Reports of Practical Oncology and Radiotherapy 25 (2020) 212–216

Available online at www.sciencedirect.com

Reports of Practical Oncology and Radiotherapy

journal homepage: http://www.elsevier.com/locate/rpor

Technical note

Obesity in patients with carcinoma cervix increases the risk of adverse events

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ARTICLE INFO

Article history:
Received 2 February 2019
Received in revised form 17 August 2019
Accepted 23 December 2019
Available online 26 December 2019

Keywords:
Carcinoma cervix
Obesity
Adverse events (AEs)
Developing countries
Chemo-radiotherapy

ABSTRACT

Obesity has become epidemic both in developed and developing countries. Socio-economic (SE) development has resulted in increased prevalence of obesity across all social groups in developing countries that is contrary to the effects of rising SE status on prevalence of obesity in the developed world. Obesity is not only associated with metabolic syndrome, cardiovascular disease, diabetes but is also a risk factor for cancer and is responsible for increased cancer mortality. Published articles have reported higher rates of treatment failure and adverse events (AEs) of anti-cancer therapy in obese patients with carcinoma cervix in comparison to their normal body mass index (BMI) counterparts. Hence, there is a need to elucidate factors that may increase the risk of AEs. Aim of this paper is to discuss the delivery of radiotherapy, concurrent chemotherapy and their effect on AEs in obese patients with carcinoma cervix.

1. Introduction

80% of incidence and mortality of carcinoma cervix occurs in developing countries, where patients are usually undernourished.[1] However, it is not uncommon to come across obese patients with carcinoma cervix as obesity epidemic is sweeping across economically emerging countries due to altered eating habits and physical activities.[2] Socio-economic (SE) development has varied effects on the prevalence of obesity. Unlike the inverse impact of a better SE status on body mass index (BMI) in developed countries, altered eating habits and limited physical activities due to SE improvement in developing countries have resulted in epidemic of obesity. In affluent and developed countries, the improvement of SE is associated with reduced prevalence of obesity due to switching-over from high calories and high fat diet to healthy, nutritious and balanced diet. However, SE improvement in developing countries gives protein-energy deficit population an access to calorie-rich high carbohydrate diet thereby increasing the prevalence of obesity across all social groups.[3] Over-weight and obesity among general population has occurred over the background of already established risk factors of cervical cancer in these regions of the world.[4,5]

Obesity being a co-morbidity in itself is a risk factor for other non-communicable diseases, like diabetes, cardio-vascular disease, metabolic syndrome, fatty and mechanical degenerative changes in almost all organs of the body.[6] Obesity has been established as risk factor for adenocarcinoma of the cervix by observational/case-control studies. Obese individuals tend to undergo lesser Papanicolaou (Pap) testing for cervical cancer screening due to patient-, physician- and health care-related barriers thereby presenting with advanced stage disease.[7] Obesity increases BMI, body surface area (BSA) – the basis for calculation of chemotherapeutic dose, inverses the ratio of lean body mass to fat thereby altering radiotherapy dosimetry, anti-cancer drug distribution.[8–11] As a result, more normal tissue may be exposed to higher dose of chemo-radiotherapy. From clinical perspective, literature has reported non-significant inferior oncological control and higher toxicity in obese patients with carcinoma cervix.[8,12–15] In view of the above, there is a need to look into clinical profile/parameters that may be responsible for poorer outcomes in obese patients with carcinoma cervix. Therefore, the aim and objective of this presentation is to elucidate the factors that are possibly responsible for sub-optimal oncologic outcome (specifically, the increased toxicity) and ways to improve delivery of anti-cancer therapy in obese patients with carcinoma cervix.

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https://doi.org/10.1016/j.rpor.2019.12.024
1507-1367/

Table 1
Depicts the measurement of anterio-posterior (AP), transverse diameter of abdominal cavity, linear thickness of subcutaneous fat over anterior, posterior abdominal wall and flank of morbid obese and non-obese patient of same age at the level of lower lumbar vertebrae.

