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A Comparative Evaluation of Accelerated Radiotherapy Versus Concomitant Chemoradiotherapy in Management of Locally Advanced Head and Neck Cancer

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Abstract

Background: The purpose of this study was to prospectively evaluate and compare the outcome of accelerated radiotherapy versus conventional chemoradiation in patients of head and neck cancers.

Methods: The study was conducted on patients with squamous cell carcinoma of head and neck region. The patients were randomly divided into two groups. Patients were treated with radical external beam radiotherapy (EBRT). Group I was given accelerated radiotherapy with dose of 66 Gy/33 fractions/5.3weeks/6 fractions per week and Group II was given conventional radiotherapy with dose of 66 Gy/33 fractions/6.3weeks/ 5 fractions per week along with cisplatin weekly. The response of primary tumor and lymph node were assessed. Acute radiation reactions were assessed on weekly basis. All the patients were re-examined monthly after the completion of treatment and analysed till six months of follow up.

Results: Patients were followed for six months after the completion of treatment. At the end of treatment, grade II & grade III acute skin reactions were seen in 53.3% of the patients in group I and 43.3% of the patients in group II. In group I, 63.3% of the patients experienced severe acute mucosal reactions, in comparison to 46.7% in group II. Overall the complete response was seen in 63.3% (19/30) of the patients in group I and in 73.3% (22/30) of the patients in group II.

Conclusion: The arm with conventional treatment with weekly cisplatin has shown slightly better outcomes in terms of disease control and toxicity profile in comparison to the arm with accelerated radiotherapy.

Keywords: head and neck, cancer, accelerated, conventional, radiotherapy, cisplatin

1. Introduction

Radiotherapy with or without chemotherapy remains the mainstay of treatment of locally advanced head and neck cancers (Mendenhall et al., 2006; Perez et al., 1991). In the past 20 years, many strategies have looked at improving the effectiveness of radiotherapy in advanced squamous cell carcinoma (SCC) of the head and neck region. This is because even the most effective radiotherapy regimen for advanced head and neck cancer results in local control rates of 50% to 70% and disease-free survival of 30% to 40% only. These have included incorporating the use of other treatment modalities such as surgery, chemotherapy and biological modifiers (Overgaard, Horsman, 1996; Peters, Ang, 1992; Withers et al., 1988). Because of high incidence of advanced

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disease at presentation and locoregional recurrences, the management of these patients is very disappointing and remains a challenge (Stupp et al., 1994).

The rationale for accelerated fractionation is that reduction in overall treatment time decreases the opportunity for tumor cell regeneration during treatment and therefore increases the probability of tumor control for a given total dose. The limitation of accelerated hyper-fractionation is acute toxicity (Withers, 1985).

Based on the information and literature available so far; the present work assessed and analysed the differences in tumor control and treatment induced toxicity by accelerated fractionation therapy (six fractions per week) and concomitant chemoradiation with cisplatin in cases of locally advanced head and neck carcinoma (LAHNC).

2. Materials and methods

The study was conducted on sixty previously untreated, histopathologically proven patients of squamous cell carcinoma of head and neck. These patients were randomly divided into two groups, group I and group II. Simple randomization was done by draw of lots.

Pre treatment Evaluation

The pre treatment evaluation in all patients included complete history, general physical examination and complete systemic examination. The assessment of patient's general condition was done using Karnofsky Performance Status (KPS). Haematological assessment was done by a complete hemogram including hemoglobin, total leukocyte count (TLC), differential leukocyte count (DLC), platelet count and peripheral blood film. Biochemical assessment to assess the kidney and liver functions was done by estimation of blood urea, serum creatinine, SGOT and SGPT levels. Radiological assessment including chest X-ray, X-ray soft tissue of neck was done in all patients. Whenever clinically indicated, computed tomography scan of face and neck was done. The patients were staged according to AJCC (American Joint Committee on Cancer) 2010.

Eligibility criteria includes KPS >70, Hb >8gm/dL, TLC >4000/cmm, platelet count > 100,000/cmm, blood urea <40mg/dL, serum creatinine <1.5mg/dL, SGOT <35 IU/L and SGPT <40 IU/L, AJCC stage III/IV and a positive biopsy for squamous cell carcinoma of head and neck.

Exclusion criteria includes distant metastases, prior radiation, surgery or chemotherapy for the disease, KPS<70, pregnant or lactating patient, associated medical conditions such as renal disease, liver disease or heart disease, patients having a primary in thyroid / salivary glands.

Group I

These patients were treated with radical external beam radiotherapy (EBRT). The accelerated treatment is being delivered with dose of 66 Gy/ 33 fractions/5.3weeks/6 fractions per week.

Group II

These patients were given concomitant radiation therapy. Conventional radiotherapy is being delivered with dose of 66 Gy/33 fractions/6.3weeks/ 5 fractions per week along with cisplatin 40 mg/m^2 on weekly basis.

Radiotherapy Technique

All the patients were treated in supine position and radiotherapy was delivered by Cobalt-60. The patients were planned by bilateral parallel opposing fields to face and neck and the dose was prescribed to the mid plane at the central axis. The shrinking field technique was used and the spinal cord was excluded from the radiation field after 44Gy.

EXAMINATION DURING TREATMENT

During the treatment, each patient was evaluated weekly. Primary tumor and lymph node response were assessed as per World Health Organization (WHO) criteria. Acute reactions that were specifically observed, included skin reactions and oral mucosa reactions, and were graded according to the Radiation Therapy Oncology Group (RTOG) criteria whereas nausea, vomiting and hematological parameters (Hemoglobin, TLC, platelets, blood urea, serum creatinine, SGOT/SGPT) were graded according to the WHO criteria. The weight loss was graded according to the SWOG (South West Oncology Group) criteria.

FOLLOW UP

All patients were followed monthly after the completion of treatment and analysed till six months of follow up. The response of tumor (primary and nodal) was assessed based on WHO criteria whereas late skin and mucosal reactions were graded based on RTOG criteria.

STATISTICAL ANALYSIS

The data thus obtained were assessed, analysed and compared to find out the differences in the two groups in terms of tumor response and toxicity using chi- square test.

3. Results

Patient characteristics

Patient characteristics are described in Table 1. Mean age of patients in group I and II was 53.9 years and 52.2 years respectively. Male: female ratio was 13:1 in both the groups. Overall 81.67% patients were from rural areas while 18.33% of the patients belonged to urban background. Overall 90% patients were smokers while 10% patients were non-smokers. Overall, base of tongue was the most common primary site; 46.67 % in Group I and 36.67% in Group II. Stage wise distribution of patients is summarized in Table 2. The baseline investigations were normal and comparable in both the groups.

Treatment

All patients were divided into two groups, group I and group II of 30 patients in each group. Group I was treated with accelerated radiotherapy (66Gy/33 fractions/5.3weeks/6 fractions per week). Group II was given conventional radiotherapy with dose of 66 Gy/33 fractions/6.3weeks/5 fractions per week along with cisplatin 40 mg/m^2 weekly.

Acute skin toxicity

All patients have developed cutaneous radiation reactions by the end of treatment. By the end of first week, 40% versus 20% of the patients in group I and group II respectively developed grade I cutaneous reactions. At the end of treatment, grade II & grade III reactions were seen in 53.3% of the patients in group I and 43.3% of the patients in group II. Though higher in group I but the difference in two groups was not significantly different.

Acute mucosal toxicity

By the end of first week, 20% of the patients in group I versus 13.3% in group II developed grade I mucosal reactions. By the end of third week, all patients developed mucosal reactions, Grade II reactions were seen in 56.7% of the cases in group I compared to 10% in group II. At the end of treatment, in group I, 63.3% of the patients experienced grade II & grade III mucosal reactions, higher than the corresponding figures of 46.7% in group II. Though higher in group I, the difference in two groups was not significantly different.

