cancer in the 75% of women who had never used HRT before starting the trial. However in the remaining women, HRT increased the risk of breast cancer after 5 years of use by 8 additional cases for every 10,000 women using combined hormones for one year. The risk returned to baseline 5 years after stopping the therapy. These women had more advanced tumors, but there was no increase in insitu breast cancer.

In the Oestrogen only arm the use of CEE alone for 7 years was not associated with an increased incidence of breast cancer among hysterectomized women.[2] Results of these trials cannot be compared directly as they involved two different populations with different characteristics and risk factors. But several authors have inferred these data and other observational data and suggested a greater risk of breast cancer in women using combined Estrogen + Progestin (E + P) therapy than women using Oestrogen therapy alone (ET) indicating progestins have adverse effect on breast cancer incidence. It is not clear whether the risk differs for continuous versus sequential use of progestogen. Available evidence suggests that oestrogen alone for fewer than 5 years has little impact on breast cancer risk.

The Million Women Study (MWS)[3] is a large observational study of 870,000 women who are followed with screening mammogram for an average of 2.6 years, for both hormone users and non-users. The relative risks for invasive breast cancer were 1.00 for women who never used oestrogen, 1.01 for women who used oestrogen at some point in the past, 1.30 for women who currently used oestrogens alone and 2.00 for women who currently used oestrogen plus progestin. The increase in breast cancer mortality in current users was not statistically significant.

Observational data suggesting that ET for longer than 5 years may increase the risk of breast cancer are limited and data on HRT's impact on breast cancer mortality are minimal. E + P therapy and to a lesser extent ET increases breast cell proliferation, breast pain and mammographic density. E + P therapy may interfere with the interpretation of mammograms.[4]

HRT and risk of breast cancer in post-menopausal women

Several randomized controlled trials have been conducted to evaluate the risk of breast cancer. Some of these trials include the following

1. With ET use alone, the average risk of invasive breast cancer was 0.81 in four randomized trials involving 12,643 women. [5]

2. With E + P therapy the average breast cancer risk was 1.24 in randomized trials involving 19,756 women. [6]

3. The absolute effect of E + P therapy in WHI and heart and oestrogen and progestin replacement study trials added 8 and 17 cases per 10,000 women per year respectively, to natural risk. [6]

4. Data from Million women study showed the increased risk to current users of ET, EPT and Tibolone as 1.30, 2.00 and 1.45 respectively but the magnitude of the associated risk was substantially greater for E + P therapy than the other types of HRT (P<0.0001).[3]

5. Six epidemiological studies including MWS showed the average relative risk with sequential and continuous progestin regimens were 1.85 and 1.94 respectively, a difference that was not significant.

6. The increased risk of breast cancer risk diminished soon after discontinuing hormones and largely disappeared by 5 years of cessation.[7]

7. Use of Low Dose HRT – Dose of oestrogen is considered low when CEE is 0.3 mg, 0.05 to 1 mg oral E_2, 25 - 75 μg transdermal E_2. For progestogen dose of MPA 1.5 to 5 mg, Levonorgestrel (LNG) 5 to 20 μg are considered low. Studies have shown that low dose regimens were as efficacious as conventional regimens for relieving vasomotor symptoms with a possible lag of few weeks in the onset of effect. [5]

The WHI randomized controlled trial reported on the extended follow-up of 10,739 women and assessed the long-term effects of oestrogen use on invasive breast cancer incidence, tumor characteristics and mortality. After a median follow-up of 11.8 yrs, the use of oestrogen for a median of 5.9 yrs was associated with lower incidence of invasive breast cancer (151 cases 0.27% per yr) compared with placebo (199 cases, 0.35% per yr) HR:0.77, 95% CI 0.62-0.95; p=0.02. In a subgroup analysis they also observed that breast cancer risk reduction with oestrogen was concentrated in women without benign breast disease (p=0.01) or a family history of breast cancer (p=0.02). In the oestrogen group, fewer women died from breast cancer (six deaths, 0.009% per year) compared with controls (16 deaths, 0.024% per yr; HR: 0.37, 95% CI 0.13-0.91; p=0.03). These findings provide reassurance for women post hysterectomy seeking relief of symptoms in terms of the effects of oestrogen use for about 5 yrs on breast cancer incidence and mortality.[8, 9]

HRT and women with benign breast disease

HRT can be prescribed to these women as the risk of developing breast cancer is not affected by it. [10]

HRT and women with risk factors for breast cancer

HRT can be offered for women with a family history of breast cancer after proper counselling. Risk of developing breast cancer is 2-4 times more if the first degree relative has history of breast cancer and the risk increases further if two first degree relatives are affected or if it occurs premenopausally. Available data suggest that the addition of HRT does not further increase the risk. [11] Armstrong et al [12] found that prophylactic bilateral oophrectomy improved life expectancy in women with BRCAI / II mutation irrespective of whether HRT was used or not after oophrectomy. These women should decide on the use of HRT based on quality of life decisions.

SERMS and breast cancer

The two drugs which belong to selective oestrogen receptor modulators which have been tried in various trials are Tamoxifen and Raloxifene.

Women who were randomly assigned to Tamoxifen showed a 36% reduction in the incidence of ductal carcinoma in situ, a 46% reduction in invasive breast cancer, a 48% reduction in oestrogen receptor (ER) positive tumors and no significant reduction in the incidence

of ER negative tumors. But it was associated with 2.4 fold increased incidence of endometrial carcinoma, a 1.9 fold increase in deep venous thrombosis and 1.5 fold increase in cerebrovascular accidents. [13]

Women who were randomly assigned to Raloxifene showed reduced incidence of all breast cancers by 62%, invasive breast cancers by 72%, invasive ER positive breast cancers by 84% and no reduction in ER negative tumors similar to the above study. There was no reduction in ductal carcinoma in situ. There was a threefold increase in thromboembolic events but no increase in uterine bleeding or endometrial cancer. [14]

HRT after breast cancer diagnosis and treatment

In survivors of breast carcinoma, use of HRT remains controversial. Menopausal symptoms may appear early and are severe in these patients either due to bilateral oophrectomy or due to chemotherapy, specifically Cyclophosphamide which is known to cause ovarian ablation as a part of treatment of breast cancer. There are no established guidelines for prescribing HRT to these women and each patient needs to be carefully counselled about the risks and benefits. Oestrogens are generally not given due to the belief that they promote breast cancer growth. It may stimulate cancer cells left behind by the primary treatment. There is also an increased risk of developing contra lateral breast cancer. HRT also increases the frequency of abnormal mammograms possibly by increasing mammographic density which could lead to a delay in diagnosis of breast cancer recurrence or a new primary.

HABITS Trial 2004 [15]

This included 434 women with menopausal symptoms treated for early breast cancer who were randomized to HRT or placebo regimen for 2 years. When trials were terminated early, interim analysis showed an unacceptably high risk with HRT with a hazard ratio of 3:3. There were 26 new breast cancer events in HRT group which included 11 local recurrences, 10 cases of distant metastasis and 5 contralateral breast cancers compared to 8 events in the placebo group.

4 year follow up of HABITS Trial [16] supports the recurrent breast cancer risk in women on HRT. At the time of this analysis 39 (17.6%) of the 221 women in HRT treatment arm had developed breast cancer recurrence or a new breast cancer compared to 17 (7.7%) of 221 women in the control arm. The estimated 5-year cumulative rate for disease recurrence was 22.2% for HRT arm and 9.5% for control arm, for an absolute increase in risk of 14.2%.

Based on various studies, HRT should not be used in breast cancer survivors and alternative therapies should be used.

The increased use of aromatase inhibitors in the treatment of breast cancer is a further cause of concern for osteoporosis risk. In postmenopausal women, they tend to accelerate bone loss due to their profound suppression of circulating oestrogen levels.

Anastrazole was associated with a significant increase in fracture risk compared to Tamoxifen. Balanced diet, exercise, supplementation of calcium, vitamin D and bisphosphonates has been found to be useful in the prevention and treatment of osteoporosis. Raloxifene was found to be useful in the reduction of risk of vertebral fracture and also in relative reduction in the risk of breast cancer. This was seen for oestrogen receptor positive tumors and not for ER negative tumors. [17]

Tibolone

It has an advantage over conventional HRT in terms of breast cancer risk. It also does not

increase breast density and therefore does not negatively affect mammographic screening for breast cancer. Women on Tibolone require fewer repeat mammograms. Dimitrakakis et al, [18] in their study to assess the safety and efficacy of Tibolone for climacteric symptoms in breast cancer survivors who were on Tamoxifen for 5 years and followed for 61 months, showed that Tibolone was effective in relieving symptoms and the cancer recurrence rate in the Tibolone group was comparable to that of untreated controls. It also prevented hot flushes and had no untoward effects on endometrium. It has a beneficial effect on mood and sexual well being and also has a beneficial effect of preventing and/or treating osteoporosis.

SERMS like Raloxifene are useful and safe in breast cancer survivors for the prevention and management of osteoporosis and for relief of vasomotor symptoms. Non hormonal treatments like Clonidine, selective serotonin reuptake inhibitors, herbal medicine, etc. can be tried for relief of vasomotor symptoms. Tibolone has beneficial effects on vasomotor symptoms and urogenital symptoms and is a safe alternative to HRT in breast cancer survivors. Urogenital symptoms like vaginal dryness can be treated with non oestrogen treatments like K-Y jelly and vaginal moisturizers and should be considered as first line treatment in breast cancer survivors. Although systemic or topical ET is the most effective method for treating hypo estrogenic urogenital symptoms, breast cancer survivors should be cautioned to avoid ET therapy in any form to avoid its potential contribution to recurrent breast cancer. [19]

HRT and Mammography

Increased breast density can impair interpretation of mammograms and increases the failure rate of breast cancer screening program. [20] HRT use is associated with lowered sensitivity with more false negative mammograms due to increased breast density. Greater mammographic density was associated with the use of E + P therapy regardless of how the progestin was given, but not with the use of oestrogen alone. [21] Progestin use is associated with increased breast density. Stopping the HRT for few weeks before mammogram may improve its diagnostic accuracy. Low dose progestin may decrease the density. HRT use does not independently predict the accuracy of screening mammography but increased breast density reduces accuracy.

HRT and Endometrial cancer

Unopposed ET is associated with an increased risk of endometrial hyperplasia and endometrial carcinoma in patients with an intact uterus treated for menopausal symptoms.

Studies have shown 5 to 10 fold increase in the incidence of endometrial carcinoma in women taking ET which is related to oestrogen dose and duration of therapy. Risk of developing endometrial carcinoma persists for at least 5 years after it is stopped. In PEPI trial, [22] CEE used in a dose of 0.625 mg unopposed resulted in a typical endometrial hyperplasia in 30% of study subjects. Recently, lower doses of oestrogens i.e. CEE in a dose of 0.3 mg for 1 to 2 years have resulted in 2-3% of cases developing endometrial hyperplasia. Use of ultra low dose unopposed transdermal oestrogen in a dose of 14μg per day for 2 years resulted in only one case of hyperplasia among 188 women treated. [23]

Addition of progestin reduces the risk. Several studies are being undertaken regarding the safety of systemic ET in conjunction with levonorgestrel releasing intrauterine system (IUS) which releases 20μg of progesterone per day to provide an excellent endometrial protection without the need for systemic progestin administration. Continuous low dose progestin may offer endometrial protection equivalent or superior to that of cyclical therapy.

So, reducing the effective minimal doses of oestrogen, using low dose progestins, not using HRT not more than 5 years, effectively reduces the incidence of endometrial carcinoma.

HRT for Endometrial carcinoma survivors

The common belief is that HRT might increase the risk of recurrence as it is an oestrogen dependent tumor. Studies have shown that HRT can be used for low risk endometrial carcinoma survivors who were Stage I, Grade 1 or 2 and less than 50% of myometrial invasion without an increased risk of recurrence to control their vasomotor symptoms. [24]

Use of Tamoxifen for a long term is associated with increased risk of endometrial carcinoma. In BCPT trial the risk of endometrial carcinoma was 2.5 times greater with Tamoxifen. [25] Patients need to be monitored while on Tamoxifen for any irregular bleeding and by transvaginal sonography with endometrial biopsy to rule out hyperplasia and cancer. Raloxifene is not associated with an increased risk of endometrial carcinoma and is useful for prevention and treatment of osteoporosis but not vasomotor symptoms. Tibolone is a better option and though the MWS study suggested a slightly increased risk of endometrial carcinoma, more randomized controlled trials are needed to confirm this finding. [26]

HRT and Ovarian cancer

Combined oral contraceptives given in the reproductive age for contraceptive purposes are known to reduce the risk of ovarian cancer by almost 50%. Studies have suggested there may be a slightly increased risk of ovarian cancer in women using ET which may be dose and duration related. The WHI investigators reported a small non-significant increase in ovarian cancer risk in women treated with E + P group compared to placebo in a 5½ years follow up study. [1] The difference was small and not statistically significant. HRT may be considered for distressing vasomotor symptoms after proper counseling.

HRT and Colorectal cancer

There is a decreased incidence of colorectal cancer with the use of combined HRT. Studies have shown that the risk is reduced by 1/3 in current and recent users of HRT. [27]

HRT and Lung cancer

In the Women's Health Initiative (WHI) randomized study, use of oestrogen plus progestin increased the lung cancer mortality. Though the incidence did not differ, women who took oestrogen and progestin were more likely to die of the disease than those who took the placebo. However there were no differences in the number of deaths from lung cancer among women who took oestrogen alone compared with those among women who took placebo. [28] After a mean follow-up of 7.9 yrs, 61 women in oestrogen group were diagnosed with lung cancer compared to 54 in placebo group. Non-small cell lung cancers were equal in number, stage and grade in both groups. Deaths from lung cancers did not differ between the groups (34 vs 33). [29]

There is very little information available regarding the relationship of HRT use with regard to cancer cervix, vagina and vulva.

Conclusion

Long term HRT use is associated with increased risks of cancer, venous thromboembolism, stroke, etc. In deciding the correct hormone replacement therapy it is important to weigh the risks and benefits. It is usually best to use HRT at the lowest doses that

work for the woman. Every woman using either oestrogen therapy or oestrogen-progestin therapy should be checked yearly by her doctor for any signs of cancer. Adding progestin to oestrogen does reduce the risk of endometrial cancer but does not protect against it completely. For women who have had hysterectomy progestin does not need to be added. The addition of progestins raises the risk of breast cancer. There is a significant risk reduction of breast cancer in women who receive oestrogen alone and who have had no benign breast disease or no family history of breast cancer. The decision to continue hormone replacement therapy should be made annually by the clinician and patient and should consider the individual needs, indications, preferences, as well as best available evidences.

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Trastuzumab in the treatment of breast cancer: current status

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Abstract

Approximately 15-20% of breast cancers over express human epidermal growth factor receptor 2 (HER2) protein. The receptor tyrosine kinase is believed to play a critical role in the pathogenesis and proliferation of these tumors. HER 2 + cancers generally have a poor prognosis and were difficult to treat till recently. In the initial studies, Trastuzumab, a monoclonal antibody targeting HER 2 demonstrated significant activity in HER 2+ metastatic breast cancer. Following this success, several studies were conducted in the adjuvant and neoadjuvant contexts with proven benefits resulting in Trastuzumab becoming the standard of care for most HER2 + breast cancer patients. Nevertheless, a significant number of patients do relapse or progress possibly due to primary or acquired resistance to Trastuzumab, the mechanisms of which are not yet clear. This paper reviews the current status of Trastuzumab in the treatment of HER2+ breast cancer. Hitherto unresolved issues in the adjuvant setting such as eligible patient population, sequential or concurrent use with chemotherapy or radiation, treatment duration, toxicity and possible mechanisms to overcome resistance are also briefly discussed.

Key words : Breast cancer, HER2, Trastuzumab, Monoclonal antibody

Introduction

Breast Cancer is the most common cancer affecting women and is a major cause of cancer related mortality in women world over. Historically, classification of breast cancer and subsequent treatment was based on clinico-pathological findings. Recently, the use of micro-array technology has enabled identification of different breast cancer subtypes characterized by distinct clinical outcomes and response to specific therapy, forming a new molecular classification. One such subtype is characterized by amplification of the HER 2 neu gene and over-expression of HER 2 receptors.

HER 2 is over-expressed in 15-20% of breast cancers. HER 2 + tumors are associated with an aggressive phenotype and have been a clinical challenge contributing to a significant fraction of cancer relapses and deaths. Antibody based therapeutics form an important means of utilizing the host immune responses by specifically targeting and directing anti-tumor activity. RhuMAb Her 2, also known as Trastuzumab (Herceptin) is a humanized monoclonal antibody that targets Her2 Neu.

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Trastuzumab has undergone extensive clinical trials in thousands of women with metastatic breast cancer demonstrating clear benefits in terms of disease relapse/ progression and overall survival. Trastuzumab was the first antibody approved by the United States Food and Drug Administration (FDA) to treat solid tumors.