	Diameter of abdominal cavity (cms)		Linear thickness of subcutaneous fat (cms)			
			Abdominal wall		Flank	
	AP	Transverse	Anterior	Posterior	Right	Left
Morbid obese	20	31	5	7.5	11	11
Non-obese	14	21	1.7	1	1.2	0.7

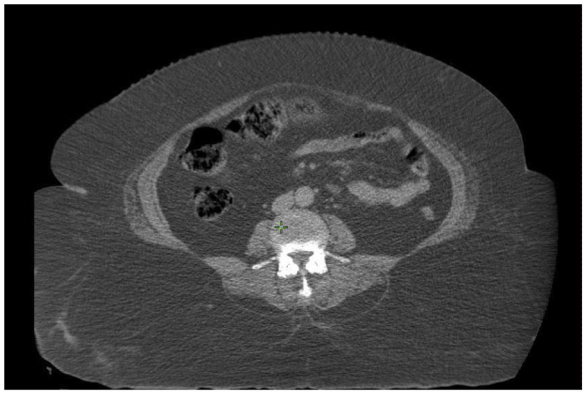

Fig. 1. Abdominal cavity is floating in the thick bag of subcutaneous fat. This may result in increased irradiated volume and pose difficulty in daily treatment position reproducibility.

2. Findings of our day-to-day clinical practice

A Ratio of diameter of the anterio-posterior (AP) and transverse abdominal cavity to the sum of linear thickness of corresponding sub-cutaneous fat (fat overlaying anterior and posterior abdominal wall in the case of AP diameter and fat overlaying both flanks in the case of transverse diameter, respectively) were 7:1 and 10:1 in normal patients, respectively. Whereas the same ratio for morbid obese patients were 1.6:1 and 1.5:1, respectively. Table 1 describes the aforementioned measurement in absolute terms of centimetres.

B As a result of inversed lean body mass to fat ratio, body floats in a thick bag of subcutaneous fat (Fig. 1).

C Obesity may be associated with degenerative changes in somatic and visceral tissue (Fig. 2).

D Treatment volume (TV) in our study was in the range of 1362–2204 cc and 2063–2799 cc for patients with AP body separation of $\leq$20 and $\geq$21 cm, respectively. Irradiated volume (IV) for the respective abovementioned patients was in the range of 6057–10874 cc vs. 8060–12590 cc.

E Obese patients treated by a conventional technique had increased risk of an extensive perineal skin reaction. Two patients died suddenly during hospitalization for management of a perineal skin reaction. Cause of death was not known as no autopsy studies were carried out. As consecutive two obese patients developed an extensive perineal skin reaction, subsequent patients were treated by 3-D Conformal Radiotherapy (3-D CRT) using high energy radiation beam (18X) as the protocol. Only 3 obese patients developed perineal reactions that were managed on an out-patient basis after the change of radiotherapy delivery protocol from a conventional technique to high energy 3-D CRT. One obese patient with carcinoma cervix treated by Volumetric Modulated Arc Therapy (VMAT) developed perineal skin reaction that required hospitalization.

F Radiotherapy dose at the corresponding perineal skin level ranged between 26–27.76 Gy and 27.5–32.38 Gy for non-obese and obese patients, respectively (Fig. 3).

G Perineal skin reaction may necessitate interruption of radiotherapy and is usually associated with pancytopenia, dys-electrolytemia and diarrhoea. Consecutive two obese patients treated by VMAT developed prolonged grade III nausea, vomiting, diarrhoea, fatigue, dys-electrolytemia and pancytopenia. One of them developed icterus after packed red blood cell transfusion that resolved spontaneously.

H After 2016, four of obese/overweight patients with carcinoma cervix presented with persistent/recurrent disease after chemo-radiotherapy. In comparison, only one treated non-obese patient returned with disease after first follow-up during this period.

3. Possible causes behind increased AEs

1 Treated volume (TV) and irradiated volume (IV [defined as volume of tissue encompassed by 95% and 50% isodose line, respectively, as per ICRU 71] are larger in obese patients.[16]

2 As the body floats in a thick bag of subcutaneous fat (Fig. 1), radiotherapy set-up errors are higher due to difficulty in reproduction of a daily treatment position. Exact mounting of a immobilization thermo-plastic mask, daily positioning of the patient and securing the mask to a base-plate may be an issue during delivery of fractionated radiotherapy. Studies have demonstrated radiotherapy set-up error of up to 4 cm with respect to morbid obesity.[13] Concerns were raised about utilization of a thermoplastic immobilization system. However, a thermoplastic immobilization system was the only immobilization method used in our set-up as most patients treated at our centre were either underweight or normal weight.