Tumor response

Overall, complete tumor response in group I and II was 70% versus 76.7% at the last follow up of six months. In T2 subgroup of patients, complete tumor response was observed in 75% (6/8) of patients in group I and 60% (3/5) of group II patients respectively. The observations were not statistically significant. In T3 subgroup of patients, complete tumor response was observed in 77.8% (14/18) of group I and 86.7% (13/15) of group II patients respectively. The observations were statistically not significant. In the T4 sub group of patients, complete tumor response was observed in 25% (1/4) of group I and 70% (7/10) of group II patients respectively. The observations were not statistically significant. Though small, the overall results were in favour of group II.

Nodal response

In N1 subgroup of patients, complete nodal response was observed in 66.7% (8/12) of group I and 91.7% (11/12) of group II patients respectively. In N2 subgroup of patients, complete nodal response was observed in 50% (4/8) of group I and 60% (3/5) of group II patients respectively. Overall, complete nodal response was seen in 60% (12/20) in group I and 82.4% (14/17) in group II patients. The observations were not statistically significant.

Stage wise response

Complete response in stage III was observed in 77.8% (14/18) of the patients in group I and 82.4% (14/17) in group II respectively. In stage IV subset, the corresponding complete responses were 41.7% (5/12) and 61.5% (8/13) respectively. For all stages, the complete response was seen in 63.3% (19/30) in group I and 73.3% (22/30) in group II patients. The observations were not statistically significant. The observations have been depicted in Table 3.

Late Radiation Toxicity

Mucosal reactions were comparable in the two groups. Though not statistically significant (p = 0.182), skin reactions were more in group I. Grade 2 skin reactions were seen in 20% and 13.3% of the patients in group I and II respectively. Grade 2 mucosal reactions were seen in 26.7% and 23.3% of the patients in group I and II respectively. None of the patients experienced grade 3 or 4 late toxicity.

4. Discussion

Meta-analysis of chemotherapy on Head and Neck cancer in 2009, based on 93 randomized trials and 17,346 patients has revealed an absolute survival benefit of 4.5% at 5-years by addition of chemotherapy to radiotherapy (RT+CT) as compared to radiotherapy (RT) alone. Out of the three groups studied (adjuvant, induction and concomitant), the maximum benefit of 6.5% in 5-year survival was observed with concomitant chemotherapy [8].

The concomitant chemoradiation has advantage in terms of local control as well as survival and is the standard of care for locally advanced HNSCC, but this is achieved at the cost of more acute toxicity, necessitating more supportive care, more treatment interruptions.

Accelerated radiotherapy applied to squamous-cell carcinoma of the head and neck yields better locoregional control than does a conventional schedule with identical dose and fractionation. There is evidence indicating that altered fractionation in the form of six fractions per week achieves better results than conventional radiotherapy in advanced head and neck cancer with acceptable toxicity (Overgaard et al., 2003; Wang et al., 2008; Lee et al., 2001; Skladowski et al., 2000; Kumar et al., 1992; Kumar et al., 2010).

Accelerated fractionated radiotherapy is known to produce more severe toxicity in head and neck cancer patients. Similar trend was seen in this study. In a study by Sharma A et al, grade III and IV toxicities were observed in 16% and 40% of the patients in RT and CRT arms, respectively (p= 0.01) (Sharma et al., 2010). In a study by Majumder D et al, grade 3 skin toxicity was observed in 47.36% of the patients on accelerated treatment, but in the concomitant group, they were 30%. Grade 3 mucositis was higher in the six fractions per week arm (63.16%) compared with concomitant arm (35%) but no statistical significance could be drawn. In our study, severe (grade 2 and 3) acute skin toxicity in group I, was seen in 53.3% of the patients and in group II, it was seen in 43.3% of the patients. Grade 2 and 3 mucositis in group I and II were seen in 63.3% and 46.7% of the patients respectively. Similar results were also observed by Majumder D et al (Cooper, Fu, 1995).

In the present study, response rate after six months of follow up was 63.3% in group I and 73.3% in group II. Similar results were also observed by Overgaard J et al and Sharma A et al (Overgaard et al., 2003; Sharma et al., 2010). Overgaard J et al observed that overall 5-year loco regional control rates were 70% and 60% for the six fraction and five-fraction group respectively (p=0·0005). The whole benefit of shortening of treatment time was seen for primary tumour control (76 vs. 64% for six and five fractions, p=0·0001), but was non-significant for neck-node control (Overgaard et al., 2003). Sharma et al reported improved response rates (79.2% vs 69.7%, p < 0.05) and 3-year overall survival (62% vs 42%, p 0.024) for concurrent weekly cisplatin as compared to radical radiotherapy alone. This however, was achieved at the cost of increased grade III-IV toxicities (40% vs 16%, p < 0.05) (Sharma et al., 2010).

5. Conclusion

This may be concluded from the present study that in the management of locally advanced head and neck carcinoma, concomitant radiotherapy group is slightly better compared to accelerated treatment group in terms of disease control and toxicity profile. Though, no statistical

significant values were obtained, results favour the concomitant radiotherapy schedules over the accelerated fractionated radiotherapy group.

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Table 1. Patient characteristics

	Group I	Group II
Age (years)		
31-40	10%	20%
41-50	33.4%	26.7%
51-60	40%	23.3%
61-70	10%	30%
71-80	6.6%	0%
Gender		
Male	86.67%	13.33%
Female	86.67%	13.33%
Smoker	93.33%	86.7%
Non smoker	6.67%	13.3%
Site of tumor		
Oral cavity		
Anterior tongue	6.67%	3.33%
Floor of mouth	-	3.33%
Hard palate	3.33%	3.34%
Retromolar trigone	-	3.33%
Alveolus	-	3.33%
Oropharynx		
Tonsil	16.67%	26.67%
Base of tongue	46.67%	36.67%
Soft palate	-	3.33%
Hypopharynx	13.33%	6.67%
Larynx	13.33%	10%
Histopathology		
WDSCC	13.33%	3.33%
MDSCC	70%	76.67%
SCC,NOS	16.67%	20%
Stage		
III	60%	56.7%
IV	40%	43.3%

Table 2. TNM stage wise distribution at presentation (n=60)

	Group I (n=30) Number of patients (%)				Group II (n=30) Number of patients (%)			
	T1	T2	T3	T4	T1	T2	T3	T4
N0	0	0	9 (30)	2 (6.7)	0	0	8 (26.7)	5 (16.7)
N1	0	6 (20)	3 (10)	2 (6.7)	0	4 (13.3)	6 (20)	2 (6.7)
N2	0	2 (6.7)	6 (20)	0	0	1 (3.3)	1 (3.3)	3 (10)
N3	0	0	0	0	0	0	0	0
Stage III	18 (60)				17 (56.7)			
Stage IV	12 (40)				13 (43.3)			

Table 3. Tumor response (stagewise) at last follow up of six months

	Stage	Total number of patients	Disease status		
			CR	PR	NR
Group I	III	18	14 (77.8%)	02 (11.1%)	02 (11.1%)
	IV	12	05 (41.7%)	03 (25%)	04 (33.3%)
	All stages	30	19 (63.3%)	05 (16.7%)	06 (20%)
Group II	III	17	14 (82.4%)	02 (11.8%)	01 (5.8%)
	IV	13	08 (61.5%)	02 (15.4%)	03 (23.1%)
	All stages	30	22 (73.4%)	04 (13.3%)	04 (13.3%)

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Effects of Obesity on Labour

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Abstract

The article focuses on effects of obesity on labour**.** The aim of the retrospective study was to reveal, if obesity has impact on duration of pregnancy and the means of conducting labour. Altogether, 960 obstetric documentary, which fulfilled our classification criteria. We have found out that a woman's BMI influences the type of labour and its mechanism. We recommend to monitor weight gain in pregnancy and to focus on educational program concerning weight reduction in the pre-conception period.