Pathophysiology of HER 2 in breast cancer

HER 2 Neu (EGFR2 or Erb B2) is a trans-membrane protein encoded by the HER 2 gene on chromosome 17q 21. It is a member of a family of receptor tyrosine kinases that includes EGFR (Her 1), Erb B3 and Erb B4. [1] Trans-membrane receptors are typically characterized by an extracellular ligand binding domain, an intracellular tyrosine kinase domain and a cytoplasmic tail. Ligand binding to the extracellular domains of Erb B1, 3 & 4 leads to formation of homo or hetero-dimers and thus causing activation of the kinase. While HER 2 has no ligand binding of its own, it is the preferred partner for dimerization with the other members of the EGFR family with subsequent activation of several intracellular signaling pathways. This causes accelerated cell growth, proliferation, angiogenesis and metastases, conferring a poorer prognosis for HER 2 + patients.

Mechanism of action of Trastuzumab

The precise mechanism of action of Trastuzumab is not yet defined. Trastuzumab appears to inhibit several major pathways that regulate tumor growth. Postulated mechanisms are:

1. Inhibition of the HER2 receptor: Although how Trastuzumab inhibits HER2 activity is not clear, some studies have suggested that the drug might promote internalization and degradation of HER2.[2] Other studies have suggested that the HER2/HER3/PI3K complex and subsequent PI3K-Akt signaling pathway plays a pivotal role in cell proliferation and Trastuzumab causes disruption of this complex.[3]

2. Modulation of host immunity activating the Natural Killer (NK) cells involved in anti-body dependent cellular cytotoxicity (ADCC) and complement dependent cell kill. [4]

3. Inhibition of angiogenesis at multiple levels leading to inhibition of pro-angiogenic factors, decrease in tumor related micro-vessel density and normalization of tumor related 'neo-vascularization'.[5]

Clinical use of Trastuzumab

Metastatic disease

The earliest reported clinical studies of Trastuzumab were conducted in patients with metastatic breast cancer. Slamon et al randomized 469 patients with chemotherapy naive metastatic breast cancer to receive standard chemotherapy alone or in combination with Trastuzumab. [6] The addition of Trastuzumab was associated with a significant improvement in time to disease progression (median TTP 7.4 months vs 4.6 months, $p<0.001$), objective response (50 vs 32%, $p<0.001$) and overall survival (OS) (25.1 vs 20.3 months, $p<0.001$). Another study by Jahanzeb and colleagues used Trastuzumab along with Vinorelbine in 40 women with metastatic cancer. [7] They reported an overall response of 78% (95% confidence interval [CI] 62%-90%) and median time to progression of 72 weeks (95% CI 37-138 weeks); median survival had not been reached at time of publication. These studies resulted in the approval of the clinical use of Trastuzumab for HER2+ metastatic breast cancer. The safety of its use in combination with Taxanes, Vinorelbine, or Capecitabine is proven. Combination treatments with Anthracyclines are associated with high incidence of cardiotoxicity and are no longer recommended.

Neoadjuvant therapy

Ever since the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-18 and B-27[8] demonstrated comparable efficacy for pre and postoperative administration of chemotherapy, neoadjuvant chemotherapy has become a valid treatment option for high risk breast cancer. Patients with pathological complete response (pCR) after neoadjuvant therapy tend to have a better outcome. Modern neoadjuvant regimens with Anthracyclines and Taxanes yield pathological complete response (pCR) rates of around 20%. Trastuzumab is the first targeted agent established in neoadjuvant regimens for the treatment of HER 2 + cancer, as it increased the pCR rates up to 67%.

A study by the M D Anderson Cancer Centre (MDACC) compared pCR for patient with stage II - IIIA breast cancer who received neoadjuvant chemotherapy with or without Trastuzumab. [9] The addition of Trastuzumab increased the pCR significantly compared with chemotherapy alone (65.2% vs 26.3%; p=.016).They reported improved 1-year(100% vs 94.7%) and 3 year (100% vs 85.3%) disease free survival (DFS) for patients receiving Trastuzumab. The effect on facilitation of breast-conservation (BCT) was small (52.6% vs 56.5%).

The Neoadjuvant Herceptin (NOAH) trial assessed the efficacy and safety of Doxorubicin and Paclitaxel followed by Paclitaxel and then Cyclophosphamide, Methotrexate and Fluorouracil (CMF) with or without Trastuzumab for HER2+ patients. A third arm containing HER2 negative patients received chemotherapy alone. HER2 + patients who received concurrent Trastuzumab had significantly better overall response (89% vs 77%; p=0.02) and pCR (43% vs 23%; p=0.002). A significant difference in pCR rates were noted for patients with inflammatory breast cancer as well (39% vs 20%; p=.002). At a median follow-up of 3 years, event-free survival (EFS) was 70.1% and 53.3% in HER2+patients who received concurrent Trastuzumab or not respectively (HR, 0.56; p=.007). [10]

Neoadjuvant Trastuzumab along with Taxanes- Anthracyclines based chemotherapy has demonstrated the highest pCR rates with acceptable safety profile for patients with HER2 + disease.

Adjuvant therapy

Following the success achieved with Trastuzumab in patients with metastatic cancer, phase III studies were conducted in the adjuvant setting.

The National Surgical Adjuvant Breast and Bowel Project trial B-31 (NSABP B-31) and the North Central Cancer Treatment Group trial N9831 (NCCTG) compared Doxorubicin and Cyclophosphamide (AC) followed by Paclitaxel with or without 52 weeks of weekly Trastuzumab. In the NCCTG N9831 study Trastuzumab was given either following or beginning with Paclitaxel. Because of the similarity of the study design of NSABP B-31and NCCTG N9831, a combined analysis was performed and the results were published. [11]

The Breast Cancer International Research Group 006 (BCIRG 006) [12] compared AC followed by Docetaxel with or without one year of Trastuzumab. This trial also tested the efficacy of a non-anthracycline regimen, consisting of Docetaxel, Carboplatin and Trastuzumab (TCH), intended at reducing cardiotoxicity.

In the Herceptin Adjuvant (HERA) study[13] patients were randomized at completion of standard adjuvant chemotherapy to either observation alone, one year of Trastuzumab or two years of Trastuzumab. Follow-up data from the observation group and one year of Trastuzumab group are available.

Table - I: Adjuvant Trastuzumab trials

Trial	N	Eligible patients	Treatment arms	Median follow up (years)	DFS Hazard Ratio (95%CI, *p* value)	OS Hazard Ratio (95%CI, *p* value)	Reference
NCCTCG & NSABP B-31 Joint	3969	N+	ACx4→T x 4 or 12 wkly vs ACx4→T x 4 or 12 wkly→H x 1yr	3.9	0.52 (0.45-0.60), p<0.001	0.61 (0.50-0.75), p=0.001	11
NCCTCG N 9831	2184	N +/- T>1cm for HR (-) & T>2cm for HR(+)	ACx4→T x 4 or 12 wkly vs ACx4→T x 4 or 12 wkly + H x 1yr	5.5	0.67 (0.55-0.82), p=0.0005	0.86 (0.65-1.13), p=0.281	17
NCCTCG N 9831			ACx4→T x 4 or 12 wkly vs ACx4→T x 4 or 12 wkly→H x 1yr	5.3	0.75 (0.60-0.94), p=0.0190	0.79 (0.59-1.08), p=0.135	17
HERA	3401	N +/- & T>1cm	Chemotherapy→ Observation vs H x 1 yr vs H x 2 yrs	4	0.76 (0.66-0.87), p<0.0001	0.85 (0.70-1.04), p=0.11	13
BCIRG 006	3222	N+/- & either T>2cm, HR (-), HG 2-3 or <35 yrs age	ACx4→D x 4 vs ACx4→D x 4 + H x 1yr	5.4	0.64 (0.53-0.78), p<0.001	0.63 (0.48-0.81), p=0.004	12
BCIRG 006			ACx4→D x 4 vs TCH x 1yr		0.75 (0.54-0.90), p=0.04	0.77 (0.60-0.99), p=0.04	12
FinHER	232	N+/- & T≥2cm &PgR (-),	D / V x 3→FEC x3 vs D/ V x 3 + H x 9 wks → FEC x 3	3	0.42 (0.21-0.83), p=0.01	0.41 (0.16-1.08), p=0.07	14
PACS 04	528	N+	FEC100 / ED 75 vs FEC100/ED 75 → H x 1 yr	3.9	0.86 (0.61-1.22), p=0.41	1.27 (0.68-2.38), NR	15

N=Node, T=Tumor size, HR= Hormone receptors, HG= Histological grade, PgR= Progesterone receptor, AC= Doxorubicin + Cyclophosphamide, T=Paclitaxel, H= Trastuzumab, D= Docetaxel, C= Carboplatin, V= Vinorelbine, FEC=5fluorouracil, Epirubicin, Cyclophosphamide, ED=Epirubicin, Docetaxel, NR= Not reported, DFS=Disease free survival, OS=Overall survival

The Finland Herceptin (FinHER) study [14] was designed to compare Vinorelbine vs Docetaxel, both followed by Fluorouracil, Epirubicin and Cyclophosphamide (FEC). HER2+ patients were additionally randomized to receive or not receive Trastuzumab during the non-anthracycline phase. In this study Trastuzumab was administered only for nine weeks.

The design of the Programmesd' Actions Concertées Sein (PACS) 04 trial[15] compared patients receiving 5-Fluorouracil, Epirubicin and Cyclophosphamide (FEC100) or Epirubicin and Docetaxel(ED75); HER2+ patients were further randomized to sequential Trastuzumab for 1 year or to observation.

In all the studies, adjuvant standard endocrine therapy was given to women with estrogen receptor or progesterone receptor positive disease.

The results of these six studies are shown in Table-I. All except the PACS 04 trial, demonstrated significant improvements in DFS (average risk reduction 50%) when Trastuzumab was used. A trend towards improved OS was reported with Trastuzumab-containing regimens, again with the exception of the PACS 04 trial. The BCIRG 006 and jointly analyzed NCCTG N9831 and NSABP B-31 results showed significant OS benefit with concurrent Trastuzumab. These studies resulted in Trastuzumab becoming the standard of care for adjuvant treatment of most HER 2+ cancers.

Who should receive adjuvant Trastuzumab?

Trastuzumab has proven benefit in patients with HER 2+ (IHC 3+ or HER 2 gene amplified) breast cancer irrespective of tumor size, nodal status and hormone status. Several retrospective studies have suggested that HER2-positivity is a poor prognostic factor even in patients with HER2+, node-negative and ≤1cm size tumors. Banerjee et al reviewed retrospective studies which followed the outcome of patients with HER2+, node-negative, and tumors ≤1cm.[16] They found long term relapse rates in such patients to increase from <10% at 10 years to 17% and 29% at 15 and 20 years respectively. While it is not yet clear whether all patients with ≤1.0cm, node-negative tumors should receive adjuvant Trastuzumab there is a definite case for clinical discussion.

Optimal duration?

The HERA study had a 2-year Trastuzumab arm in addition to the observation and one year treatment arm.There is as yet no efficacy or safety data for the 2 year arm.[13] In the FinHER study Trastuzumab treatment was for only 9 weeks, concurrently with Vinorelbine or Docetaxel. [14] Shorter duration Trastuzumab provided a comparable efficacy, with a HR of 0.42 for relapse free survival. Multiple randomized trials comparing the 1 year of Trastuzumab therapy with a shorter duration are ongoing, the results of which are expected to provide more information regarding the optimal duration of adjuvant Trastuzumab. Until then, one-year Trastuzumab should be considered the current standard, because this was the duration used by the majority of the randomized trials and particularly where overall survival benefit was observed.

Concurrent or Sequential?

Joint analysis of the NCCTG N9831 and NSABP B31 trials, in which Trastuzumab was given concurrently with Paclitaxel, produced the notable HR for DFS of 0.49. Analysis of individual data for theNCCTG N9831 comparing the non-Trastuzumab arm with a sequential Trastuzumab arm and the HERA study in which Trastuzumab was given only sequentially to chemotherapy, yielded HR for DFS of 0.67 and 0.76 respectively both of which are less robust than that in the joint analysis of NCCTG N9831 and NSABP B31 trials.

[11, 13, 17] Further, the DFS of concurrent arm was also superior to the sequential arm (HR=0.75; p=0.01). In addition, OS enhancements were noted when Trastuzumab was used concurrently. Therefore, it appears that Trastuzumab is more beneficial when given concurrently with chemotherapy.

Timing with radiotherapy?

In all the adjuvant Trastuzumab trials except the HERA, PACS 04 and FinHER, radiotherapy was given concurrently with Trastuzumab. The cardiotoxicity rates in the HERA and FinHER trials were low suggesting that it is possible that radiation adds to the cardiotoxicity. However an unplanned analysis of the patients treated in the NCCTG N9831 trial with Trastuzumab showed no difference in cardiac events between those who had received radiotherapy or not.[18] Therefore concurrent Trastuzumab and radiation is generally considered safe.

Cardio-toxicity

Trastuzumab is generally well tolerated. Nevertheless, it can cause impairment of cardiac function which is not a dose-dependent phenomenon. The exact mechanism of cardiotoxicity is not clear but it is suggested that HER2 may be protective for cardiomyocytes. The incidence of cardiac dysfunction and severe chronic heart failure (CHF) in Trastuzumab-containing treatment in the phase III trials ranged from 3.0% to 14.2% and from 0.4% to 3.8%, respectively. [11,12] Although no consistent risk factors for Trastuzumab associated cardiotoxicity could be identified, older age, need for antihypertensives and baseline left ventricular ejection fraction (LVEF) <55% were found to be associated with incidence of cardiac events in the NCCTG N9831 and NSABP B31 trials.[11] Baseline and periodic assessments of cardiac function while on Trastuzumab are recommended and withholding drug even in the event of asymptomatic cardiac compromise till functional recovery, appears to be a prudent approach. In most instances the cardiac dysfunction seems to be reversible.

Resistance to Trastuzumab

Only about 50% of HER2 + patients are known to benefit with Trastuzumab suggesting that there is inherent or acquired resistance, the exact mechanisms of which are uncertain. Proposed mechanisms that may mediate denovo and acquired resistance to Trastuzumab include decreased expression of HER2 receptors, mutation of HER2 leading to decreased binding affinity, expression of truncated forms of HER2 and activation of alternate cell signaling pathways. Some ongoing efforts to overcome resistance include continued use of Trastuzumab beyond disease progression and combination with other HER family targeting agents such as Lapatinib. Experiments with other EGFR inhibitors, agents such as Pertuzumab, Bevazivumab, mTOR inhibitors, targeted delivery of chemotherapy in combination Trastuzumab-MCC-DM1 (T-DM1) are underway with early encouraging results.

Conclusions

The incorporation of Trastuzumab has significantly improved treatment outcomes in patients with HER2 + breast cancer in early and advanced stages. Concurrent use with Taxanes, Capecitabine or Vinorelbine has been proven to be safe. For adjuvant or neoadjuvant therapy, although no particular regimen can be considered superior, Anthracycline based regimens followed by concurrent Trastuzumab and Taxanes appears to be most beneficial. Results of ongoing studies are expected to provide further answers with regard to optimal use.

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Original Article

Dosimetric comparison of Tandem and Ovoids versus Tandem and Ring applicator for cervical cancer brachytherapy

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Abstract

Introduction

Radiotherapy for cancer cervix mainly consists of External Beam Radiotherapy and Brachytherapy. However, there is no uniformity in HDR treatments, either in prescription doses or in the use of applicators.

Objectives

We studied and compared the dosimetric parameters of the tandem and ovoid (TO) and tandem and ring (TR) cervical brachytherapy applicators.

Methods and Materials

Fifty patients with cervical cancer (Stages II-IV) were randomized into two groups and underwent two HDR applications of 9 Gy each with the assigned applicator. Patients underwent orthogonal X-rays with contrast in bladder and marker for the posterior vaginal wall and were prescribed 9 Gy to ICRU points A, with additional optimization to maintain the pear-shaped dose distribution and minimize bladder and rectum doses. Bladder and rectum point doses, pelvic wall point doses and trapezoidal point doses, mean and maximum doses were calculated. Total volumes treated to the prescription dose were compared. Dose variation between the two applications was also calculated for each applicator.

Results

There were no significant differences between TO and TR applicators with respect to doses to the prescription points and other ICRU points. The rectal doses were significantly different ($p<0.001$) between the two applicators.There were significant differences ($p <0.001$) between the applicators in treated volumes as well. Within each patient, when the applications were compared, treated volumes and point doses were also found to be more consistent for the TR applicator between applications. These results show that the 2 applicators deliver the prescribed dose to points A but vary in critical organ doses and treat significantly

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different volumes. We have also demonstrated that the rectal retractor is inferior when compared to good vaginal packing to reduce rectal doses. The impact of the larger TO treatment volume is unclear.