Keywords: obesity, BMI, type of labour, mechanism of labour.

1. Introduction and relevance

Obesity/adiposity is, according to WHO, abnormal or exceeding storage of fat in organism, which can endanger or damage health. Obesity in adults is diagnosed using **body mass index** (BMI), which serves as an index of life prognosis and level of risk of complications (Béder, 2005; Češka, 2010; WHO, 2013a; WHO, 2013b).

Effect of adiposity is linked to serious chronic diseases, which reduce overall quality of life and bring about higher risk of a premature death (Kiňová, 2013). Obesity afflicts also women in the fertile age and affects their fertility – increases a risk of sterility; the women do not have regular menstruation, which increases risk of contraception failure, unplanned pregnancy, and increased risk of miscarriage (Zera, 2011). Prevention before pregnancy significantly lower obstetrical and neonatal morbidity, therefore it is recommended to monitor weight gain (Oteng-Ntim, 2013).

Furber (2013) recommends in obese pregnant women a weight gain during pregnancy not higher than 5.0 – 9.1 kilograms. Losing weight is not recommended during pregnancy. As several studies suggest, risks connected with losing weight lowered incidence of preeclampsia, however, some of them show that in such cases, more frequently hypotrophic newborns are born. Thus, it is necessary to determine exact values of lowering weight in obese pregnant women, which are going to be safe.

Obesity during pregnancy is linked to a whole group of adverse foetomaternal complications and may be a real risk factor of maternal morbidity and mortality (Iyoke, 2013). Obesity is related to gestational diabetes mellitus (GDM), foetal macrosomy, excess joint stress, preeclampsia and thromboembolic, complications in labour, higher incidence of Caesarean sections (Oteng-Ntim, 2013; Čech, 2006). Excessive weight gain is connected with gestation complications like

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hypertension, diabetes, preeclampsia, foetal macrosomy. In case of preeclampsia and hypertension it was proved, that these women have a higher risk of hypertension and heart diseases in older age (Thorsdottir, 2002). Higher incidence of thromboembolic increases risk of pregnancy termination with a Caesarean section, as well as perinatal morbidity and mortality (Oteng-Ntima, 2013).

Zera (2011) states that identification of obesity before conception enables proper counselling within gravidity preparation.

According to Kaplan-Sturk (2013), obese women are considered high risk. They have a higher risk of dystocia during labour, and higher risk of a Caesarean section. They surprisingly stressed a point that obese women with BMI over 30 kg/m^2, who are otherwise healthy and have normal course of pregnancy, delivered vaginally more often than women whose BMI was under 30 kg/m^2.

Bogaerts (2014) in his study states that during the first stage of labour obese women suffer from insufficient contractions of uterus. Arrowsmith (2011) claims that obesity brings about prolonged gravidity that contributes to more frequent induction of labour. Link between obesity and prolonged pregnancy is associated with uterine inaction or suppressed activity of myometrium.

Higher insulin resistance during pregnancy increases levels of circulating glucose and other nutrients, which pose predisposition to neonatal macrosomy and later to child obesity (Herring, 2011). Macrosomy may cause complicated vaginal labour and it is associated with higher frequency of Caesarean section. After vaginal delivery of a macrosomy foetus a risk of uterine atony increases (Oteng-Ntim, 2013).

2. Materials and methods

The main aim was to evaluate the degree of overweight and obesity effect on the date and course of labour in conditions of Slovak health service.

The retrospective study was conducted at University Hospital in Bratislava – Ružinov at II. Gynaecology-obstetrics clinic. The research was approved by the chief consultant of the medical centre. We analysed data from obstetric documentary of women in labour hospitalized in the obstetrics department from January 1st 2012 to June 30th 2012. The women in labour had to fulfil the following criteria: obstetric documentary was completely processed, the women gave birth to 1 live foetus in the maternity hospital and had normal prenatal care. These conditions were followed by 960 women in labour. In the next step, the women were divided, according to the latest BMI classification (WHO, 2013d), into 2 groups:

Group 1 consisted of women with pre-obesity and obesity before pregnancy (BMI ≥ 25 kg/m^2) – 204 women in labour (21.25 %)

Group 2, as a control group, consisted of women with normal weight and underweight before pregnancy (BMI ≤ 24.9 kg/m^2) – 756 women in labour (78.75 %).

For comparison of the results, we used pivot tables, odds ratio, chi – square test, Fisher exact test, Wilcoxon test, Monte Carlo test and rank test. The relations of explored variables were significant, the level of significance $p < 0.05$.

3. Results

Characteristics of the study group (Table 1)

The studied group consisted of 960 patients (n=960). Average age of the para was 30, 99 year (SD = 4,801). Average height was 166,85 cm (SD = 6,167). Average weight before pregnancy was 62,793 kg (SD = 11,9269) and in time of labour 77,3125 kg. Average BMI before pregnancy was 22,5248 kg/m^2, in time of labour 27,7419 kg/m^2. From the overall number of the patients the pre-pregnancy BMI was within normal limits in 79, 2%, 15, 5% was preobese and 5, 3% had obesity.

Table 1. Demographic data (960 patients)

	N	Minimum	Maximum	**Mean**	Std. Deviation
Age	960	18	47	**30.99**	4.801
Height	960	142	187	**166.85**	6.167
Weight before pregnancy	960	42.0	126.0	**62.793**	11.9269
BMI before pregnancy	960	15.43	46.10	**22.5248**	3.93556
Weight at delivery	960	49.00	146.00	**77.3125**	12.83197
BMI at delivery	960	18.73	51.73	**27.7419**	4.18047
Valid N (listwise)	960				

Does obesity effect the term of delivery?

We supposed that women with the BMI ≥ 25, 00 kg/m2 gives birth before and after the term more often than women with the BMI ≤ 24, 99 kg/m2. In the studied group 89, 9% of the patients gave birth at term, 7, 1% gave birth before the term and 3, 1% after the term (Figure 1). Thereafter we analysed solely preterm and post term deliveries in overall number 98. Correlation between the BMI before pregnancy and the type of delivery was confirms using the Fisher's exact test (p = 0,029).

Concerning the effect of the BMI on the risk of pre- or –post-term delivery find out that BMI influences the type of the delivery (OR = 0,198). The risk of the preterm delivery is lower OR (CI95 %) = 0,712 (0,571 – 0,899). Based on the above data we conclude, that type of the deliver correlates with the BMI before pregnancy. Using the Mann-Whitney test we analysed the significance in case of the comparison of the delivery type and the age – results without statistical significance.