Conclusion

We conclude that the TO and TR are not identical dosimetrically and the TO applicator should be used when feasible to reduce rectal dose and that the TR applicator is more suitable for large volume brachytherapy centers.

Keywords: Brachytherapy, Tandem, ring, ovoids

Introduction

Cervical cancer is the second most common cancer of women worldwide, with 471,000 incident cases estimated in 2000, [1] and a 5-year prevalence of more than 1.4 million cases. The cancer burden (incidence and mortality) is disproportionately high (~80%) in the developing world. Radiotherapy for cancer cervix mainly consists of External Beam Radiotherapy and Brachytherapy. Brachytherapy can be used as a primary modality in early stage cancers whereas it serves as an adjunct to EBRT in advanced stage cervical cancers.

Intracavitary brachytherapy has been shown to improve outcome in cervical cancer patients.[2-4] A survey by the American Brachytherapy Society (ABS) on the practice of brachytherapy in the United States showed that cervix is the most common site treated with brachytherapy. [5] Cervical brachytherapy has been delivered with low-dose-rate (LDR) and high-dose-rate (HDR) treatments. [6] However, surveys on the practice of brachytherapy have shown that there is no uniformity in HDR treatments, either in prescription doses or in use of applicators, [6, 7] although the ABS has published recommendations regarding HDR treatments. [6]

According to the ABS survey, [6] the 2 most common applicators in use are the Fletcher, consisting of a tandem and 2 ovoids (TO) and the tandem and ring (TR). The TR applicator was introduced by manufacturers as clinically identical to the TO, but with additional benefits. [8, 9] These include increased patient comfort, applicability in patients with a narrow proximal vagina or with obliteration of the vaginal fornices [10] and better repeatability due to a fixed geometry of the ring relative to the tandem. [11] However, these claims of dosimetric identity have not been substantiated in any systematic study.

Erickson et al, compared dose distributions of the TR with those of the TO applicator. [12] The results of their study showed that TO applications had consistently higher bladder and rectal point doses with similar point B doses as compared to the TR. They also found that the height, width and thickness of the isodose curves, i.e., the isodose volumes, were greater for the TO than the TR applicator. Other studies investigated issues of spatial reproducibility of the TR applicator. [13] No rigorous, methodic, volumetric and dosimetric comparison of the TR and the TO has been performed to date.

Methods and Materials

Fifty patients, ages 35 to 69 years, with cancer of the cervix Stages II-III, were included in this study. All patients received external beam therapy of 50 Gy followed by 2 brachytherapy applications of 9 Gy each, delivered once a week.

For this study, we randomized patients using a computer program into two groups and they received treatment with a particular applicator. Nucletron applicators were used for this study. A Foley's catheter filled with 2cc of contrast and 5 cc of saline was inserted into the bladder. The TR applicator includes a rectal retractor to reduce the rectal dose. Points A and B were determined according to the Manchester protocol and following ICRU 38 recommendations. [14] The prescription dose was 9 Gy to points A. The TO assembly and the TR applicator are shown in Figure – I.

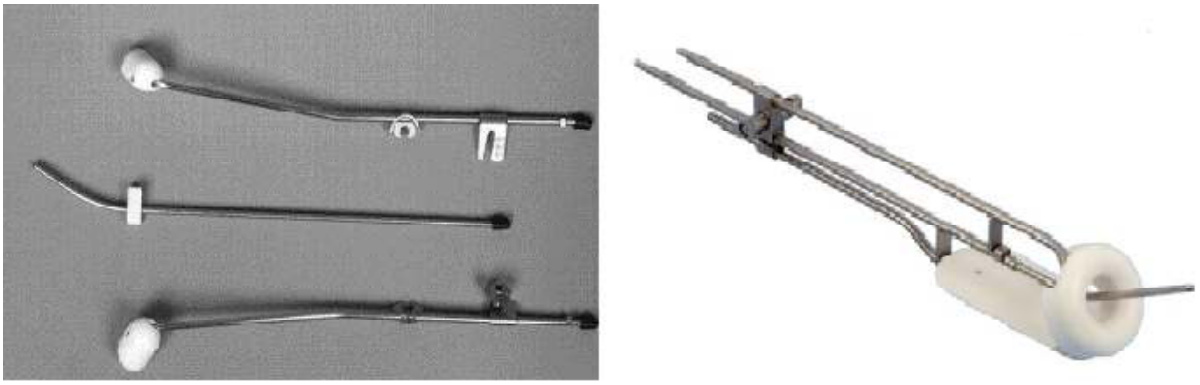

Figure - I:
Tandem and Ovoid Tandem and Ring applicators

Planning and optimization was done using Oncentra Brachytherapy software (Nucletron Medical Systems, Veendal, Netherlands). For both type of applicators, optimization goals were to achieve the prescription dose at points A, maintain the traditional pear-shaped distribution, and limit the doses to rectum and according to ABS guidelines. Dosimetric parameters calculated included the ICRU rectum and bladder dose points, as well as other ICRU points.Time Dose Pattern, width and thickness of 9 Gy isodose curve and difference in dose delivered to above mentioned points between two applications for each applicator were also measured.

Statistics

We used the Mann-Whitney ranksum test to test for significant differences in the dosimetric parameters between the TO and TR groups. Mean doses to the prescription points, ICRU points and mean isodose volume measurements were made for each group. The means were compared using Student t test. Within each patient, we used the paired t test to check for significant differences in the dosimetric parameters.

Results

50 patients received 2 treatments each, for a total of 100 treatments. The dosimetric results for these applications are presented in Tables I, II & III. Of the measured parameters, only the dose to the ICRU rectal point was significantly different between the 2 treatment methods.The ICRU rectal point dose was significantly higher for the TR. This is most likely due to the use of a rectal retractor with the TR, a component that is not included with the TO applicator. The rectal retractor, although claimed to be equivalent to vaginal packing was not as effective in reducing rectal dose.

APPLICATOR POINT	TANDEM AND OVOID		TANDEM AND RING	
	MEAN DOSE	SD	MEAN DOSE	SD
Bladder	50.61%	13.6	48.44%	13.6
Rectum	43.08%	9.05	53.07%	4.27
Left PW	19.23%	3.58	19.84%	3.03
Right PW	17.96%	4.16	18.1%	3.09
Left T1	14.4%	3.22	15.78%	3.74
Right T1	13.12%	3.08	13.55%	2.56
Left T2	11.63%	3.51	11.71%	2.85
Right T2	10.63%	3.16	10.77%	2.73
Left T3	4.55%	1.3	4.49%	0.79
Right T3	4.43%	1.37	4.47%	0.84

Table - I: Doses to various points sorted by applicator type
PW –Pelvic Wall Point, T1, T2, T3 – Trapezoidal Points

PARAMETER	APPLICATOR	MEAN (in cm)	SD
Iso Length	T&O	8.2580	0.40763
	T&R	7.5960	0.15513
Iso Width	T&O	5.2500	0.20923
	T&R	5.1660	0.16734
Iso Thickness	T&O	4.0330	0.16709
	T&R	3.5660	0.10616

Table - II: Isodose parameters between the two applicators

Parameter	Applicator	Mean	SD
Left Pt B Difference	T&O	2.198800	2.2799238
	T&R	0.812000	0.6976030
Right Pt B Difference	T&O	3.080400	3.2678745
	T&R	0.792000	0.8314195
Bladder Difference	T&O	8.784000	8.6199976
	T&R	8.127200	9.7880316
Rectum Difference	T&O	5.320400	4.8952345
	T&R	2.703200	1.7613128
RPW Difference	T&O	3.519600	3.1588018
	T&R	1.262800	0.6545515
LPW Difference	T&O	3.193200	2.6668563
	T&R	1.420000	1.2107883
Right T1 Difference	T&O	1.726000	1.7027282
	T&R	1.073600	0.6558447
Left T1 Difference	T&O	1.948800	1.7543715
	T&R	1.765600	1.4925651
Right T2 Difference	T&O	2.117200	2.0634589
	T&R	1.035200	0.6421002
Left T2 Difference	T&O	1.975200	2.1011190
	T&R	1.172000	0.8117420
Right T3 Difference	T&O	0.803200	0.6914039
	T&R	0.529200	0.3522774
Left T3 Difference	T&O	0.826800	0.6909759
	T&R	0.474800	0.4172741

Table - III: Difference between doses delivered to various points in two applications
RPW – Right Pelvic Wall Point, LPW – Left Pelvic Wall Point, T1, T2, T3 – Trapezoidal Points

Discussion

The tandem and ring applicator is the second most widely used in HDR brachytherapy, after the Fletcher type applicator, which consists of a tandem and 2 ovoids. In the current study, we found that the 2 applicators delivered very different treatments in terms of the volume treated for the same prescribed dose. The TR applicator treated a significantly smaller volume and over a significantly shorter period of time.The conclusion is that the 2 applicators are not dosimetrically equivalent and should not be used interchangeably.

The prescription points are determined relative to the tandem, using the same method for both applicators. However, the surrounding anatomy is dependent on the type of applicator used. Thus, dosimetric difference should be expected. This result is in agreement with the study carried out by Erickson et al, [12] which also compared TR and TO dose distributions.

The clinical significance of this difference is not clear. The use of individually contoured clinical target volumes would assist in resolving this question, but requires appropriate imaging techniques.The importance of more suitable imaging modalities, such as magnetic resonance (MR) or Positron Emission Tomography (PET-CT) has been recognized for cervical cancer. The development of MR and CT compatible applicators has facilitated the implementation of these modalities for HDR treatment planning. [15]

The treated volume is significantly different between the tandem and ring vs. the tandem and ovoid applicator and more appropriate imaging modalities such as MR, are needed to accurately delineate the tumor volume to be treated, to ensure that there is neither over nor under treatment of the relevant volumes.

The issue of higher rectal doses in TR applicators as compared to TO applicators is due to the inadequacy of the rectal retractor as compared to good vaginal packing. However, between applications, the TR applicator was found to be more consistent in delivering similar doses to all points highlighting its spatial reproducibility. This could have implications for high volume brachytherapy centers such as our center where we treat up to 30 applications per week for cervical cancer alone. A single plan may be adequate for executing both treatments if the radiographs are found to be similar.

Conclusions

TO and TR applicators delivered the same prescription dose to points A, with TR applicator delivering a higher rectal point dose. The "classical" pear-shaped distribution was maintained for both applicators. However, TO consistently and significantly treated larger volumes. The TR applicator had better spatial reproducibility both physically as well as dosimetrically. Clearly, the TO and TR applicators are not equivalent and should not be used interchangeably without further study.

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Original Article

Comet assay to study the effect of radiotherapy on the DNA of peripheral blood lymphocytes in patients with oral cancers

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Abstract

Objectives

To study and estimate radiation induced DNA damage, with increasing dose of radiation, in the peripheral blood lymphocytes (PBL) of patients with squamous cell carcinoma of oral cavity on radiotherapy.

Methods and Materials

30 patients with oral cavity cancers receiving radiation therapy were recruited from December 2009 to May 2011 in the Department of Radiotherapy, JIPMER. Two ml of heparinized whole blood samples were collected from each patient, within two hours before and after the first fraction of radiation and within two hours after the 16th and the last fractions and were analyzed using Comet assay.

Results

The mean tail length was 14.7+/- 3.23 um and the mean % DNA in tail was 26.7+/- 5.13. The linear trend of increase in the means from sample 1 to 4 yielded a slope of +3.584, p value of 0.0001 for tail length, slope of +0.4768, p value of 0.0018 for % tail DNA.

Conclusion

There was conclusive evidence for cumulative increase in DNA damage occurring over the course of radiation treatment till the last fraction. This is a reflection of the intrinsic radiosensitivity of this patient sample.

Keywords : Comet Assay, DNA damage, Peripheral blood lymphocytes, Radiation Therapy.

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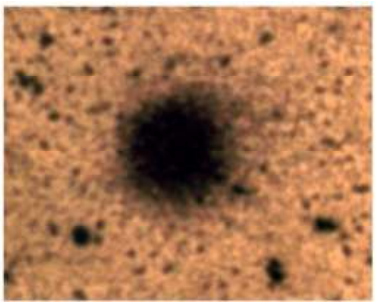
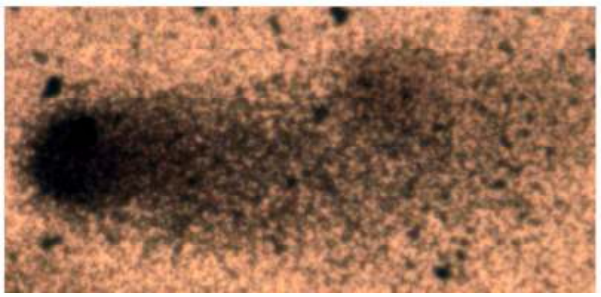
Introduction

Oral cancers are the most common cancers among males in India. Radiation is the mainstay of current therapy for oral cancers. However, the difference in intrinsic radio sensitivity among individuals has a significant effect on the treatment outcome. There are several methods to assess response to radiation including clinical scoring systems, tissue function assays, clonogenic assays, etc. DNA damage assessment is one such method. Comet assay is a highly versatile and sensitive tool for this purpose. The principle of comet assay is that, radiation induces DNA strand breakage and when subjected to electrophoresis, the broken ends of these negatively charged DNA strands become free to migrate in the electric field towards the anode, thus forming a comet like appearance with the undamaged DNA in the nucleus as the head and the migrated broken DNA, the tail (Figure I). The comet tail length observed is directly proportional to the extent of DNA migration, which in turn depends on the size and the number of broken ends of DNA.



A



B

Figure I: A) Undamaged DNA
B) Comet appearance due to DNA damage

DNA damage has been assessed in various cancers using Comet assay in response to various treatment modalities including radiation.[1] These studies include both investigations on human tumor cell lines and on tumor cells extracted from patients with different cancers. Also, studies have shown that peripheral blood lymphocytes are suitable surrogate markers to quantify DNA damage in patients exposed to radiation and have also proven their advantages over tissue samples with respect to easy availability, synchronous population, low frequency of spontaneous chromosomal aberrations, convenient culture methods, simplicity of procedure and patient compliance. [2] Several studies have documented the effect of different doses of single fraction radiation on the DNA. However there are fewer studies, especially in head and neck malignancies, that have quantified the cumulative DNA damage acquired over the course of a radiation treatment schedule. In this study, we aimed to document the cumulative DNA damage in peripheral blood lymphocytes with increasing doses of radiation and document the inter-individual differences in intrinsic radiosensitivity in terms of inter-individual variation in the amount of DNA damage.

Methods and Materials

The study was conducted over a period of 18 months from December 2009 to May 2011 in the departments of Radiotherapy and Anatomy, JIPMER, Puducherry. 30 patients with histologically proven cancers of the oral cavity, including 25 cases of primary buccal mucosal cancers and five cases of primary tongue cancers were recruited for the study. The sample included 17 male and 13 female patients with ages ranging from less than 50 to more than 70 years. All the patients were treated with a curative intent with

radical dose of radiation as per the department protocol. Informed consent was obtained from them after proper explanation of the procedure. Two ml of heparinized whole blood samples were collected from each patient within two hours before (group-1) and after the first fraction of radiation (group-2) and within two hours of radiation after the 16th (group-3) and the last fraction (group-4). A total of 120 samples were obtained. The samples were analyzed for DNA damage using Comet assay and the comet parameters were obtained. The data were then documented and statistical analysis performed using repeated measures ANOVA, independent't' test and test for linear trend to compare means. Comet Tail length and % DNA in tail were analyzed for quantification of DNA damage.

Results

The patient blood samples were divided into four groups based on the time of sampling with respect to radiation delivery. The basal values (group 1) for mean tail length was 14.7+/- 3.23um (Table I) and mean % DNA in tail was 26.7+/- 5.13 (Table II). The values for mean tail length showed statistically significant increase with irradiation (groups 2, 3 and 4). With % tail DNA, mean values increased with groups 3 and 4, but the intersample differences were not significant except for sample 2 vs. 3 (Table II).

The difference between means of the four groups in both tail length and % tail DNA was analyzed by repeated measures ANOVA and the p values were <0.05 with both the parameters (Table I, Table II).These point to an overall statistically significant increase in DNA damage, in terms of tail length and % tail DNA, with increasing cumulative doses of radiation received during the course of the treatment. The test for linear trend, which looks for the linear increase in means from the beginning of the radiation treatment schedule to the end (i.e., from group 1 to group 4), is in an indicator of the cumulative increase in DNA damage. When analyzed, it yielded a slope of +3.584 (p=0.0001) for tail length (Figure II) and a slope of +0.4768 (p= 0.0018) for % tail DNA (Figure III). These results point to a significant cumulative increase in DNA damage in terms of tail length and % tail DNA, accumulated along the course of the radiation treatment schedule.