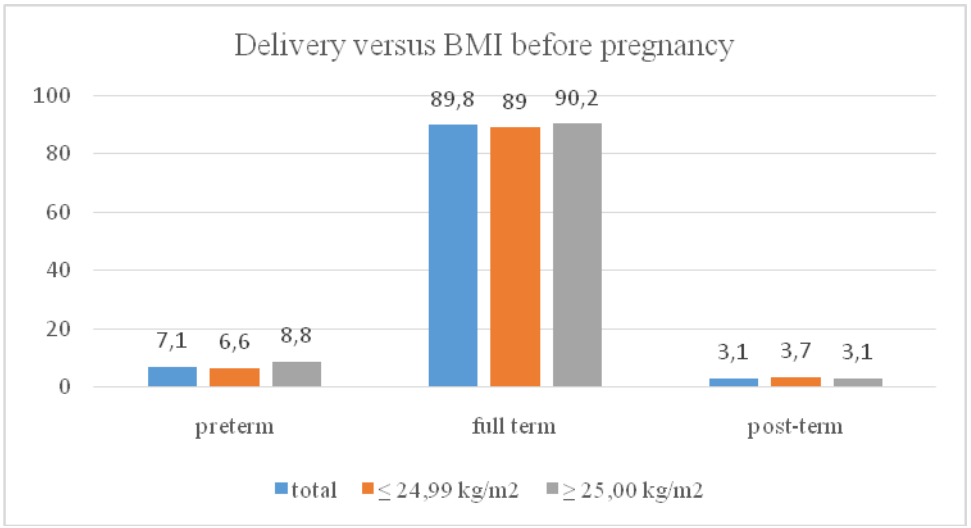

Fig. 1. Correlation between the type of the delivery and BMI before pregnancy

Does obesity affect the mean of pregnancy termination?

We supposed that women with the BMI ≥ 25, 00 kg /m2 have operative delivery more common than women with the BMI ≤ 24, 99 kg /m2. Regardless of the ante-conception- BMI, the most common mean of delivery was vaginal delivery (n = 594). Operative delivery (n = 366) consisted of the caesarean section, forceps and vacuum extraction (Figure 2). Chi-quadrate test was used for the analysis. We found out, that BMI before conception effects the mechanism of the labour (p – 0,004). If we focus on the impact of the BMI on the labour mechanism we find out, that BMI decreases the number of operative deliveries OR (CI 95 %) = 0,761 (0,639 – 0,907). By using the Mann-Whitney test we studied the significance of the influence of age on the delivery mechanism. Results were significant (0,043) which means that age effects if the delivery will be carried out by vaginal or operative mechanism.

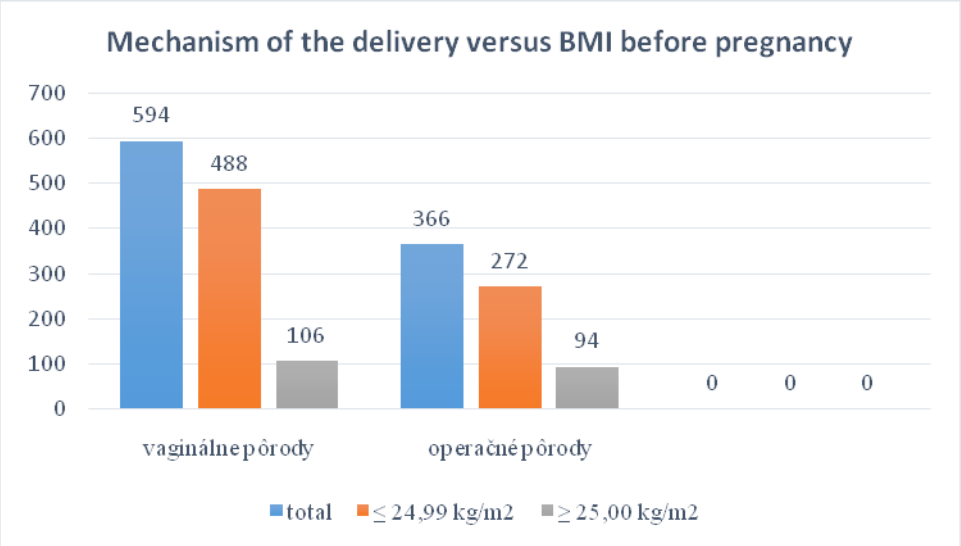

Fig. 2. Mechanism of the delivery and correlation to the BMI before pregnancy

4. Discussion

WHO (2013a; 2013b) reports that since 2000, the incidence of adult obesity has significantly increased. In Europe there are more than 50 % of women with BMI ≥ 25 kg/m², 23 % of which are obese (Herring, 2011). Obesity is constantly the subject of many discussions and experts contradict in significance of the impact of obesity in individual potential risk factors. In our research, we have focused on weight, BMI and age of women in labour, because these factors are considered to be some of the key ones associated with occurrence of complications. Despite a global increase of obesity in the population, in the study group monitored by us, as many as 79,2 % of women had a normal BMI before pregnancy. Although the result was surprisingly positive, in the group of women with preobesity and obesity, which were together 200, we found that obese women accounted for 20,8 %, so we are quite close to the European "standard".

As stated by Cnattingius (2013), women who are overweight or obese have an increased risk of extreme preterm labour. However, Arrowsmith (2011) connects obesity with reduced activity of uterus, resulting in giving birth to children after the term of labour. With our results we are inclined to Cnattingius, whereby we have not followed extremely premature births, but generally births before completed 38th week of gestation.

Several studies have shown that in obese women the caesarean delivery is more frequent. To this conclusion inclined Ovesen (2011), Chu (2007). However, Kaplan-Sturk (2013) has shown that healthy women with BMI over 30 kg/m² are more often delivering vaginally. Vaginal delivery is much safer for the patient in terms of postpartum complications, reduced self-sufficiency after surgery, limited mobility, inability to care for their child after Caesarean section, the risk of surgical site infection and postpartum hemorrhage. We agree with the first statement that obese women are more often performed Caesarean section (27,2 %). However, preference of termination of pregnancy in women at risk follows the current trends of labor management in the world (Odent, 2014).

Studies describe in addition to obesity, especially the incidence of GDM, DM and hypertension. Surprising is the fact that in our research sample were 51 obese women and only two of them were treated for obesity.

As described in a study (Herring, 2010), the reason of such a result may be a fact that general practitioners, gynecologists, midwives and nurses do not pay much attention to BMI. It may also be an incorrect definition of overweight and obesity by professionals providing qualified care, but also the situation that experts do not perceive preobesity and adiposity as a disease and do not indicate examination of blood glucose within other samplings o pregnancy card around 8 weeks of gestation and between weeks 24. – 28. of gestation, when oral glucose tolerance test is performed.

5. Conclusion

Obesity and gravidity is associated with considerable risks for the mother and her child. These are particularly metabolic diseases such as DM, hypertension and mechanical diseases, mainly of orthopedic character. Obesity generally increases the morbidity and mortality of both mother and foetus. During pregnancy macrosomy can occur and thereby the more often performance of Caesarean section.

Women with overweight and obesity often do not perceive their weight as problematic, and therefore do not feel the need to do something with it. The diagnostics of overweight and obesity by the nursing and caring stab is also absent. There is evidence that moderate weight loss reduces the risks for both the mother and the child.

The aim of the research was to assess the extent of influence of preobesity and obesity on process of labour. After comparing our results with studies, some of them were confirmed in our study as well. The incidence of preobese and obese women was 20,8 %. These women were more often delivering preterm and by Caesarean section.

We concluded that a woman´s BMI before pregnancy influences the type of labour and its mechanism.

On that basis, we would like to propose:

- determination of exact rates of weight loss in obese pregnant women to be safe; precise monitoring and evaluation of weight gain during pregnancy;
- nutritional consulting with classes of exercises that can be performed in preconception period and during pregnancy as part of specialized prenatal classes; completing a psychophysical preparing course for delivery – providing of concrete advice to reduce energy intake and exercises to increase physical activity.