Group	Number of Samples	Tail Length(um)				Overall Significance (p Value)	Inter Comparison of Means (p Value)
		Minimum	Maximum	Mean	Standard Deviation		
1	30	10.2564	22.2352	14.7	3.23	<0.05	
2	30	12.7648	28.7864	18.87	4.8		<0.05 (1 vs. 2)
3	30	17.4543	51.2454	29.95	8.48		<0.05 (2 vs. 3)
4	30	19.7689	45.6654	34.9	6.2		<0.05 (3 vs. 4)

Table I: Comparison of Tail length between study groups

Group	Number of Samples	% Tail DNA				Overall Significance (p Value)	Inter Comparison Of Means (p Value)
		Minimum	Maximum	Mean	Standard Deviation		
1	30	16.5198	35.6356	26.71	5.13	<0.05	
2	30	18.2576	34.8762	25.95	4.14		>0.05 (1 vs. 2)
3	30	19.6782	45.2908	29.75	6.23		<0.05 (2 vs. 3)
4	30	18.4818	36.6276	28.61	4.07		>0.05 (3 vs. 4)

Table II: Comparison of % Tail DNA between study groups

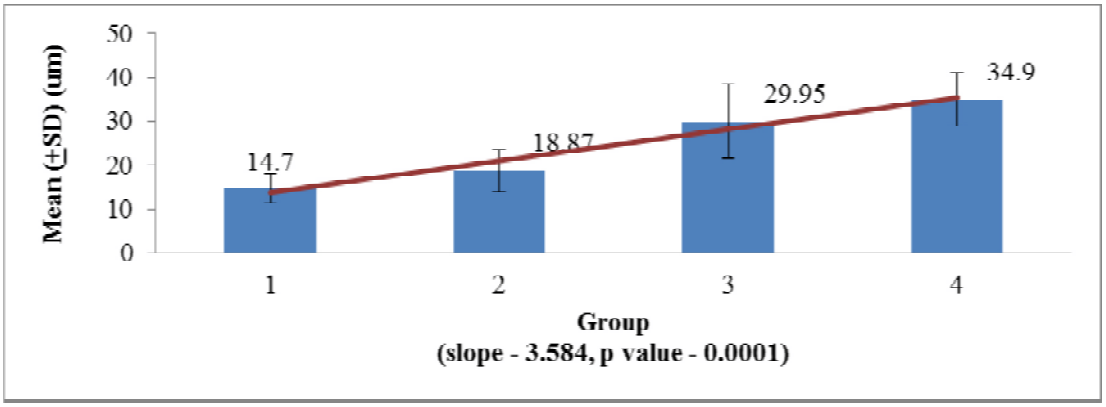


Figure II: Linear trend in mean Tail length

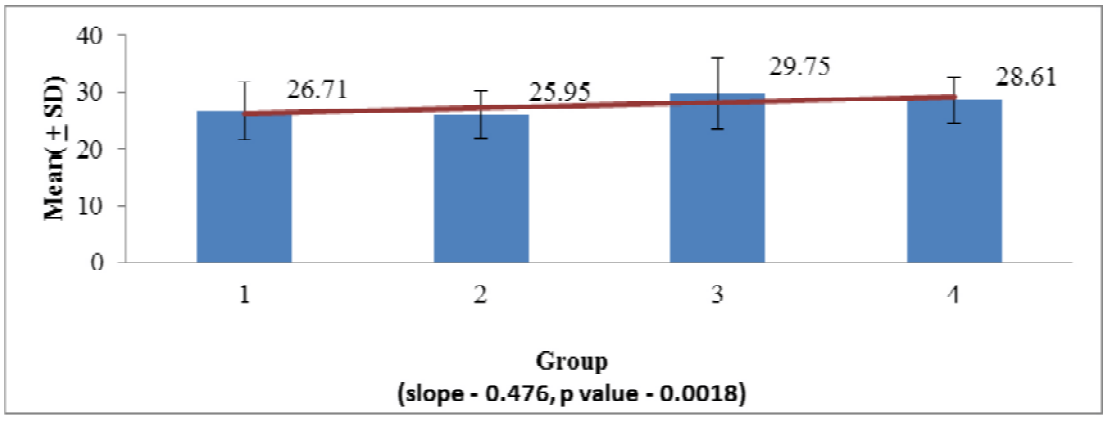


Figure III: Linear trend in mean %Tail DNA

Discussion

The presence of basal DNA damage in the PBL of cancer patients is evidenced from the pre-irradiation (group 1) comet parameter values (Table I & II). These results are in accordance with the earlier studies. [3] The difference between minimum and maximum values of each of the two comet parameters and their standard deviation in group 1 reflects the individual variation in the amount of baseline DNA damage among these patients. This basal DNA damage can be attributed

to the cancer per se as well as to other factors including smoking, tobacco chewing, exposure to UV rays, occupational exposure, etc. The analysis of various parameters after irradiation revealed a significant increase in the values pointing to a significant radiation induced DNA damage, which is in accordance with previous studies. [4] The minimum and maximum values and the standard deviations in groups 2, 3 and 4 point to the inter-individual differences in the levels of radiation induced DNA damage and hence the variation in the intrinsic radiosensitivity among these patients. There are few studies that have done in vivo assessment of the cumulative DNA damage in patients receiving radiation treatment for head and neck cancers. [5, 6] However none of these studies has shown statistically significant results. In our study, the cumulative effect of radiation on DNA was observed from the increasing mean values of the comet parameters. Mean tail length showed a statistically significant increase with each consecutive sample taken during and after the course of radiation (Table I). The analysis of linear trend showed significant increase in the means of tail length (Figure II) and % tail DNA (Figure III), from the beginning of radiation to the end (groups 1 to 4), which is in an indicator of the cumulative increase in DNA damage. All these observations point to the fact that there is a statistically significant cumulative increase in DNA damage with increasing doses of radiation and this damage continues to accrue till the last fraction, which has not been documented in the earlier studies. The significant linear increase in the means of all the three comet parameters points to the interplay between constant accumulation of DNA damage and repair mechanisms throughout the course of radiation till the last fraction. This is a reflection of the intrinsic radio sensitivity of the patients in this sample which is an important factor that affects the tumor response to radiation. Thus, quantifying DNA damage in the peripheral blood lymphocytes using Comet assay can be a useful surrogate marker for the intrinsic radiosensitivity of each patient.

Conclusion

This study has shown a conclusive evidence for cumulative increase in DNA damage occurring over the course of radiation treatment. This is a reflection of the intrinsic radio sensitivity of the patients in this sample. Though comet assay has the advantage of being sensitive, reproducible, easy and inexpensive, it has its disadvantages. It only gives an overall quantification of the DNA damage but does not specifically point to the location of the damage in the genome or the exact type of damage. This requires more accurate and specific methods like Fluorescence in situ Hybridization, Polymerase Chain Reaction etc. These methods can be utilized to further substantiate the evidence obtained in this study.

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Comparison of two indices of serum galactomannan assay for diagnosing invasive pulmonary aspergillosis in neutropenic patients

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Abstract

Introduction

Pneumonia in neutropenic patients, in particular invasive pulmonary aspergillosis (IPA) is associated with a high case fatality rate. Therefore the early diagnosis of fungal pneumonia is paramount to guide empirical anti-fungal treatment.

Objectives

The aim of our study was to compare the sensitivity and specificity of two indices of serum galactomannan assay for diagnosing invasive pulmonary aspergillosis (IPA) in patients with febrile neutropenia not responding to broad- spectrum antibiotics.

Methods and Materials

We included hematology patients (acute leukemia/aplastic anemia) with febrile neutropenia in this study. We did high resolution contrast tomography scan (HRCT) of the chest when fever had lasted for more than 4 days of antibiotic therapy. Blood samples for galactomannan were taken from patients with signs of pulmonary infection and tested for galactomannan by Platelia Aspergillus test (Bio-rad).The ELISA results were analysed at two different positive cut-offs- >1.5 (manufacturer's recommended positive cut off) and >1.0. After all samples were analysed, data were combined with the clinical data which had been collected independently.

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Conflict of interest
The authors declare that they have no conflict of interest.
Funding source
This study required no additional funds.

Results

We studied 80 febrile episodes. The sensitivity, specificity, positive predictive value and negative predictive value of the test were 72.7%, 94.4%, 96% and 65.4% respectively using an index of 1.0. With an index of 1.5 the sensitivity dropped to 42.4% without any change in specificity.

Conclusion

We conclude that a lower cut-off of 1.0 may be appropriate in neutropenic patients with suspected fungal pneumonia to facilitate early diagnosis of IPA, as this approach is associated with higher sensitivity and comparable specificity.

Key words: Febrile neutropenia, fungal pneumonia, galactomannan

Introduction

The incidence of pneumonia in neutropenic patients (eg, patients with acute leukemia) is 17 [1] to 24% [2] and the clinical response to broad spectrum antibiotic therapy eventually supplemented by antifungal treatment active against Aspergillus species is 60 to 65%, while the infection-related fatality rate in these patients is as high as 38%. [2]

Conventional chest radiographs show lung infiltrates in less than 10% of patients who remain febrile despite antibacterial therapy, whereas simultaneous computed tomography (CT) scans, particularly those using high resolution techniques, detect suspect or characteristic lung findings in approximately 50% of these patients.[2] Microbiological diagnosis may be based on blood cultures or cultures from throat swabs, washes from the mouth and nose, sputum, saliva and bronchial secretions obtained by broncho-alveolar lavage (BAL) or on serological assays for circulating galactomannan (a constituent of the aspergillus cell wall). Aspergillus is rarely isolated from blood cultures and the diagnosis is often based on clinical symptoms or radiological criteria. Empirical anti-fungal therapy is justified in patients not responding to broad-spectrum antibiotics due to the high mortality of established fungal pneumonia.

Histological findings from lung tissue obtained by biopsy or autopsy are generally regarded as the diagnostic gold standard for invasive aspergillosis. However, the choice of patients undergoing biopsy or autopsy is highly selective, which invalidates conclusions regarding the sensitivity and specificity of biopsy techniques.

The aim of our study was to compare the sensitivity and specificity of two indices of serum galactomannan assay for diagnosing invasive pulmonary aspergillosis (IPA) in febrile neutropenic patients not responding to broad-spectrum antibiotics.

Methods and Materials

Hematology patients greater than 5 years of age with febrile neutropenia were included in the study. During hospitalization we evaluated patients for fever and respiratory symptoms. Physical examinations were carried out daily. We performed chest x-rays at admission and at onset of fever or development of pulmonary signs and symptoms. We did HRCT scan of the chest prospectively when fever had lasted for more than 4 days of antibiotic therapy or when chest X rays showed abnormalities and these were read by an experienced chest radiologist. Patterns of parenchymal infiltrates were noted and the presence of nodular lesions,

halo sign, cavitations, air crescent sign and fungal ball were considered suggestive of fungal pneumonia. Patients with these findings were empirically started on anti-fungal therapy effective against aspergillus.We did CT guided BAL where possible for a microbiological diagnosis if the general condition of the patient permitted.

Response to therapy was defined as stable defervescence within 72 h after the initiation of antimicrobial treatment with or without resolution of chest infiltrates. Treatment end points were defined as cure (response to and final withdrawal of antimicrobial treatment) or death.

We took blood samples for galactomannan serology from patients with signs of pulmonary infection & serum was separated and stored at -70^0C and tested for galactomannan by Platelia Aspergillus test (Bio-rad) by an investigator blinded to the sample source and clinical data. Platelia Aspergillus is a one-stage sandwich immune-enzymatic technique for the semi-quantitative detection of circulating galactomannan in human serum. Coded serum samples were thawed and analysed in batches. Optical densities were read at 450 and 620 nm. All samples were tested in duplicate. Samples were re-tested if the co-efficient of variation between duplicates was more than 20%. The ELISA results were analysed at two different positive cut-offs- >1.5 (manufacturer's recommended positive cut off) and >1.0.

After all samples were analysed, data were combined with the clinical data which had been collected independently. Sputum, blood, tissue and BAL bacterial and fungal cultures were taken as clinically indicated.

Invasive Fungal Infections (IFIs) were classified according to criteria or case definitions developed by consensus of the European Organization for Research and Treatment of Cancer and the National Institute of Allergy and Infectious Diseases Mycoses Study excluding radiological criteria.[3]

i) **Proven** invasive pulmonary aspergillosis– cytopathological evidence of acutely branched, septate hyphae from a fine needle aspiration/biopsy with evidence of associated tissue damage and a positive culture for aspergillus species from sputum or BAL fluid.

ii) **Probable** invasive pulmonary aspergillosis – positive culture for aspergillus species from sputum or BAL fluid or cytopathology showing acutely branched, septate hyphae together with 1 major or 2 minor clinical criteria.(Major clinical criteria includes halo sign, air-crescent sign, cavitations on HRCT scan, while, Minor clinical criteria was defined as symptoms of lower respiratory tract infection pleural rub, any new infiltrate not fulfilling major criteria)

iii) **Suspected** Invasive pulmonary aspergillosis-1 major criterion with negative bacterial & fungal cultures from respiratory tract specimens & no evidence of viral disease.

Statistical Analysis

Sensitivity, specificity were calculated for the two cut-offs of serum galactomannan index. Patients with proven or probable IPA were included in the IPA group and the control group consisted of patients not fitting into the above IPA categories and without response to anti-fungal therapy.

Results

We studied 80 patients. The median age was 30 years (range 6-65 years). Males comprised 65% of patients. The disease distribution is shown in Table I.

Microbiological diagnosis

A total of 14 cultures were positive, blood culture in 9 patients, throat swab/ sputum in 3 patients, BAL fluid in 1 patient and postmortem tissue specimen in 1 patient(Table III). The bacteria isolated in culture comprised methicillin resistant Staphylococcus aureus, coagulase negative Staphylococcus, ESBL producing E.coli, Klebsiella pneumoniae, Acinetobacter species and methicillin sensitive Staphylococcus aureus. Fungi isolated in culture included Candida tropicalis and Candida albicans from throat swab and sputum, Rhizopus sp from blood and throat swab and Aspergillus flavus from postmortem biopsy of necrotic palatal mass.

Nine patients underwent fibre-optic bronchoscopy and broncho-alveolar lavage from the affected segment. All patients at the time of bronchoscopy were on broad- spectrum antibiotics and 4 patients were also on anti-fungals. BAL fluid grew Acinetobacter species on culture in 1 patient. Transbronchial biopsy was done in 1 patient with endobronchial nodular lesions, which on histopathological examination revealed ill-defined granulomas though cultures of the specimen and AFB stain yielded negative results.

Radiological abnormalities

Chest x-ray abnormalities were present in 49 (61%) of which bilateral involvement was present in 30 (63%) patients. We did HRCT chest in 76 patients of which 64 (84%) showed abnormalities. Typical CT findings included nodules in 24 (43%), nodules with halo sign in 19 (34%), segmental consolidation in 34 (61%), cavitations/air crescent sign in 9 (16%), fungal ball in 4 (7%), pleural effusion in11(20%) and hilar/paratracheal lymphadenopathy in 7 (13%) patients. Multiple abnormalities were seen in 47% of our patients (Table II).

Serum galactomannan

Serum galactomannan assays were done in all patients. The mean number of samples per patient was 2. To get the galactomannan index the Optical Density (OD) of the test serum was divided by the mean O.D of the calibrator serum. An investigator blinded to the patient data performed the ELISA according to the manufacturer's instructions. Each sample was run in duplicate. Samples were re-tested if the co-efficient of variation between duplicates was more than 20%.

The ELISA results were analysed at two different positive cut-offs >1.5 (manufacturer's recommended positive cut off) and >1.0. Using a positive cut-off >1.5 sequential ($\geq$2 consecutive) positive results were recorded in 14 febrile episodes. On reducing the positive cut-off to >1.0, there was 28 sequential positive results.

Based on microbiological and radiological criteria and histopathology (where available) the final diagnoses were: definite / proven IPA-none, probable IPA - 1, suspected IPA-32 and pulmonary tuberculosis - 2.

The sensitivity, specificity, positive predictive value and negative predictive value of the test were 72.7%, 94.4%, 96% and 65.4% respectively using an index of 1.0 (Table IV).With an index of 1.5 the sensitivity dropped to 42.4% without any change in specificity. BAL fluid galactomannan assay was done in 6 patients. The sensitivity, specificity, PPV and NPV were 75%, 100%, 100% and 66.7% respectively.

Discussion

Using a positive cut-off >1.5 sequential ($\geq$2 consecutive) positive results were recorded in 14 febrile episodes. On reducing the positive cut-off to >1.0, there was 28 sequential positive results. The sensitivity, specificity, positive predictive value

and negative predictive value of the test were 72.7%, 94.4%, 96% and 65.4% respectively using an index of 1.0.With an index of 1.5 the sensitivity dropped to 42.4% without any change in specificity.

Early diagnosis and treatment of IPA has been shown to improve clinical outcome in several studies [4] and serial serum galactomannan monitoring is now recommended in high risk patients on chemotherapy and those undergoing transplant to enable early detection of antigenemia. Maertens et al [5] prospectively monitored allogenic hematopoietic stem cell transplantation (HSCT) patients. Patients underwent aggressive evaluation for IA, including frequent chest radiographs and CT scans, weekly surveillance cultures, and Aspergillus antigen testing twice weekly. An assay cut-off of 1.5 was considered to be positive and consecutive positive results were required to be classified as a true positive assay result. Based on the autopsy-updated classification, the sensitivity was 94.4%. These findings substantiate their earlier experience, where they reported a sensitivity of 92.6% in autopsy-confirmed cases. Diagnosis by detection of antigenemia was more sensitive and specific than other procedures, including radiography, CT scan and culture.

A number of prospective studies report excellent sensitivities (90-95%) and specificities using the Platelia Aspergillus for the diagnosis of invasive aspergillosis. [6] Other studies demonstrate poorer sensitivities (0-50%) and controversy exists over the most appropriate cutoff. [7] This wide variation may be secondary to critical differences in the study population, in the case definitions of IA, the frequency of sampling and the requirement for demonstration of persistent positivity for classification as a true positive. [8] Using different cutoff levels for defining a positive sample may also contribute to variations in the performance of the assay. The manufacturer recommends a cutoff point of $\geq$1.5, whereas an index between 1 and 1.5 is considered indeterminate. In their analysis of the reproducibility of the test, Verweij et al [9] suggested that the threshold may be reduced for negative samples from 1.0 to 0.8 and for positive samples from 1.5 to 1.0.

In our study the sensitivity, specificity, positive predictive value and negative predictive value of the test were 72.7%, 94.4%, 96% and 65.4% respectively using an index of 1.0. The lower sensitivity of the test in our patients when compared to published reports may be due to the fact that in our patients anti-fungal therapy was most often started early on in the course of fever on an empirical basis. This may have led to a number of false negative results.

The manufacturers of the GM EIA suggest that a sample index between 1 and 1.5 should be considered within the 'gray zone' of positivity. However other investigators have suggested that the cut off for positivity could be safely decreased to 0.7 or 0.8 [10] without compromise in specificity. Herbrecht et al [10] have recommended that the cutoff value should be lowered to 0.7, at least in adult non-allogeneic HSCT patients, though it was associated with a loss of specificity from 99.4% to 88.7%. Maertens et al [5] recommended two new cutoff points, a 'static' cutoff at 0.8 and a 'dynamic' cutoff at 0.5.They concluded after studying the performance of the assay in 124 neutropenic episodes with a high pretest probability for IA that a single assay with an OD index $\geq$0.8 warranted the initiation of anti-aspergillus therapy. A further lowering of the 'static' threshold was not feasible due to a drop in the PPV. However the demonstration of at least two sequential sera with an OD $\geq$0.5 ('dynamic' threshold) increased the specificity and the PPV to 98.6% and the efficiency to 98%. We observed that the sensitivity of the test dropped sharply from 72.7% to 42.4% without any

increase in specificity when the cut-off was increased from 1.0 to 1.5.

False-positive results have been observed in all studies, but the prevalence has varied considerably. Major variables affecting specificity include the selection of the cut-off to define positivity and the requirement for demonstration of persistent positivity for classification as true positive. Maertens et al [5] reported a specificity of 98.8% if two or more positive results were required vs. 85.4 % if only one was required for clas-sification as true-positive. However, false-positive results also have been reported in up to 20% of cases in studies requiring consecutive positive results. Herbrecht et al [10] reported a specificity of 99.4 % using a cut-off of l.5, 93.9% with a cut off of 0.7, but only 88.7% with a cut-off of 0.6. We did not find any change in specificity when the cut-off was reduced from 1.5 to 1.0 and this remained uniformly high at 94.4%.

Maertens et al [5] reported false positive galactomannan tests in 5 consecutive samples in a patient treated with amoxicillin-clavulanate for neutropenic fever due to Escherichia coli bacteremia. The index gradually decreased after the patient was switched to quinolone therapy. There was no other data supportive of invasive aspergillosis. One week later the same patient was started on treatment with piperacillin-tazobactam followed by an immediate re-emergence of antigenemia (OD index $\geq$2.5). We had only one false positive result amongst patients classified in the IPA category and this patient was not receiving piperacillin-tazobactam or amoxycillin-clavulinic acid preparations.

The detection of antigenemia during twice-weekly monitoring facilitates early diagnosis of IA. Sulahian et al [11] reported that antigenemia preceded CT evidence of IA by more than a week in 65% of cases. Three patients in our series with initially negative serum assays had detectable antigenemia in samples taken four days to one week later.

Effect of therapy

Three patients in our series had initially positive assays which became negative in follow-up assays one week later. These patients with clearance of antigenemia had early response to anti-fungal therapy. Monitoring for antigen clearance or rebound may provide useful information for assessing the effectiveness of therapy. Bretagne et al [12] and Maertens et al [5] described declining levels in patients who responded to therapy and rising concentrations in those with fatal outcomes. Rohrlich et al [13] reported clearance of antigenemia in patients who responded to therapy and reappearance in those who relapsed. Becker et al [16] observed that antigenemia was no longer detectable in BAL after three days of therapy.

Microbiological diagnosis

A total of 14 (out of 160) cultures were positive, blood culture in 9 patients, throat swab / sputum in 3 patients, broncho-alveolar lavage fluid in 1 patient and postmortem tissue specimen in 1 patient. Fungi isolated in culture included Candida tropicalis and Candida albicans from throat swab and sputum, Rhizopus spp. from blood and throat swab and Aspergillus flavus from postmortem biopsy of necrotic palatal mass.

Aspergillus species are detected very rarely from materials like throat swabs, oral washings or saliva. Therefore routine surveillance samples from these areas do not help in early detection of invasive fungal infection. However, if such a specimen shows Aspergillus species, this finding has a high predictive value in severely immune-compromised patients. [15] The low culture positivity rate in our patients could be explained by the fact that our

patients were started empirically on intra venous (i.v.) antibiotics and anti-fungals at an early date immediately after onset of fever and the majority of patients were on anti-fungal and antibiotic prophylaxis even prior to the development of fever.

Bronchoscopy and BAL

A total of 9 patients underwent fibre-optic bronchoscopy and bronchoalveolar lavage from the affected segment. Many of our patients were critically ill and therefore unfit for bronchoscopy. Reichenberger et al [16] in their outcome analysis on bronchoscopy and BAL in 23 patients with histologically proven IPA reported a 30% (7 of 23) positivity rate for aspergillus in BAL. The microbiological yield of BAL was 11% in our series. This low positivity rate can be explained by the fact that all patients at the time of bronchoscopy were on broad spectrum antibiotics and 4 patients were also on anti-fungals.

BAL fluid galactomannan assay was done in 6 patients. The sensitivity, specificity, PPV and NPV were 75%, 100%, 100% and 66.7% respectively. Becker et al reported [14] detection of antigen in the BAL of all 18 cases of IA (sensitivity of 100%), while antigenemia was present in only 47%. They reported the sensitivity, specificity, PPV and NPV of GM detection in CT based BAL fluid as 100%. These figures were based on BAL fluids obtained before start of anti-fungal therapy. For GM detection in serially sampled serum, the sensitivity was 47%, specificity 93%, PPV 73% and NPV 82%. They also observed that GM-positive serum often became negative as soon as antifungal were started and the early start of treatment may have prevented detectable antigenemia in a number of patients.

Follow-up

The overall mortality in our patients classified as proven or probable IPA was 44% and that in control group (as defined earlier) was 33.33%. Response to antibiotic therapy was seen in 12.5% of our study patients, response to anti-fungal therapy in 40% and to anti-tubercular therapy in 2.5%.

Hohenthal et al [17] in their series of patients undergoing stem cell transplantation or intensive chemotherapy reported an in-hospital mortality of 30% for all episodes of clinical pneumonia and 55% for patients with pulmonary aspergillosis. They concluded that typical radiological signs on CT scans, a suggestive clinical course i.e., non-response to broad-spectrum antibiotics in patients at high risk for invasive fungal infections, and sequential positive results from serial galactomannan assay tests is good reason for early institution of systemic anti-fungal therapy. Increasing the sensitivity of this assay by lowering the cut-off for a positive test without increasing the false-positivity rate will therefore enable early detection of patients with aspergillus pneumonia.

The limitation of this study was lack of validation by histology (except in 2 cases) as majority of the patients were not fit for lung biopsy/ BAL.

Conclusion

We conclude that using a serum galactomannan index cut-off of 1.0 rather than 1.5 will facilitate early diagnosis of IPA and this will guide decisions regarding starting or delaying empirical anti-fungal therapy.

Table - I : Disease distribution

Diagnosis	Number of Patients	Percentage(%)
AML	38	47.50
ALL	12	15.00
Aplastic anemia	17	21.25
APML	5	6.25
Miscellaneous diseases	8	10.00

Table - II : CT scan abnormalities

CT abnormalities	Number	Percentage (%)
Nodule	24	42.9
Halo sign	19	33.9
Cavitation / air crescent	9	16.1
Fungal ball	4	7.14
Effusion	11	19.6
Segmental consolidation	34	60.7
Lymphadenopathy	7	13.8
Multiple abnormalities	35	47.3

Table - III : Positive cultures

Culture	Organism
Blood- bacterial	MRSA in 2, CONS in 2, ESBL E.coli in 2, Klebsiella pneumoniae in 1, MSSA in 1
Blood-fungal	Rhizopus spp.in 1
Throat swab	Rhizopus spp.in 1, C.tropicalis in 1, C.albicans in 1
BAL	Acinetobacter spp. in 1
Tissue	Aspergillusflavus in 1

Table - IV : Galactomannan assay

Serum	%	BAL	%
Sensitivity	72.7	Sensitivity	75
Specificity	94.4	Specificity	100
PPV	96.0	PPV	100
NPV	65.4	NPV	66.7

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Original Article

Review of male breast carcinoma in Indian patients: a single institution experience

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Abstract

Introduction

Male breast cancer is a rare entity. Patients present in advanced age with large primary tumours with higher receptor positivity than female breast cancers. Various risk factors have been proposed but lack of sufficient number of cases makes large scale prospective trials impractical. Treatment principles are guided by those of female breast cancer. Overall survival is reported to be worse.

Methods and Materials

Retrospective analysis studied data on 11 male patients with breast cancer treated between January 2001 and December 2008. Clinical presentation and natural history were evaluated.

Results

Incidence of male breast cancer was 0.94% of total breast cancer cases with mean age of 56.5 years. Thirty six percent cases presented as locally advanced and 36% as metastatic disease. Nodal involvement was present in 36% cases. Breast lump was the most common presentation. Most cases were of infiltrating ductal type and 73% presented with high grade tumours. Also 36% had ER expression while 27% had PR expression, but only 9% showed Her-2-neu expression. 73% cases underwent radical surgery, 55% received adjuvant chemotherapy. 36% received adjuvant radiotherapy, while 18% cases received palliative radiation. 27% showed CR and 18% of patients showed PR.

Conclusions

Male breast cancers account for around 1% of breast cancer cases in our scenario. In our institute, presentation of cases was a decade earlier. Treatment was decided according to stage, receptor status and post-operative histopathology. Longer follow up with a larger number of cases is required for determining overall survival and disease free rates.

Key words: Male breast cancers, clinical behavior, chemotherapy, radiotherapy.

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Introduction

Male breast carcinoma is a rare entity: accounting for <1% of all breast carcinoma. [1, 2] According to SEER data, males were significantly older than females with mean age at diagnosis being 66.2 and 62.1 years respectively. [3] Various risk factors such as lifestyle (tropical climate, pollution), exposure to aromatic hydrocarbons, genetic disorders, hyper-estrogenism, age have been implicated in the pathogenesis of these tumours. [4] Though mortality rates have been largely static, incidence rates have risen in the last 3 decades.

Lack of sufficient cases makes conducting large-scale prospective clinical trials impractical. Hence clinical management of male breast cancers is guided by research on the disease in females or by data from small case series. [5] Overall survival has been reported to be worse for males, [6] but after adjusting for age, T stage and number of positive nodes, survival in men and women is seen to be similar. [7-9] Many institutions offer adjuvant radiotherapy following mastectomy to all male breast cancer patients because of a perception of a high tumor to breast size ratio [10]; in contrast to cases of female breast cancer, where adjuvant radiotherapy is only offered for specific indications such as tumor size, margin status and number of positive nodes. [11] There is continued debate about whether post-mastectomy radiotherapy should be guided by the same principles used in women, or given routinely to all men with breast cancer. [12]

As no large scale prospective Indian studies are available, in this retrospective analysis, we have reviewed cases of male breast cancer in an Indian population according to a hospital based registry and have tried to find out if there are any significant differences in Indian patients when compared with existing western literature.

Methods and Materials

From 1st January 2001 to 31st December 2008, a total of 11 male patients with carcinoma of the breast registered in our department were analyzed in this study. Any patient whose treatment started before this period was excluded from the present study. All patients were required to have histopathological confirmation of carcinoma of the breast. Patient's evaluation included TNM staging, estrogen receptors (ER), progesterone receptors (PR) and HER2 measurements, tumor grade by Scarff–Bloom-Richardson and margin status. Metastatic workup included imaging of thorax and abdomen, bone scan, CT scan of brain (as and when required). Response to treatment was evaluated at the time of first follow up visit and was graded using WHO criteria.

A retrospective analysis was done on the patient profile, presentation, disease load, receptor status and their response to treatment. This was then compared with existing literature. Conclusions have been attempted as to whether there is any difference in the presentation and behavior of Indian patients as seen in our institution when compared to standard literature.

Results

In our series, patients were between 32 and 95 years of age at the time of diagnosis (Table I). 63 % of the patients were more than fifty years. One patient was 95 years old at the time of diagnosis. The mean age at diagnosis was 56.5 years while median age was 58 years. Majority of cases showed a slower disease progression with mean duration of disease being 1.54 years from the time of first presentation and 63.6% of cases having duration of symptoms for more than 1 year. Number of male breast carcinoma patients registered in our study in this period between January 2001 and December 2008 was 11 out of a total of 1170 breast carcinoma patients. This

constituted 0.94% of the total breast cancer burden. The male to female case ratio was 0.0095. The most common side involved was the left (45%), with bilateral breast disease seen in 2 patients (18%). Hence the left side was seen to be involved in up to 63% of cases. Also in a majority of patients (82% of cases), the disease involved either the central area (73% of cases) or whole of the breast (9% of cases). The upper outer quadrant was involved in around 18% of cases. There was no exclusive involvement of inner quadrants or lower breast. Lymph node involvement was seen in 4 cases (36%), while distant metastases were seen in 4 cases (36%). The sites involved were liver, lung, omentum and bone. The largest size of axillary node dissected was 3 cm x 2 cm, and the highest nodal involvement was N2.

Majority of patients presented above stage II (8 of 11 cases). Four patients (36% of cases) presented with Stage III and another four patients presented with Stage IV disease (Table II). All patients presented with breast lump at time of diagnosis. Local pain occurred in four patients (36%). Skin ulceration was seen at the time of presentation in 3 patients (27%), while at presentation nipple was involved in seven patients (64%), with nipple retraction seen in six cases (55%) and nipple discharge in one case (9%).

On histopathological review infiltrating ductal type (82%) was the most common, pathological subtype while 2 cases were poorly differentiated tumours (18%). Majority of cases (73%) showed a higher tumor grade. No lobular or in situ carcinoma was seen. Unknown (46% cases) or positive (27% cases) resection margins were seen in 73% of cases. Nipple-areolar complex was involved in nine cases (82%) while skin was involved in seven cases (64%). Chest wall invasion was seen in five cases (46%) and lymphovascular space invasion was seen in one case (9%).

More than one third of patients (36%), showed expression for ER receptors; while three cases (27%) showed expression for PR receptors (Figure I). 36% of cases had unknown ER status and 45% of cases had unknown PR status; including 36% of cases who had unknown ER and PR status. Around 27% of patients did not express either ER or PR hormone receptors. Her-2-neu expression was seen in 9% of the patients, and significant numbers showed either no expression (36%) or unknown status (55%). Two cases (18%) had triple negative disease (ER, PR and Her-2-neu negative).

Majority of cases (73%) underwent curative surgery; modified radical mastectomy was done in five cases, simple mastectomy in two cases and lumpectomy in one case (Table III). No palliative surgical procedures were done in any case. Also majority of cases received chemotherapy (55%), all of them in the adjuvant setting. Four cases (36%) received adjuvant radiotherapy, while two cases (18%) received palliative radiation for bone metastases. Three cases (27%) were started on hormonal treatment with either Tamoxifen (2 cases) or aromatase inhibitors (1 case).