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Diagnostic Challenges and Treatment Conflicts for Pure Primary Non Gestational Choriocarcinoma Ovary

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Abstract

Pure primary NGCO (non-gestational choriocarcinoma of ovary) is a type of ovarian germ cell tumor with elevated human chorionic gonadotrophin (hCG), posing diagnostic challenges in the patients of reproductive age group. Clinically and histopathologically, NGCO is indistinguishable from GCO. The both are differentiated on the basis of DNA polymorphism analysis and presence of mRNA for BMG (β2-microglobulin) in NGCO. Diagnostic criteria set by Saito et al helps to make a diagnosis of NGCO. It is possible to cure NGCO while preserving fertility, which is an important consideration as most are young age group patients. As these are rare tumors, recommendations for treatment of primary nongestational choriocarcinomas are not available. The principles of surgical management of NGCO are similar to the ovarian epithelial tumors. GCO is treated by methotrexate based chemotherapy, but some studies reported that NGCO is resistant to this chemotherapy, and it requires more aggressive combination chemotherapy as later has bad prognosis as compared to GCO. Various chemotherapy regimens are BEP, EMA/CO, EMA/EP, VAC etc. The serial quantitative measurement of urinary or serum β-hCG is essential for diagnosis, monitoring efficacy of the treatment, and follow-up of the patients. Role of radiation therapy is limited as a palliative setting in metastatic NGCO. In this article, we have tried to conclude the diagnostic methods and best possible treatment protocol.

Keywords: nongestational, choriocarcinoma, chemotherapy.

1. Introduction

Ovarian germ cell tumors include neoplasms derived from the primordial germ cells of the embryonal gonad. Five percent of these germ cell tumors are malignant which represent only three to five percent of all the ovarian carcinomas. Pure primary NGCO (non-gestational choriocarcinoma of ovary) accounts for less than one percent of all ovarian tumors (Gon et al., 2010; Scully, 1979). Because of elevated human chorionic gonadotrophin (hCG), these tumors pose diagnostic challenges in the patients of reproductive age group Primary ovarian choriocarcinoma could be gestational or nongestational in origin (Gon et al., 2010). Gestational choriocarcinoma is a variety of Gestational trophoblastic neoplasms (GTNs) which comprise conditions arising from

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abnormal fertilization, and consist of five different entities: PHM (partial hydatidiform mole), CHM (complete hydatidiform mole), IM (invasive mole), CCA (choriocarcinoma), and PSTT (placental site trophoblastic tumors) (Goldstein et al., 2015). GCO (gestational choriocarcinoma of ovary) occur following pregnancy and it is characterized by uterine cavity presentation (Choi et al., 2013; Park et al., 2009). These tumors represent less than 1 % of the gynecologic malignancies, and they are curable with reproductive potential preservation if treated at early stage and according to established guidelines (Goldstein et al., 2015). NGCO most of the time arises from the ovarian germ cell tumors but they can originate from any epithelial cancer, including cancer of the stomach, bowel and lung (Oladipo et al., 2007). NGCO differentiates in the direction of trophoblastic structures along the extraembryonic chorionic tissue and it is usually mixed with other types of neoplastic germ cell elements (Radotra, 2001; Jacobs et al., 1982; Russell, Farnsworth, 1997; Scully et al., 1998). It is possible to cure NGCO while preserving fertility, which is an important consideration as most are young age group patients (Cannistra et al., 2015). NGCO is indistinguishable from GCO morphologically and immunohistochemically as both has similar histopathological features. The both are differentiated on the basis of DNA (deoxy ribonucleic acid) polymorphism analysis and presence of mRNA (messenger ribonucleic acid) for BMG (β2-microglobulin) in NGCO (Tsujioka et al., 2003; Tanaka et al., 1981). GCO is managed by single agent chemotherapy in low risk disease and by multiagent chemotherapy in high risk disease, while NGCO is treated by polychemotherapy as later has bad prognosis as compared to GCO. Role of radiation therapy is limited as a palliative setting in metastatic NGCO. The aim of this study is the in depth review of the case reports documented so far to conclude the optimal treatment strategy for NGCO.

2. Materials and methods

EPIDEMIOLOGY

Ovarian germ cell tumors are less common than ovarian epithelial tumors, accounting for only 2% to 3 % of all ovarian cancers in Western countries. NGCO usually occur in younger women, with peak incidence in early 20s. An increased incidence of NGCO is found in blacks and Asian societies, where they represent about 15% of all ovarian cancers (Cannistra et al., 2015).

PATHOLOGY

Choriocarcinoma of the ovary can develop in association with gestational ovarian choriocarcinoma; or as a part of metastatic choriocarcinoma from non-ovarian (chiefly uterus) gestational choriocarcinoma; or as a germ cell tumor with trophoblastic differentiation which is known as non-gestational choriocarcinoma (Park et al., 2009). Table 1 shows WHO classification of ovarian tumor (Park et al., 2009). The germ cell tumors of the ovary are usually divided into dysgerminoma and nondysgerminoma (Cannistra et al., 2015). Choriocarcinoma is usually characterized by the presence of two types of cell lines: cytotrophoblast, which lie in sheets to form villus like structures, and syncytiotrophoblast, which secretes human placental lactogen and beta-human chorionic gonadotrophin; and is usually seen at advancing edge of the tumor (Rao et al., 2015; Kidd et al., 1998). Pure ovarian choriocarcinoma is defined as a tumor occurring in the absence of other germ cell tumors (Russell, Farnsworth, 1997; Scully et al., 1998).

CLINICAL FEATURES AND SPREAD

NGCO mainly occurs in young females, and approximate 50% of cases are diagnosed at an early stage (Hayashi et al., 2015). Abdominal distension, lower abdominal pain, urinary symptoms and pelvic fullness are chiefly encountered symptoms. Severe abdominal pain may be present in minority of patients, which is usually the result of rupture, hemorrhage, or ovarian torsion. The rapid growth of NGCO cause moderate to severe pain as a result of ovarian capsule stretching, and prompts the patient to seek medical attention (Cannistra et al., 2015). Approximate 60% to 70% of ovarian germ cell tumors are diagnosed at stage I, stages II and IV disease are not common, and 25% to 30% of tumors are diagnosed at stage III. Bilateral involvement of ovary is uncommon in most germ cell tumors, although mature cystic teratoma and dysgerminoma may be bilateral in 10% to 15% of cases (Cannistra et al., 2015).

Clinical diagnosis of NGCO is usually difficult, not solely owing to rarity of the tumor but also due to similar presentation as that of GCO. Pure NGCO is histopathologically not distinguishable

from GCO, except in the patients who have never had sexual intercourse or who are not able to conceive (Kong et al., 2009). Most NGCO cases occur in adolescence and children (Radotra, 2001; Jacobs et al., 1982). The primary extra uterine choriocarcinoma is difficult to diagnose because the clinical features are usually nonspecific and they can mimic other common conditions occurring in the young women, such as tubo-ovarian abscess, hemorrhagic ovarian cyst, ectopic pregnancy and ovarian torsion (Gerson et al., 2007). The symptoms of pelvic pain, vaginal bleeding, an adnexal mass and elevated hCG level, usually lead to incorrect diagnosis of cervical polyp, threatened or incomplete abortion, ectopic pregnancy, or other types of malignancy (Imai et al., 2001).

NGCO most commonly metastasizes to multiple peritoneal surfaces and retroperitoneal lymph nodes, although ascites is uncommon (Cannistra et al., 2015). The metastasis is usually hemorrhagic because of innate capacity of the trophoblastic cells to invade and erode vessel walls (Kidd et al., 1998). NGCO usually spread to the lungs (80%), vagina (30%), pelvis (20%), and kidney, brain, liver, gastrointestinal tract and spleen (10%) (Cannistra et al., 2015; Kidd et al., 1998). The central nervous system involvement is seldom in the absence of lung metastases (Kidd et al., 1998). Around 10% of NGCO metastasize to brain while on treatment or as a relapse after partial remission. Brain metastasis is a poor prognostic indicator and is a leading cause of death (Choi et al., 2013; Dadlani et al., 2010).

DIAGNOSIS

Patients mostly have a palpable adnexal mass which is usually evaluated by transvaginal ultrasonography (TVU), demonstrating a complex cyst comprised of cystic and solid regions. Serum levels of AFP (α-fetoprotein) and β-HCG (β-human chorionic gonadotrophin) often helps to diagnose embryonal carcinoma (both β-HCG and AFP elevation), endodermal sinus tumor (AFP elevation only), or choriocarcinoma (β-HCG elevation only). Patients with pure immature teratoma of ovary mostly have normal levels of β-HCG and AFP, although AFP may get elevated in 30% of the patients. Patients with dermoid cyst (mature cystic teratoma), a benign germ cell tumor, usually have normal levels of β-HCG and AFP. Measurement of β-HCG and AFP levels is also useful to measure the effectiveness of postoperative therapy and in monitoring for recurrence of the disease. Patients with choriocarcinoma, occasionally, may have extreme β-HCG elevation resulting in hyperthyroidism due to homology between TSH (thyroid-stimulating hormone) and β-HCG. Hyperthyroidism may also be seen in patients with mature cystic teratoma, which is related to the tumor-derived thyroxine secretion, (struma ovarii) (Cannistra et al., 2015).

Saito *et al* in 1963 first described the diagnostic criteria for nongestational choriocarcinoma which include exclusion of molar pregnancy, absence of disease in the uterine cavity, pathological confirmation of disease and exclusion of coexistence of intrauterine pregnancy (Saito et al., 1963). Distinction of gestational choriocarcinoma from non-gestational choriocarcinoma is not possible on histopathology unless other germ cell neoplasms are encountered or there is an evidence of pregnancy. The distinction between the two entities is not easy, but it is necessary, as the non-gestational type has got bad prognosis (Lv Lin et al., 2011). However, no distinctive immunohistochemical or ultra structural differences have been reported between gestational and nongestational choriocarcinomas (Yamamoto et al., 2007). Tsujioka et al showed that DNA polymorphism analysis using two or three appropriate variable number of tandem repeats (VNTR) loci from the tumor, and the patient for paternal sequences identification, establishes the diagnosis of non-gestational or gestational choriocarcinoma (Tsujioka et al., 2003; Yamamoto et al., 2007). Tanaka *et al* reported a lack of effective mRNA (messenger ribonucleic acid) for BMG (β2-microglobulin) in cell lines of human choriocarcinoma of gestational origin, as well as the presence of mRNA for BMG in nongestational choriocarcinoma (Tanaka et al., 1981). Kato *et al* investigated choriocarcinoma cells that produced moderate amounts of surface and secreted BMG (Kato et al., 1991). Norman *et al* demonstrated that in choriocarcinoma, serum BMG level was elevated (Norman et al., 1983). These studies showed that BMG may be clinically used as a serum marker for NGCO in the future. However, the cause for BMG expression in NGCO remains unclear (Hayashi et al., 2015).

Speculum examination helps to rule out metastases to vagina. Ultrasound of the pelvis rules out pelvic spread and retained trophoblastic tissue, if any. Chest imaging rule out metastases to lungs, as most common site for metastases is lung. CT scan (computed tomography scan) detects lung metastases in upto 40% of the patients with negative chest imaging (Muller, Cole, 2009).

Brain and liver metastases are rare when there are no metastases to lung and vagina, brain imaging is omitted usually. Contrast enhanced magnetic resonance imaging (MRI) of brain is mandatory in metastatic disease and in all patients with biopsy proven choriocarcinoma. As the tumor is highly vascular, histopathological examination may be skipped. Positron emission tomography (PET) scan identify active disease sites (Goldstein et al., 2015; Berkowitz et al., 1983). NGCO is staged as per FIGO staging in table 2 (Prat, 2015).

MEASUREMENT OF β-hCG

Any woman in the reproductive age group who presents with abnormal bleeding or evidence of metastatic disease should undergo β-hCG screening to rule out choriocarcinoma (Goldstein et al., 2015; Berkowitz, Goldstein, 2009). The serial quantitative measurement of urinary or serum β-hCG is essential for diagnosis, monitoring efficacy of the treatment, and follow-up of the patients. hCG is a glycoprotein consisting of two subunits, an alpha subunit (common to other glycoproteins), and hormone specific beta subunit. So, hCG measurement should be performed by beta subunit measuring assays only (Hancock, 2006). hCG is produced by the choriocarcinoma itself (Cole, Butler, 2008). Persistence of β-hCG levels represent either local or metastatic disease, which allows for early detection and intervention. During the treatment, response of beta-hCG is used as a tool to decide whether to continue the treatment with the agent or switch to some other agent. Monitoring of beta-hCG levels after the treatment allows for identification of the relapsed disease that requires additional treatment measure (Goldstein et al., 2015). A false-positive β-hCG result must be suspected if the laboratory results and the clinical features are discordant, or if the patients with persistent low β-hCG levels do not respond appropriately. False-positive findings on the β-hCG tests occur with the presence of heterophile antibodies that usually interfere with the immunoassay. False-positive tests led to inappropriate treatment protocol, in the form of chemotherapy, surgery or both. In rare situations, especially in women of menopausal group, pituitary gland is β-hCG source (Khanlian, Cole, 2006). A urinary assay must be performed when a false-positive β-hCG test is suspected, because renal tubules are not crossed by heterophile antibodies (Goldstein et al., 2015). Once elevated and/or rising β-hCG level is determined, a thorough evaluation is required to determine the disease extent, including blood tests to assess hepatic and renal function, peripheral blood counts, and baseline serum β-hCG levels (Goldstein et al., 2015; Berkowitz et al., 1983).

TREATMENT

Non-gestational choriocarcinomas are resistant to single agent chemotherapy, have a poor prognosis, and so require aggressive combination chemotherapy in comparison to GCO (Lv Lin et al., 2011). Pure primary NGCO is an extremely rare tumor and is a diagnostic challenge to the oncologists. However, differentiation between non-gestational and gestational choriocarcinoma is necessary in view of the prognostic value and the management (Dadlani et al., 2010). As the tumor is rare, published literature on clinical features and treatment options is less. Methotrexate based chemotherapy is used to treat GCO, but NGCO is chemotherapy resistant, and aggressive combination chemotherapy is needed for it (Balat et al., 2004). Weiss et al suggested either to treat this tumor as GCO and decide single-agent or combination chemotherapy; or to treat as a germ cell tumor protocol, such as BEP (bleomycin/etoposide/ cisplatinum) or VAC (vincristine/actinomycin-D/cyclophosphamide) (Park et al., 2009; Weiss et al., 2001).

SURGERY

The principles of surgical management of NGCO are similar to the ovarian epithelial tumors, with the important caveat that fertility can be preserved in most of the patients by sparing uterus, fallopian tube and contralateral ovary (Cannistra et al., 2015). If the contralateral ovary is grossly abnormal, biopsy or cystectomy can be performed. In case of a dysgenetic gonad, bilateral salpingo-oophorectomy may be undertaken. After opening the peritoneal cavity, peritoneal washings are collected, and all the fluids are sent for histopathological examination. In case of pelvic confined disease, random biopsies are taken as in the early stage of ovarian epithelial carcinomas. Particular attention is paid to pelvic and para-aortic lymph node enlargement, because these are the sites which are frequently involved in advanced NGCO (Cannistra et al., 2015). Although sentinel lymph node sampling is usually done for staging, no evidence suggests any benefits of lymphadenectomy. Billmire et al found that the less comprehensive surgical staging did

not compromise the survival (Billmire et al., 2004). Further studies for the extent of the surgical staging are warranted. Cytoreductive surgery for NGCO is recommended as in ovarian epithelial tumors. As extensive disease of NGCO is usually more chemosensitive than ovarian epithelial tumors, so, whether such an aggressive approach for surgery is necessary in the selected patients with extensive NGCO remains unresolved. There is no established role of routine second-look operations in NGCO patients who are declared clinically free of the disease after chemotherapy. Especially, if primary tumor is completely resected and no teratomatous components are seen, then second-look operations after the chemotherapy are of no proven benefit. If teratomatous components are seen, then the second-look operations may be beneficial. Such type of patients may have residual mature teratoma, which is insensitive to chemotherapy, therefore, a second-look operation may be considered if technically possible. The rationale for this is based on the experience with the testicular germ cell cancer, in which residual teratoma are known to enlarge and cause local complications or rarely may transform to an undifferentiated sarcoma or carcinoma. However, extent to which the residual teratoma may transform to a more aggressive histology in NGCO patients is not well studied (Cannistra et al., 2015).