Response evaluation was done at the end of treatment using WHO criteria for tumor response. Median follow up of cases was 16 months. Complete response to treatment was seen in 27% cases, while another 18% cases showed partial response. Two patients (18%) had stable disease at the end of treatment. Disease progression during treatment was not seen in any patient. Four patients (36%) did not complete their treatment. Of the three cases that showed complete response, two were early stage breast cancers (EBC) (Table II) and one case was locally advanced. The two cases showing partial response were both locally advanced cases (LABC) (Table II) and of the four metastatic breast cancer patients (MBC) (Table II), two showed stable disease on follow up

and the other two did not come for treatment. At one year after treatment complete responders were able to maintain their responses. On the other hand, of the two cases which showed partial response to treatment, only one patient was able to maintain his response while the other case showed further disease progression. One of the responders was hormone positive and one was a triple negative disease, while cases showing progression were either hormone negative or showed weak positivity. Thus there was no definite correlation of response with hormone receptor expression.

Discussion

Male breast carcinoma is rare; accounting for around 1% of all breast carcinoma, with data from the US showing less than 1500 cases per year and from the UK showing less than 300 cases per year. [1, 2] This was also seen in our study with male breast cancer being 0.94% of total breast cancer burden at our institute in the last eight years. A recent review of the Surveillance, Epidemiology, and End Results (SEER) Program data and a large single-institution series revealed no improvement in survival in male breast cancer over the last 25 years, with overall survival reported to be worse in male patients compared to similar stage female patients. [5]

According to SEER data, male to female breast cancer ratio was 0.7%. Men were more likely to be black than were women, black-white male to female breast cancer ratio was 1.4 ($p<0.001$). [3] Males were significantly older than females with mean age at diagnosis being 66.2 and 62.1 years respectively. [3] The median age of presentation at our institute was 58 years. It was seen that male breast cancers demonstrated and unimodal age frequency of 70 years, whereas female breast cancer patients had bimodal age distribution with early-onset (premenopausal) and late-onset (postmenopausal) peaks at 49 and 68 years, respectively.[3] Also males had significantly larger primary tumors ($p<0.001$), more positive axillary lymph nodes and higher estrogen and progesterone receptor positivity than women.[3] Histological grade was similar for men and women.[3] Between 4 and 40% of patients with male breast cancer have been shown to have mutations in BRCA2 gene, most of which are frame shift mutations. [13] However in absence of a family history, a BRCA2 mutation is unlikely to be seen.[13]

Most patients present with painless breast lumps, typically presenting as a mass beneath the nipple-areola complex. [3, 14] Local pain, axillary nodes, nipple discharge or retraction or gynaecomastia may also be seen. [14] In our study all patients presented with breast lumps with nipple-areolar involvement seen in 64% cases clinically and 82% cases pathologically. Males have been reported to have a higher percentage of locally advanced cancer at presentation than females. [15] This may be due to the fact that male breast tissue is much lesser than female breast with less tissue for the tumor to traverse before involving skin or chest wall. The prognosis depends on lymph node status, size of primary tumour, presence or absence of distant metastasis, as well as duration of symptoms; and in general, prognosis in male breast cancer patients is considered worse than in females. [6]

Most cases (90%) are of invasive ductal type on histopathological review with majority of them being of a higher grade with studies indicating a higher prevalence of grade III tumours in male breast cases. [1, 16] Others may also present with inflammatory carcinoma or with ductal carcinoma in situ (DCIS) or Paget's disease of the nipple. [16] However lobular carcinoma in situ (LCIS) is not seen in male breast cancer patients and lobular carcinoma is very rare. [14] Majority of cases (> 90%) express both estrogen and progesterone receptors and an inverse correlation has been seen

between receptor positivity and age. [3, 17] This is similar to that seen in females with breast cancer. Similarly, most cases in our study were of infiltrating ductal type with ER expression seen in 36% and PR expression seen in 27%.

In women, ER expression is usually a marker of differentiation and indicates that the cancer is still under hormonal influence, thereby implying that the tumor should be less aggressive and hence more responsive to hormone therapy. However, in one of the largest population-based studies of hormone receptors in male breast cancer, there was only a marginally significant trend for patients with ER positive tumors to present with higher stage disease.[18] Many studies have also confirmed that male breast cancer has a higher proportion of ER positivity than female breast cancer, although this finding does not correlate with a better prognosis as it does in women. [17] Also male breast cancers are less likely to express Her-2-neu as well as p53 than women with a large scale Canadian retrospective review showing 9% p53 expression in male breast cancers compared to 28% in females. [19, 20] This indicates that the process of carcinogenesis is probably different in male and female breasts and may explain the difference in survival rates despite similar treatment.

Treatment options include surgery, radiotherapy, chemotherapy and hormonal treatment. Even though majority of male breast cancers present as locally advanced cases, operability rates range from 74% - 95%, [14] with radical mastectomy being recommended if pectoralis major muscle is involved. [14] If the muscle is not infiltrated, modified radical mastectomy can be performed. [14] Breast conservation surgery (BCS) is rarely performed in view of scanty breast tissue in men and because of sub-areolar location of tumor in most cases.

The role of post-operative radiation therapy in case of male breast cancer has not been adequately evaluated with most recommendations mirroring those of similar stage female breast cancer. [10, 11] This is because a similarity has been noted in the patterns of disease recurrence as well as metastases between male and female breast cancers. Men undergoing BCS should receive mandatory post-operative radiation therapy; while in post mastectomy cases, radiation has shown to decrease local recurrence rates, but there does not seem to be a significant effect on overall survival. [21] Two trials have suggested that post mastectomy radiation should be given in node positive cases in both males and females, [22, 23] while other studies have indicated that similar to females, post mastectomy radiotherapy can be withheld in early stage male breast cancer patients. [11, 12]

Benefit of adjuvant systemic chemotherapy in male breast cancer has also not been adequately evaluated given the paucity of cases, and the guidelines are generally the same as those employed for treating female breast cancer cases, guided by prognostic factors and hormone receptor status. Two small retrospective studies have also shown improved survival with adjuvant systemic chemotherapy. [24, 25]

Hormonal therapy plays a major role in treatment of male breast cancer as more than 90% of cases are ER and PR positive; [3, 17] with response rates of 50-80%. Orchiectomy has been the historical standard hormonal treatment with response rates of around 50-60%. [26] This has now been replaced by the use of Tamoxifen [27] which has similar response rates (80% in ER positive cases). There is also a trend for increasing usage of aromatase inhibitors. Surgical methods of hormone ablation are reserved for patients with multiple failures to other methods.

Conclusion

Male breast carcinoma typically presents as a locally advanced disease and generally behaves more aggressively despite being hormone receptor positive in most cases. These cases accounted for 1% in our institute and survival and response rates were poor. Radical surgery is still the treatment of choice after which postoperative radiotherapy should be considered in all locally advanced cases especially those which are node positive. Guidelines of treatment followed are at present the same as those for female breast cancers. Longer follow up with a larger number of cases have to be done to determine overall survival and disease free rates in response to treatment.

Table I: Patient age, site and side distribution.

Age Distribution	Number (%)
30 – 50 years	4 (36.4)
>50 years	7 (63.6)
Side Involved	
Left	5 (45.4)
Right	4 (36.4)
Bilateral	2 (18.2)
Quadrant Involved	
Upper outer	2 (18.2)
Central	8 (72.7)
Whole	1 (9.1)

Table II: Patient stage and presenting symptoms.

Stage Presentation	Number (%)
EBC	3(27.3)
LABC	4 (36.4)
MBC	4 (36.4)
Presenting symptoms	
Lump	11 (100)
Pain	4 (36.4)
Nipple discharge	1 (9.1)
Nipple retraction	6 (54.5)
Skin ulcer	3 (27.3)

Table III: Treatment received by studied cases.

Treatment	Radical (%)	Palliative (%)	No treatment (%)
Surgery	8 (72.7)	0 (0)	3 (27.3)
Radiotherapy	4 (36.4)	2 (18.2)	5 (45.5)
Chemotherapy	6 (54.5)	0 (0)	5 (45.5)
Hormonal	3 (27.3)	0 (0)	8 (72.7)

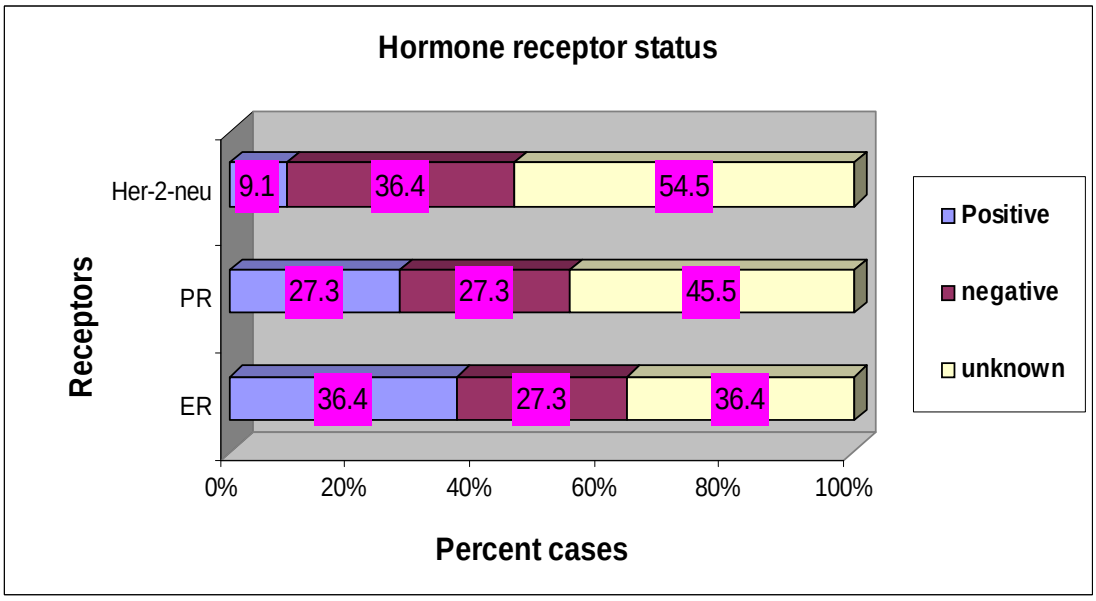

Figure I: Distribution of patients, including ER, PR and Her-2-neu status.

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Response to Taxanes based chemotherapy in metastatic eccrine porocarcinoma with extensive cutaneous involvement

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Abstract

Eccrine porocarcinomas are rare malignancies of eccrine sweat gland with a high incidence of local recurrence after surgery. Even though surgical resection is the best option in the management of malignant eccrine porocarcinoma, the management of recurrent, extensive or metastatic disease remains unclear. The use of chemotherapy gives good palliation in inoperable disease. Taxane based chemotherapy gives good symptom control in palliative setting and should be considered in the management of this rare neoplasm.

Here, we report a case of a 56 year old man with recurrent eccrine porocarcinoma with widespread cutaneous lesions over the lower chest and the anterior abdominal wall with axillary lymph node involvement. We describe the role of palliative chemotherapy with Taxanes in inoperable extensive disease.

Introduction

Eccrine porocarcinomas are malignant tumors related to the sweat gland duct, showing both intra-epidermal and dermal components. They represent around 0.005% of epithelial cutaneous neoplasms. They were first described by Pinkus and Mehregan in 1963. [1] They have a propensity for lower extremity followed by trunk and head and neck area. Eccrine porocarcinoma tends to affect the elderly, with an average age of 68 years. These tumors are characterized by high local recurrence rate following surgical resection and generally an aggressive clinical behaviour. Approximately 20% of eccrine porocarcinomas recur after excision. Regional lymph node metastasis occurs in 20% of patients, while 12% develop distant metastases.

Case Report

A 56 year old male patient presented with extensive nodular lesions over the upper part of anterior abdominal wall and the anterior lower chest. He had extensive nodulo-ulcerative plaques with bleeding and foul smelling discharge from the ulcerated lesion. Clinical examination revealed bilateral axillary lymph node enlargement largest being 10x8 cm, hard and fixed. Liver was not enlarged and examination of the respiratory system

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was clinically normal. Biopsy from the lesion showed malignant adnexal tumor consistent with eccrine porocarcinoma. Cytological analysis of lymph node was positive for malignant cells. Computed tomography scan showed a hypoechoic lesion with few hyperechoic foci in the abdominal wall infiltrating the subcutaneous tissue. There was no evidence of any other systemic spread.

As the disease was inoperable with fixed axillary lymph nodes, the patient was started on palliative chemotherapy. He was initially started on multi agent chemotherapy with Doxorubicin, Mitomycin, Vincristine, 5-Fluorouracil, administered every 4 weeks in rotation with Cisplatin and Bleomycin. He developed progressive disease after one cycle. Subsequently, the chemotherapy was changed to single agent Paclitaxel 175mg/m2 every 3 weeks, which showed minimal response. Bleeding and discharge from the lesion reduced (Figure - I). Hence Carboplatin was added to the subsequent cycles. He had a partial response to this regimen in the form of pain relief, decrease in the size and number of skin lesions and the size of the axillary nodes which reduced to 2x2 cm. Patient tolerated the chemotherapy well, but eventually developed neuropathic changes. Hence he was switched on to single agent Docetaxel 75mg/m2. This treatment was well tolerated and resulted in marked symptom control and clinical response. He succumbed to his illness after a follow up of 14 months.

Discussion

Eccrine porocarcinomas may arise de novo or as a malignant transformation in a pre-existing poroma. [2] 18 to 50% of eccrine porocarcinomas are associated with pre-existing eccrine poromas.

Pathological features show intraepidermal and dermal nests and cords of epithelial cells with pale cytoplasm. The tumor masses form clearly demarcated and frequently rounded nests of polygonal cells with pleomorphic and irregularly shaped nuclei, prominent nucleoli and numerous mitotic figures (Figure – II & III). Modified Bloom and Richardson grading system, usually applied to carcinomas of breast is used by some pathologists to grade the tumor. [3] High mitotic index, lymphovascular invasion and a depth of invasion more than 7mm are generally regarded as indicators of poor prognosis. [4] Clinically, the disease may appear as nodular, infiltrative, ulcerated or polypoidal lesions.

Recommended treatment is wide local excision with histological clear margins. Moh's micrographic surgery is being used frequently with good local control. [5] Lymph node dissection has been recommended if regional lymphadenopathy is present, or in cases of recurrent or poorly differentiated tumor with intra-lymphatic permeation. Eccrine porocarcinomas with an infiltrative pattern may benefit from further surgery if doubt exists regarding the completeness of the excision. [6] There are no definite recommendations favoring adjuvant therapy in this setting. There are no recommendations regarding the management of extensive or metastatic disease owing to the rarity of this condition. The role of radiotherapy remains doubtful. There are recent case reports of postoperative radiation in eccrine porocarcinoma. [7]

Various chemotherapeutic agents have been used in the management of metastatic eccrine porocarcinoma with varying response. Swanson et al reported a complete response of three months duration by using a 96-hour infusion of 5-fluorouracil in a patient with multiple systemic metastasis. [8] One complete response lasting 16 months was described in a case of sweat gland carcinoma metastatic to the lungs and bone treated with Doxorubicin, Mitomycin, Vincristine and 5 Fluorouracil (5 FU) for nine cycles followed by maintenance therapy with Cyclophosphamide,

Vincristine and 5 FU. [9] Docetaxel was used with good symptomatic relief in a patient reported by Plunkett et al. [3] There is report of a patient with multiple cutaneous and lymph nodal recurrence treated with lymphadenectomy, radiotherapy and oral isotretinoin, subsequently substituted by Tegafur without any evidence of distant metastases after a 5.6-year follow-up. [10] There is a case report of successful use of melphalan and intra-arterial 5 FU combined with regional hyperthermia by Briscoe et al. [11] Perilesional injection of INF alpha and IL 2 have also shown benefit. [12] Bree et al, described a case in which topical 5-fluorouracil application and intra-arterial chemotherapy with Docetaxel resulted in a histologically confirmed complete response of multiple regional skin metastases for more than 2 years. [13] A complete remission lasting 2 years was reported in a patient treated with a four drug regimen using Adriamycin, Cyclophosphamide, Vincristine and Bleomycin. [14]

Conclusion

Currently there are no uniform treatment guidelines for an extensive cutaneous involvement from eccrine porocarcinoma or metastatic disease. We have presented successful control of symptoms and a good response to palliative Taxane based chemotherapy in an extensive and inoperable case of eccrine porocarcinoma. Our patient had good symptomatic control with a combination of Carboplatin and Paclitaxel. Available literature shows the use of a wide range of chemotherapeutic agents which showed varying response. Considering the rare nature of this disease, reports of individual experience will help greatly in the management of subsequent cases. A Taxane based regimen will provide good response and quality of life.

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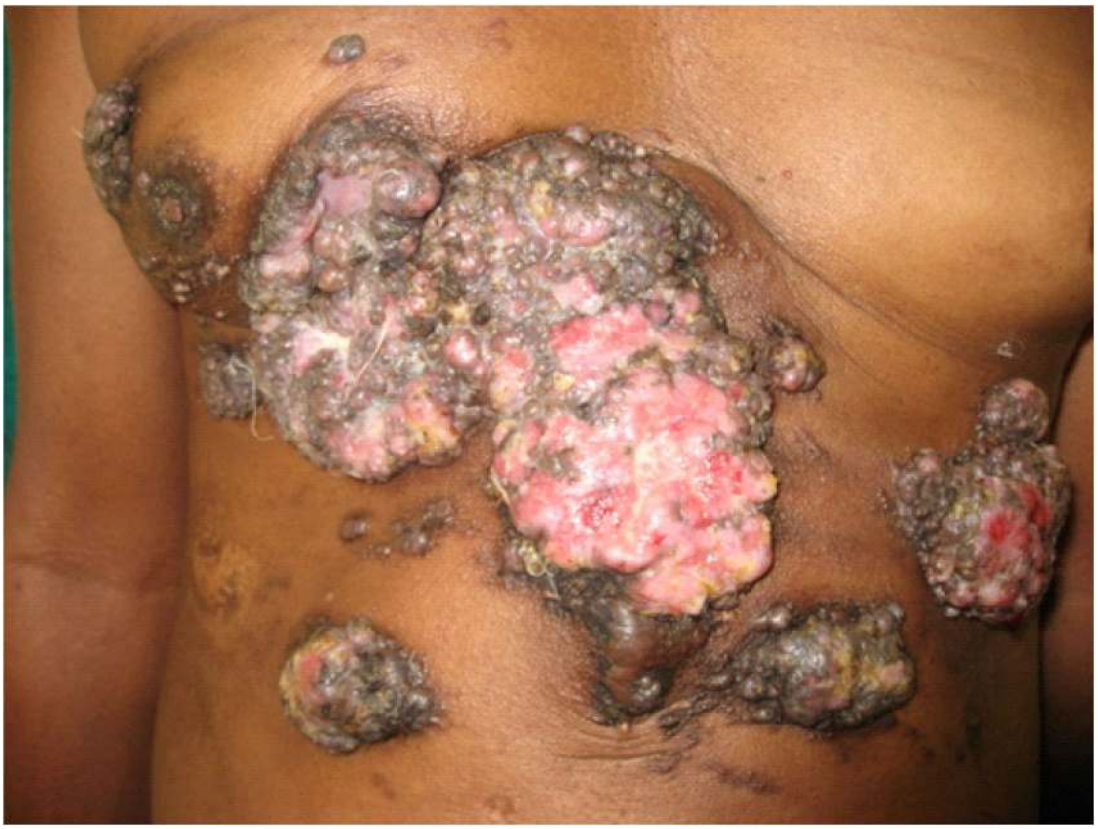

Figure - I:
Extensive nodulo-ulcerative plaques in the anterior chest wall

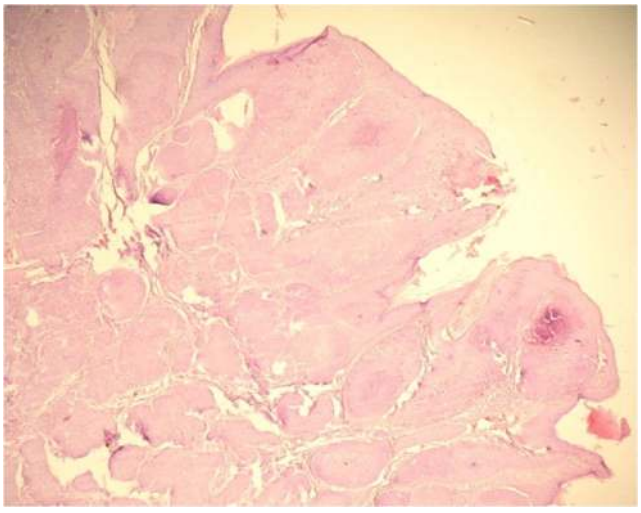

Figure – II:
Nests and islands of tumor cells arising from epidermis and extending into dermis (H&E x 100)

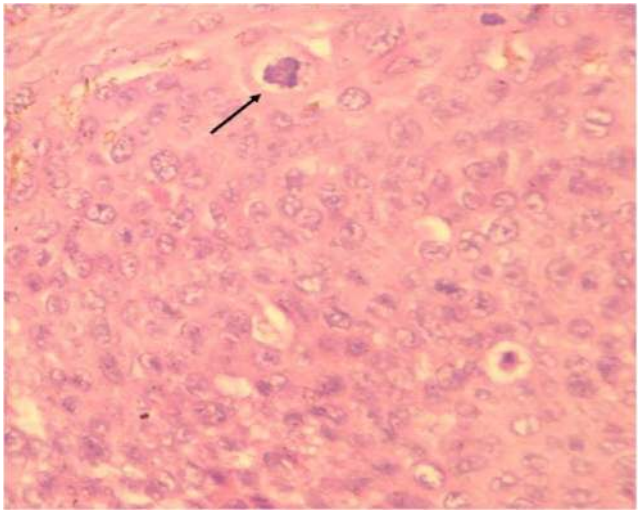

Figure – III:
Higher magnification of tumor cells showing prominent nucleolus and high mitotic rate (H&E x 400)

A rare case of primary vaginal primitive neuroectodermal tumour: diagnostic and treatment challenges

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Abstract

Primitive neuroectodermal tumor of the genital tract of women is scarcely described in literature but vaginal involvement is still rarer. We present an extremely rare case of primitive neuroectodermal tumor. A 45-year old woman presented with a vaginal mass that was diagnosed as a malignant round cell tumor. Immunohistochemistry (IHC) showed positivity for vimentin, CD99 and periodic acid Schiff (PAS) and was negative for cytokeratin (CK), epithelial membrane antigen (EMA), desmin, leucocyte common antigen (LCA), chromogranin, S-100 and neuron specific enolase (NSE). A diagnosis of primitive neuroectodermal tumor was made. She was treated with induction chemotherapy followed by local RT followed by adjuvant chemotherapy. This report emphasizes the role of induction chemotherapy followed by radiotherapy and adjuvant chemotherapy as a primary modality of treatment of this rare neoplasm.

Introduction

Primitive neuroectodermal tumor (PNET) and Ewing's sarcoma represent a single group of bone and soft-tissue tumors in which typical undifferentiated Ewing's sarcoma lies at one end of the spectrum and PNET with clear evidence of neural differentiation lies at the other. [1-3] PNET of the female genital tract is very unusual, but has been reported to involve the ovary, uterine corpus, uterine cervix and vulva. [3-6] To our knowledge, very few cases of PNET of vagina have previously been reported in the literature. [3-7]

Case Presentation

A 50 year old post-menopausal lady presented with complaints of irregular vaginal bleeding for two years. She also had a history of difficulty in initiation of micturition for two months.

On clinical examination, she was found to have a hard, smooth indurated mass lesion in the anterior vaginal wall extending to the lower third of vagina. Uterus, cervix and all fornices were normal. Rectal mucosa and bilateral parametria appeared free on digital rectal examination.

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Her routine hemogram, renal function tests and liver function tests were within normal limits. Her chest X-ray and CECT thorax revealed no abnormalities. Bilateral lung parenchyma, pleural spaces, heart, great vessels, bilateral bronchi were normal. Her abdominal CECT revealed bilateral hydroureteronephrosis. Other organs were normal. No lymphadenopathy was identified.

Her pelvic CECT scan [Figure IV] showed a moderately defined heterogeneously enhanced mass lesion measuring 7.0 x 3.4 x 6.3 cm involving the anterior vaginal wall with a mass effect on the urethra. Fat plane was not clearly maintained with the urethra and bladder. She had evidence of endometrial fluid collection. There was also evidence of a right fundal fibroid. The mass was seen as extending up to the introitus along the anterior vaginal wall. Bilateral adnexae were normal. There was no ascites or lymphadenopathy. Punch biopsy of the vaginal mass showed multiple polypoidal sheets of stratified squamous epithelium. Epithelium showed dilated blood vessels. Perivascular collections of round cells were present in the subepithelium. Immunohistochemistry of these cells revealed strong positivity for MIC2/CD99, [Figure II] Vimentin [Figure III] and PAS [Figure I]. IHC was negative for CK, EMA, Desmin, LCA and Chromogranin, S-100 and NSE. Bone marrow trephine biopsy showed normocellular marrow with no evidence of neoplasia. Histopathological diagnosis of PNET of anterior vaginal wall was thus made.

Following diagnosis of PNET of the vagina, she was treated with induction chemotherapy with VAC regimen for 3 cycles. The VAC regimen consisted of Inj. Vincristine (1.5mg/m^2) IV Bolus Day 1, Inj. Adriamycin (60mg/m^2) IV Bolus Day 1 and Inj. Cyclophosphamide (1200mg /m2) IV Infusion over 1 hour on Day 1. The induction phase was followed by local radiotherapy. Radiotherapy was delivered using LINAC 6 MV with AP/PA pelvic fields. 50Gy in 25 fractions was delivered followed by 18Gy in 2 weekly fractions as vaginal mould brachytherapy. After completion of radiotherapy, she was found to be clinico-radiologically free of the disease. Following this she received adjuvant chemotherapy for 15 weeks with alternating VAC/IE chemotherapy regimen for a total of 12 cycles. The VAC regimen (phase I) consisted of vincristine (1.5mg/m^2) IV Bolus Day 1, Cyclophosphamide (600 mg/m^2) IV Infusion over 1 hour Day 1 and Doxorubicin (60 mg/m^2) IV Bolus Day 1, given 3 weekly alternating with Ifosfamide (1800 mg/m^2) with Mesna from Day 1 to Day 5 and Etoposide (100 mg/m^2) IV Bolus from Day 1 to Day 5. [Inj Adriamycin was replaced with Inj Actinomycin D after 4th cycle of VAC as maximum dose of Adriamycin (300 mg/m^2) was reached]. She completed adjuvant chemotherapy after which she was followed up. After 4 months of completion of treatment, her clinical and radiological assessment showed no evidence of disease. She is presently on follow up.

Discussion

PNET and Ewing's sarcoma were considered distinct in the past. Recently, studies have shown that the small round-cell tumors seen in both tumor types share common phenotypic and molecular features, supporting the concept of a single tumor category. Therefore, the term Ewing sarcoma/PNET family of tumors is currently employed. [8-10] Ewing's sarcoma/PNET is now defined as a group of small round-cell sarcomas that show varying degrees of neuroectodermal differentiation. Ewing's sarcomas are tumors that lack evidence of neuroectodermal differentiation when assessed by light microscopy, immunohistochemistry or electron microscopy. PNET are tumors that show neuroectodermal features when evaluated by one or more of the above modalities.[1-3]

PNET can arise in the soft tissue of the chest wall, extremities, paravertebral and retroperitoneal regions, pelvis and abdomen, skin, visceral organs and head and neck, but rarely occur in the female genital tract. [3-6] The diagnosis of PNET is based on histological and IHC features. Uniform small round cells with round nuclei containing fine chromatin, scanty, clear or eosinophilic cytoplasm with glycogen content and indistinct cytoplasmic membranes are common microscopic features of Ewing's sarcomas. Although the presence of glycogen in a round-cell tumor was considered to be diagnostic of Ewing's sarcoma, it is now known that Ewing's sarcoma may be glycogen-negative. In cases of PNET, the tumors comprise small to medium sized cells with moderate amounts of cytoplasm, variable glycogen content and variable degrees of neuroectodermal differentiation. Immunohistochemical markers currently used in the diagnosis of Ewing's sarcoma / PNET family of tumors include MIC2 (also designated CD99), neurofilament proteins, neuron-specific enolase, vimentin and HBA-71. [2, 8] CD99 is expressed in the membranes of nearly all Ewing's sarcoma/ PNET tumors. [8] MIC2 expression is a highly sensitive and reliable marker for the diagnosis of Ewing's sarcoma/PNET when used as part of a panel of immunohistochemical stains, despite the lack of complete specificity. The diagnosis in our patient was revised from undifferentiated carcinoma to PNET based on the results of immunohistochemical staining. Management of PNET vagina remains controversial due to its rarity of presentation. On literature review of the six reported cases of primary vaginal PNET [Table 1] multiple modalities of treatment like surgery in the form of wide excision or hysterectomy with bilateral salpingo-oophorectomy, chemotherapy

Table – I:
Literature review of 6 cases of primary vaginal Ewing's sarcoma/primitive neuroectodermal tumor (PNET)

Case reports/series	Age	T-size	IHC profile	Mol. Results	Treatment	Outcome
Vang et al (2000) [5]	35	3 cm	VIM+MIC2+	EWS/FLI1+	WE+CT+RT	
Farley et al (2000) [4]	35	4 cm	MIC2+	NP	CT+EBRT+ICBT	
Petkovic et al (2002) [11]	45	9 cm	MIC2+	NP	CT+EBRT+ICBT	
Liao et al (2004) [3]	30	5 cm	VIM+MIC2+	NP	TAH+BSO_CT	
			FLI1+, synaptophysin+, 2 neuron specific enolase (NSE) +, S-100+			
McCluggage et al (2007) [12]	40	8 cm	VIM+, MIC2+,	FLI1, EWS-	□	□
Rekhi et al (2009) [7]	17	10 cm	VIM+, MIC2	EWSR1/FLI1+	CT+ Local RT	On Follow-up
Present case (2011)	45	7 cm	FLI1+BCL2+ VIM+, MIC2+	NP	CT+ Local RT	On Follow-up

T-size, tumor size in largest dimension; IHC, immunohistochemistry; VIM, Vimentin; Mol., molecular; NK, Not known: +, positive; -, negative; NP, Not Performed; □, Details cannot be procured; WE, wide excision; CT, Chemotherapy; EBRT, external beam radiotherapy; ICBT, intracavitary brachytherapy; TAH+BSO, total abdominal hysterectomy + bilateral salpingo-oopherectomy; FOD, free of disease; mo, months; AWD, alive with disease.

and local radiotherapy have been employed. Out of six documented cases so far, two cases reported by Farley et al and Petkovic et al used chemotherapy and external beam radiotherapy with intracavitary brachytherapy. [4,11] Rekhi et al [7] used both induction and maintenance chemotherapy with local radiotherapy and both the studies reported good clinical response to treatment. Our patient was successfully treated with induction chemotherapy, local radiotherapy and adjuvant chemotherapy and remains disease free at the end of four months.

Conclusion

This case is being reported due to the rarity of presentation of PNET of vagina. This report emphasizes the need of immunohistochemical analysis for aiding the diagnosis. It also discusses the successful management of primary primitive neuroectodermal tumor of vagina with combined modalities of treatment including induction chemotherapy, local radiation and adjuvant chemotherapy.