LAPAROSCOPIC AND FERTILITY-PRESERVING APPROACH IN NGCO

The use of laparoscopy and thus, fertility-preserving procedures in the non-epithelial ovarian malignancies is extremely controversial. Xin et al reported that a 23-year-old woman underwent emergency laparoscopy and left oophoroplasty was performed, and primary NGCO was diagnosed. Approximately after 3 weeks, laparoscopic staging surgery was performed, including left adnexectomy, retroperitoneal lymphadenectomy, peritoneal biopsies and omentectomy. Patient received ovarian suppression with goserelin followed by adjuvant chemotherapy of bleomycin, etoposide, and cisplatin. No sign of recurrence was seen post 9 months and she reassumed normal menstrual cycles with normal levels of tumor markers and gonadotrophin. This study brings new insights into the possibility of using the minimally invasive surgery and fertility-preserving methods for NGCO treatment (Xin et al., 2015).

CHEMOTHERAPY

Treatment for NGCO is surgery followed by combination chemotherapy, as early stage NGCO patients have a significant risk of the relapse and that can be reduced by postoperative adjuvant chemotherapy (Cannistra et al., 2015). The treatment consists usually of polychemotherapy, including regimens that have generally shown to be beneficial with acceptable high cure rates and low recurrences (Axe et al., 1985; Berkowitz, Goldstein, 1996). Mostly used chemotherapy regimen is BEP. The Gynecologic Oncology Group (GOG) reported that those patients were remained free of disease after 3 cycles of adjuvant chemotherapy with BEP whose tumors were completely resected (Boyd, Rubin, 1997). Toxicities of BEP include the risk of etoposide-induced leukemia; bleomycin induced pulmonary damage, and platinum-induced nephropathy and neuropathy. Most of the patients receiving BEP regimen regain fertility after treatment completion. Several studies have reported that at least 80% of the patients with ovarian germ cell tumors who were treated with the fertility-sparing surgery and postoperative adjuvant chemotherapy regained normal menstrual cycle, and normal pregnancies (Tonin et al., 1996). However, patients are at increased risk for the development of the premature menopause following chemotherapy (Cannistra et al., 2015).

The primary treatment for all patients is multiagent chemotherapy. Table 3 summarizes the regimens which are most commonly used like EMA/CO, which includes etoposide, methotrexate, actinomycin-D, and cyclophosphamide and vincristine having 70-90% cure rates (Cagayan, 2012). Another regimen EMA/EP having cisplatin (in place of vincristine) is used if resistance is found against EMA/CO (Xiang et al., 2004). Dose-intensive treatment is done at an interval of 2 to 3 weeks, toxicity permitting. The treatment is continued till β-hCG level becomes undetectable for a period of 3 continuous weeks. It is recommended that three cycles of remission regimen should be administered after achieving remission. Death can occur due to advanced disease, drug resistance, inadequate treatment, life-threatening complications like central nervous system hemorrhage and respiratory failure (Xiang et al., 2004).

Extreme rarity of NGCO hinders therapeutic considerations (Ozaki et al., 2001; Ramarajapalli et al., 2012). Beta-HCG is a good predictive indicator of prognosis and recurrence (Rao et al., 2015). Adjuvant polychemotherapy with EMA (etoposide 100mg/m2, methotrexate

100mg/m2, actinomycin-D 0.5mg) regimen may be given, for six to nine courses at seven days interval (Choi et al., 2013).

RECURRENT OR PROGRESSIVE DISEASE

Serum β-hCG levels should be monitored weekly during the treatment, then every 2 weekly for next 3 months, then monthly for the next 3 months, and then every 2 months for the next 6 months. If the treatment fails to demonstrate a continuous fall in the β-hCG titers, or if disease recurs after chemotherapy cessation, then reevaluation of the patient is performed, and therapy different from the one that previously employed should be initiated. Alternatively, if β-hCG level becomes undetectable, then chemotherapy should be continued for two more cycles in case of GCO, but more extended chemotherapy should be considered in case of NGCO (Park et al., 2009; Hammond et al., 1978).

ROLE OF RADIATION THERAPY

Radiation therapy has limited role in patients with NGCO except in the selected patients with brain metastases. The use of whole or localized brain radiotherapy in combination with chemotherapy may prevent a debilitating or life-threatening, so it should be initiated promptly (Brace, 1968). Alternatively, intrathecal methotrexate may be given in combination with polychemotherapy, particularly in the presence of meningeal involvement (Newlands et al., 2002).

ROLE OF BONE MARROW TRANSPLANTATION

Metastatic NGCO is curable with the cisplatin-based multiagent chemotherapy with or without surgery. Second-line chemotherapy with cisplatin and ifosfamide combination is given to the patients who fail or relapse after first-line therapy and have only 15–25% salvage rate. Initial experience with high-dose multiagent chemotherapy using carboplatin and etoposide containing regimens showed that 10–15% of heavily pretreated (two or more cycles) patients could achieve long-term remissions (Mandanas et al., 1998).

Patients with the relapsed or refractory NGCO may be treated with high-dose chemotherapy and marrow transplantation (HDC/BMT). The patients had received at least two prior chemotherapy regimens or had cisplatin-refractory disease (defined as progression within 4 weeks of a cycle of cisplatin-based chemotherapy). HDC regimens used are mostly combinations of cyclophosphamide with etoposide and cisplatin or carboplatin. Other combinations are carboplatin plus thiotepa plus cyclophosphamide, carboplatin plus etoposide plus ifosfamide. Times to engraftment of granulocytes and platelets were reasonable with only the patients receiving growth factors. HDC/BMT provides significant long-term disease-free survival as salvage therapy for relapsed germ cell tumor patients who are not refractory to cisplatin (Mandanas et al., 1998).

A comparison of case reports of ovarian choriocarcinoma is presented in Table 4. The summarized cases show limitations in that they are not all fully staged and the chemotherapy protocols are diverse. Analysis of the cases documented thus far suggests that the disease responds well to the combination of surgery and postoperative adjuvant chemotherapy. However, long term effects of such therapy should be further studied with more cases.

3. Conclusions

Because of the small number of patients with pure NGCO, a consensus on the treatment regimen including surgery and chemotherapy is lacking. Despite aggressive management of primary disease, prognosis is poor. Complete excision of the primary tumor, followed by combination chemotherapy may prolong the survival. Radiotherapy is useful in metastatic presentation. A long follow-up with regular beta HCG level estimation is advised to deal with the risk of delayed metastases even when the primary has been well controlled.

4. Conflict of interest

We have no conflict of interest to declare.

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Table 1. World Health Organization classification of malignant ovarian tumors (Park et al., 2009)

COMMON EPITHELIAL TUMORS

Malignant Serous Tumor
Adenocarcinoma
Papillary adenocarcinoma
Papillary cystadenocarcinoma
Surface papillary carcinoma
Malignant adenofibroma, cystadenofibroma
Malignant Mucinous Tumor
Adenocarcinoma, cystadenocarcinoma
Malignant adenofibroma, cystadenofibroma
Malignant Endometrioid Tumor
Carcinoma
Adenocarcinoma
Adenoacanthoma
Malignant adenofibroma, cystadenofibroma
Endometrioid stromal sarcoma
Mesodermal (mullerian) mixed tumor:
homologous and
Heterologous
Other
Clear cell (mesonephroid) tumor, malignant
Carcinoma and adenocarcinoma
Brenner tumor, malignant
Mixed epithelial tumor, malignant

Undifferentiated carcinoma
Unclassified

SEX CORD-STROMAL TUMORS
Granulosa-Stromal Cell Tumor

Androblastoma: Sertoli-Leydig Cell Tumor
Well differentiated
Tubular androblastoma
Sertoli cell tumor
Tubular androblastoma with lipid storage
Sertoli cell tumor with lipid storage
Sertoli-Leydig cell tumor
Leydig cell tumor, hilus cell tumor
Of intermediate differentiation
Poorly differentiated (sarcomatoid)
With heterologous elements
Gynandroblastoma
Lipid (lipoid) cell tumors
Unclassified

GERM CELL TUMOR
Dysgerminoma
Endodermal sinus tumor

Embryonal carcinoma
Polyembryoma
Choriocarcinoma
Immature teratoma
Mature dermoid cyst with malignant transformation
Monodermal and highly specialized
Struma ovarii
Carcinoid

Struma ovarii and carcinoid
Others

Granulosa cell tumor	Mixed forms
Tumor in the thecoma-fibroma group	**GONADOBLASTOMA**
Fibroma	Pure
Unclassified	Mixed with dysgerminoma or other form

Table 2. International Federation of Gynecology and Obstetrics Staging System for Ovarian Cancer (Prat, 2015)

Stage I	*Tumor limited to ovary or ovariesa*
IA	One ovary, without malignant ascites, positive peritoneal washings, surface involvement, or rupture
IB	Both ovaries, without malignant ascites, positive peritoneal washings, surface involvement, or rupture
IC	Malignant ascites, positive peritoneal washings, surface involvement, or rupture present IC1: Surgical spill IC2: Capsule rupture before surgery or tumor on ovarian or fallopian tube surface IC3: Malignant cells in ascites or peritoneal washings
Stage II	*Ovarian tumor with pelvic extensiona*
IIA	Involvement of the uterus or fallopian tubes
IIB	Involvement of other pelvic organs (e.g., bladder, rectum, or pelvic sidewall)
Stage III	*Tumor involving the upper abdomen or lymph nodes*
IIIA	Positive retroperitoneal nodes only or microscopic peritoneal disease outside of the pelvis. IIIA1: Positive retroperitoneal nodes as the only site of extrapelvic spread IIIA1(i): Metastases up to 10 mm in greatest dimension IIIA1(ii): Metastases >10 mm in greatest dimension IIIA2: Microscopic extrapelvic peritoneal involvement (with or without nodal involvement)
IIIB	Macroscopic peritoneal metastases ≤2 cm in diameter (with or without nodal involvement)*b*
IIIC	Macroscopic peritoneal metastases >2 cm in diameter (with or without nodal involvement)*b*
Stage IV	*Distant organ involvement, including pleural spacec or hepatic/splenic parenchyma* IVA: Pleural effusion with positive cytology IVB: Parenchymal metastases (e.g., hematogenous spread to liver) or metastases to extra-abdominal sites such as inguinal lymph nodes

a Patients with disease that appears to be confined to the ovaries or pelvis require nodal biopsy for complete staging, in order to exclude the possibility of occult nodal involvement

b Disease measurements for staging purposes are made before debulking has been attempted.

c Pleural effusion must be cytologically proven to be malignant if used to define stage IV disease.

Table 3. Protocol for various chemotherapy regimens (Cagayan, 2012)

S.No.	Day	Drug	Dose
FIRST LINE CHEMOTHERAPY			
1.			**Protocol for BEP 46**
	1-5	Cisplatin	20 mg/m2 IV
	1-5	Etoposide	100 mg/m2 IV
	1,8,15	Bleomycin	30 mg IV
			3 weekly for 3-4 cycles
2.			**Protocol for EMA/CO Regimen**
	1	Etoposide	100 mg/m2 by infusion in 200 ml saline over 30 min
		Actinomycin D	0.5 mg IV push
		Methotrexate	100 mg/m2 IV push
			200 mg/m2 by infusion over 12 h
	2	Etoposide	100 mg/m2 by infusion in 200 ml saline over 30 min
		Actinomycin D	0.5 mg IV push
		Folinic acid	15 mg q 12 h × four doses IM or PO beginning 24 h after starting MTX
	8	Cyclophosphamide	600 mg/m2 by infusion in saline over 30 min
		Vincristine	1.0 mg/m2 IV push
3.			**Protocol for EMA/EP Regimen**
	1	Etoposide	100 mg/m2 by infusion in 200 ml saline over 30 min
		Actinomycin D	0.5 mg IV push
		Methotrexate	100 mg/m2 IV push
			200 mg/m2 by infusion over 12 h
	2	Etoposide	100 mg/m2 by infusion in 200 ml saline over 30 min
		Actinomycin D	0.5 mg IV push
		Folinic acid	15 mg q 12 h × four doses IM or PO beginning 24 h after starting MTX
	8	Cisplatin	60 mg/m2 with prehydration
		Etoposide	100 mg/m2 by infusion in 200 ml saline over 30 min
4.			**Protocol for EMA**
		Etoposide	100 mg/m2 IV
		Methotrexate	100 mg/m2 IV
		Actinomycin-D	0.5 mg IV
			Weekly 6 to 9 courses
SECOND LINE CHEMOTHERAPY			
1.	1	Vincristine	2 mg/m2 IV
	1	Actinomycin-D	1.5 mg/m2 IV
	1	Cyclophosphamide	1 gm/m2 IV
2.	1	Cisplatin	100 mg/m2 IV
	1	Ifosfamide	1200 mg/m2 IV
3.	1-5	Cisplatin	20 mg/m2 IV
	1-5	Ifosfamide	1200 mg/m2 IV
	1-5	Etoposide	75 mg/m2 IV

EMA/CO, etoposide, methotrexate, and dactinomycin alternating with cyclophosphamide and vincristine; actD,
actinomycin-D (Cosmegan, Whitehouse Station, NJ); IV, intravenous; MTX, methotrexate; IM, intramuscular; PO,
by mouth; EMA/EP, etoposide, methotrexate, actinomycin D, and cisplatin.

Table 4. Clinicopathological characteristics of 35 cases of non-gestational pure ovarian choriocarcinoma

Variable	Value
Mean age, years	14.3±4.2
Duration of abdominal pain	weeks 3-16
Side, %	
Right	69
Left	31
Stage, %	
I	49
II	17
III	17
IV	17
Surgery, %	
UO/SO	74
AH+BSO	20
BSO	4
hCG, mU/ml	0.034-200,000
Treatment, n	
Bone marrow transplant	2
Chemotherapy	
Methotrexate-based	11
Vinblastin, bleomycin and cisplatin	4
Cisplatin, etoposide and bleomycin	5
Outcome, %	
Succumbed	31
Alive	69

UO/SO, unilateral oophorectomy/salpingo-oophorectomy; hCG, human chorionic gonadotropin; BSO, bilateral salpingo-oophorectomy; AH, abdominal hysterectomy