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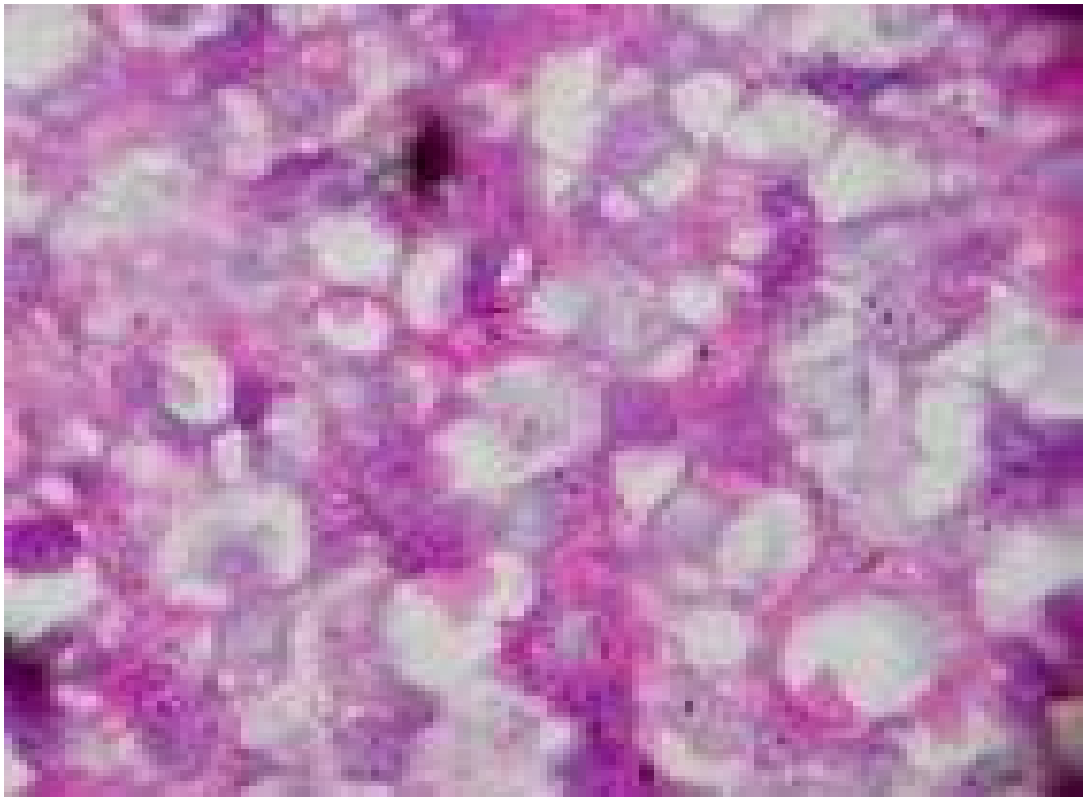

Figure I: High Power view showing PAS positivity

Figure II: IHC staining showing CD99 positivity

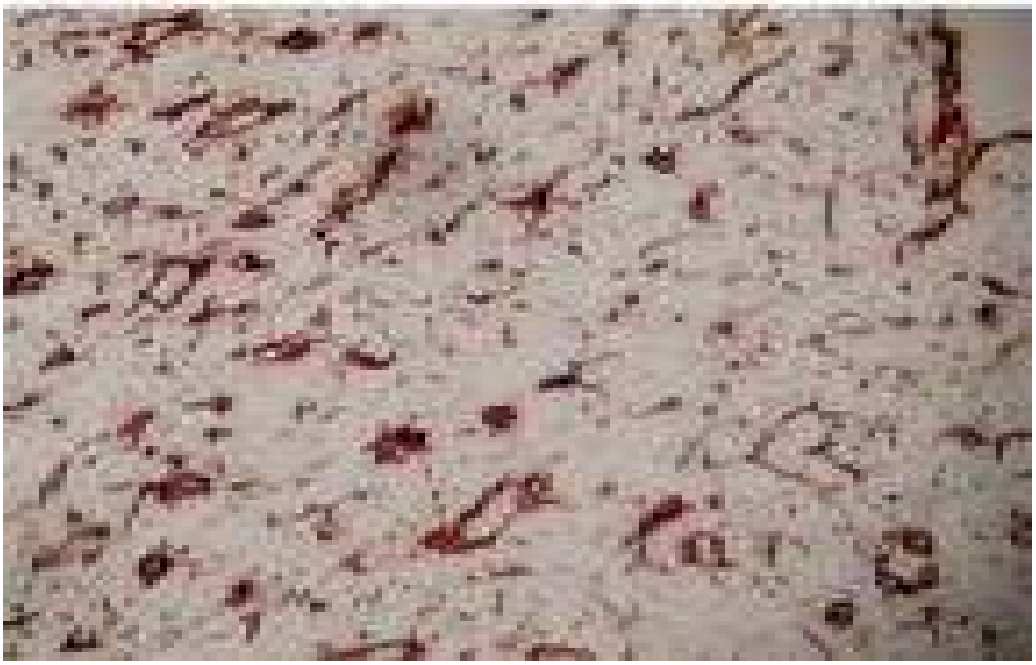

Figure III: IHC Staining showing vimentin positivity

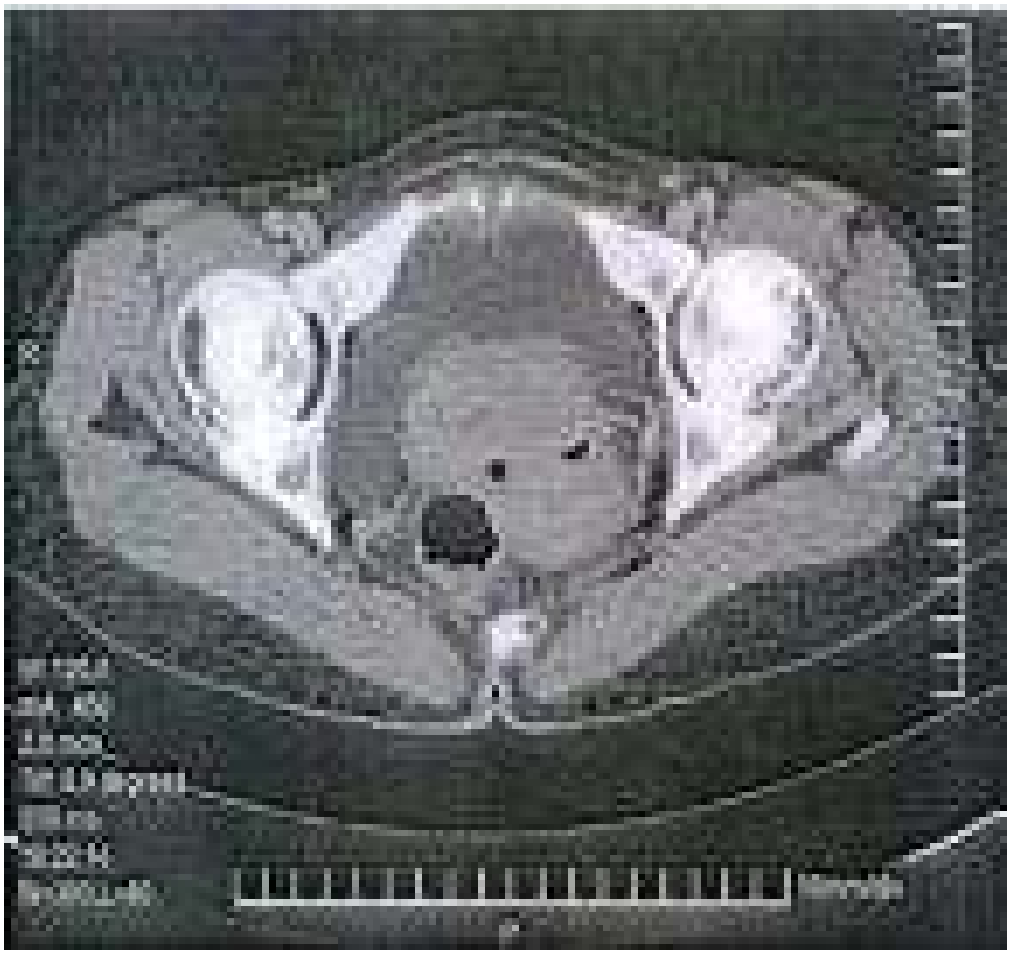

Figure IV : Contrast enhanced CT showing growth in the anterior vaginal wall

Local and distant recurrence occuring after 20 years in carcinoma breast

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Dear Sir,

Breast cancer is the most common malignant cancer among women in the developed world and amongst the five most common cancers in the developing world. [1]

Natural history of breast cancer, as observed by John Hunter in 1837 indicates a risk of relapse for twenty or more years even after successful removal of the primary disease. Although the risk of relapse is highest during the first 5 years after surgery, a definite risk remains throughout life. [2] We report two cases of late recurrence occurring more than 20 years after surgery.

CASE 1:

A 55 year old post menopausal lady presented with swelling of left arm and painful nodules over left chest wall of 2 months duration. She was previously treated for carcinoma of the left breast by modified radical mastectomy 20 years ago. She did not receive any adjuvant therapy. Examination revealed hard, fixed, tender nodules 3 in number over the medial edge of the mastectomy scar. There was no axillary, cervical or supraclavicular lymphadenopathy.

Fine needle aspiration cytology from the chest wall nodule revealed ductal carcinoma of the breast which was positive for ER, PR and Her-2-neu. Ultrasound of the abdomen and bone scan were normal. Chest X-ray revealed multiple nodular opacities bilaterally involving mainly lower and middle lobes. A computed tomography of the thorax showed bilateral focal opacities with "feeding vessel" sign suggestive of metastases. The patient was advised anthracycline based chemotherapy.

CASE 2:

A 46 year old post menopausal lady presented with pain and swelling in the right axilla. She was diagnosed with carcinoma of the right breast 22 years ago for which she underwent a simple mastectomy. She did not receive any adjuvant treatment. In March 2008 she developed both nodal and skeletal recurrence. She underwent local excision followed by loco-regional radiotherapy as well as palliative radiotherapy to pelvis for bony metastases at a private centre. At presentation in August 2008, she had an 8 x 6 cm mass in the right axilla extending over the right chest wall. There were no palpable supraclavicular or cervical nodes.

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A tru-cut biopsy from nodal mass showed infiltrating duct carcinoma which was ER and PR positive and Her-2-neu negative. Ultrasound of the abdomen and chest x-ray were normal. Bone scan showed increased uptake in right femur. MRI pelvis showed diffuse alteration in marrow signal in bilateral proximal femur with cortical thinning and erosion suggestive of metastases. She was started on combination chemotherapy with taxanes and anthracyclines.

Discussion

Women with breast cancer carry a definite risk of relapse for a long period of time, even after successful control of the primary disease by multimodality therapy. Adjuvant chemotherapy and/or endocrine therapy help to prevent relapses by targeting subclinical disease and occult metastasis.

Although the risk of relapse is highest during the first 5 years after surgery, a lifelong residual risk remains. [2] According to an analysis of various ECOG study groups, the peak hazard of recurrence occurred 1-2 years post-surgery. [3] The hazard decreased consistently by 2-5 years and at more than 5 years, risk of recurrence decreased. [3] Patients with more than three positive nodes had a higher hazard of recurrence at all time intervals. [3] The longest interval period has been reported by Chauffard in 1932 in a mastectomy scar 50 years after the primary surgery. [4] According to another study by Hanrahan, [5] patients who received adjuvant radiation, axillary lymph node surgery, or had at least six axillary lymph nodes (ALNs) examined were less likely to die as a result of breast cancer than were patients who did not receive radiation/ALNs surgery, or had fewer than six ALNs examined. At 5 and 10 years after diagnosis, probability of death due to breast cancer was 0.02 and 0.04, respectively, while probability of death from other causes was 0.08 and 0.20 respectively. [5]

The site and time of the late recurrence is diverse among patients and the survival time after the recurrence depends on the site of recurrence. Two definite patterns of local recurrence have been noted. Most commonly the recurrent mass/lesion is localized and salvageable by surgery. [6] Diffuse breast involvement is sometimes seen which is multifocal and infiltrative and appears to be a local manifestation of a highly aggressive cancer. [6] This type is usually followed by distant metastases and is rarely amenable to surgical salvage.

Local recurrence is often a part of systemic failure, which can appear either synchronously or metachronously and is an independent predictor of systemic failure. [2] Recent studies have shown that an excess of local recurrences may subsequently increase the incidence of distant metastasis and eventually lead to a decrease in overall survival. [2] This was seen in both our reported cases where the local recurrences, synchronously presented with distant metastases.

Conclusion

Cases not having received adjuvant therapy are at increased risk of relapse even after many years, as was seen in both our reported cases. The treatment of a recurrence is similar whether it occurs immediately or several years after apparent control of the primary. The control of symptoms with surgery, radiotherapy, chemotherapy and/or endocrine therapy is of importance since these patients can achieve palliation for a long time.

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Primary intra osseous hemangioma of the skull base – CT and MR imaging features

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Intraosseous hemangiomas of the skull base are exceedingly rare tumours. A 13 year old female was diagnosed with primary intraosseous hemangioma of the skull base. We present the imaging features and a brief review of literature.

A 13 year old girl presented with progressive painless loss vision in both eyes since 3 months. This was associated with mild holocranial headache. There was no history of seizures. Ophthalmological examination revealed bilateral primary optic atrophy and decreased visual acuity {right eye (RE) – no perception of light, left eye (LE)- 1/60}. She had no other focal neurological deficits. Magnetic resonance imaging (MRI) with three-dimensional constructive interference in steady state (CISS-3D) sequences and contrast enhanced tomography (CECT) of the brain demonstrated an expansile, extradural lesion in the skull base encasing both internal carotid arteries (ICA) (Image I). The optic nerves were grossly stretched and displaced superiorly over the tumor capsule (Image I). The lesion involved the floor of the anterior cranial fossa and extended up to the upper 1/3 of the clivus posteriorly (Image II). The sphenoid and posterior ethmoid sinuses were involved. CT demonstrated the classic 'honeycomb-like' bony trabeculae within the lesion (Image II). Digital subtraction angiography (DSA) showed a tumor blush arising from the cavernous segment of the ICA (Image III). The initial working diagnosis was that of skull base osteosarcoma. Transnasal endoscopic biopsy of the lesion was done. Histopathological examination revealed the lesion to be a hemangioma. Endocrine profile revealed subclinical hypothyroidism (pituitary hormone levels were within normal limits except for raised TSH). In view of the size, location and vascularity of the tumor, complete excision was deemed difficult and she was planned for 3D conformal radiotherapy. A dose 40Gy was prescribed in 20 fractions using 6MV photons. She developed no fresh complaints after completion of radiotherapy.

Hemangiomas of the skull are benign, exceedingly rare tumours that account for 0.2% of all bone tumours and 10% of all benign tumours of the skull. [1] The most common locations for these tumours are the frontal and parietal bones. Classic CT findings include the "sun burst appearance" and "honeycomb" appearance due to the presence of bony trabeculae. [2, 3, 4] Intraosseous hemangiomas are to be differentiated from osteogenic sarcomas, which also destroy the bone cortex and have areas of new bone formation. [2] The magnetic resonance (MR) signal characteristics of a haemangioma are dependent on the quantity of slow-moving venous

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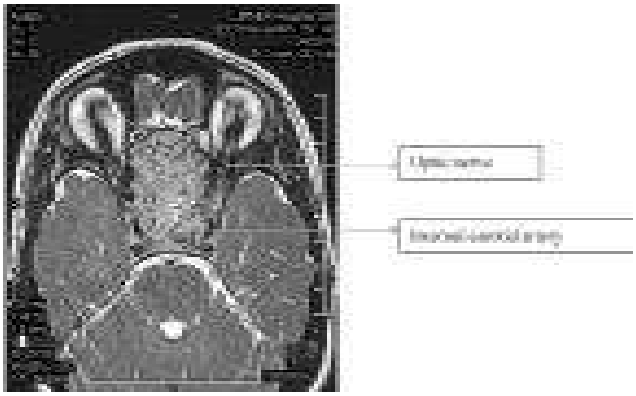

Image - I : Axial CISS 3D image showing both optic nerves encased within the lesion as well as both internal carotid arteries engulfed by the tumor

blood and on the ratio of red marrow to converted fatty marrow present within the lesion [2, 3] Lesions with a predominantly fatty matrix show high signal intensity on T1, intermediate to high signal intensity on T2 and a loss of signal fat-suppressed T2 weighted images. If the vascular elements predominate, the lesions appear hypointense on T1 and extremely hyper-intense on T2 weighted images. MR imaging helps in definition of intraosseous extent and in detection of simultaneous soft tissue involvement. In the present case the MRI images showed iso-intense signal with central mixed low and high signal areas in T1 weighted images and heterogeneous hyper-intense signals in T2 weighted images. CISS 3D images confirmed extradural nature of the tumor. CT demonstrated trabeculated 'honeycomb' appearance. DSA demonstrated tumour blush arising from the cavernous segment of the internal carotid artery.

It was deemed impossible to achieve a radical extirpation of this lesion owing to its location, size, vascularity and involvement of critical neurovascular structures. One option in such cases would be to place the patient on cardiopulmonary bypass with cooling of the body to produce profound hypothermia. Actual circulatory arrest to the brain would be feasible for up to 30 minutes in such a situation, but this window of time was deemed inadequate to dissect and excise so large a

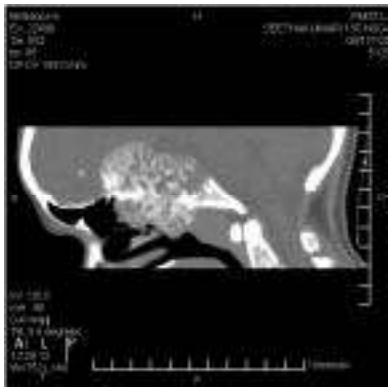

Image - II: Sagittal reconstruction of a CT image showing the bony trabeculae within the lesion (honeycomb pattern); it extends from the anterior cranial fossa (ACF) base till the clivus posteriorly

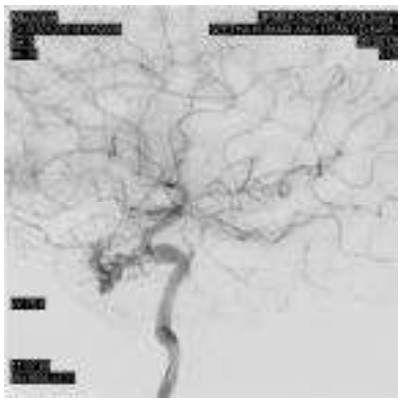

Image – III: DSA, Left ICA injection showing the tumor blush arising from the cavernous segment of the ICA. This is the extradural segment of the ICA

tumor. An alternative strategy, as was followed in this case, would be to irradiate the lesion with the expectation that it would stabilize in size or regress. If the visual complaints persist, surgical decompression of the optic apparatus alone can subsequently be carried out, with the expectation of reduced vascularity as a result of radiation.

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Collage by a 3year old cancer survivor

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