3 Radiation delivery by a conventional four-field box technique may deliver higher dose to the skin and sub-cutaneous tissue due to increased exposure time needed for radiation to penetrate to the treatment depth. 3-D CRT with beam energy of 6X may again have the same effect. Substitution of low energy radiation beam by that of higher energy (10X, 15X or 18X) may reduce the dose to the skin and sub-cutaneous tissue. Intensity Modulated Radiotherapy (IMRT) or VMAT may or may not reduce the dose to aforementioned tissues albeit with increase in irradiated volume and integral dose[17] (Fig. 3).

4 Dosimetry in obese patients may be less conformal even with IMRT or VMAT due to increased scatter as a result of the use of radiation beam of higher energy and weightage.[8]

5 Dose of chemotherapeutic agents calculated based on BSA may not be appropriate. Also drugs do not get equally distributed between lean and fat components of the body. Drug concentration in lean compartment of the body may be higher.[10,11]

6 Obesity per se and related co-morbidities may reduce the capacity of a body to recover from AEs of chemo-radiotherapy

7 Degenerative changes decrease the capacity of a body to effectively handle the pharmacokinetics and pharmacodynamics of drugs. Already declined reserve of viscera along with compromised ability to regenerate the normal tissue may aggravate the AEs of anti-cancer therapy (Fig. 2).

8 Obese patients tend to lose more weight as compared to lean counterpart. This may result in inadvertent irradiation of normal tissue and overdosing of chemotherapeutic agents.[9]

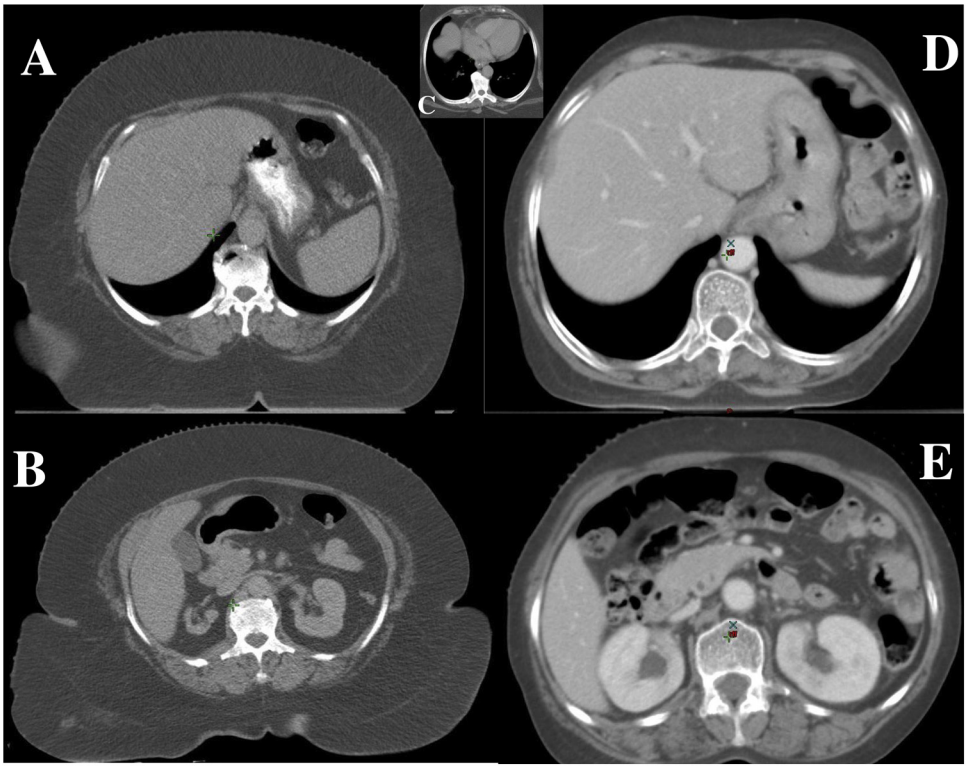

Fig. 2. Comparison of axial CT image of morbid obese vs. the non-obese women with cancer. Gross multiple vertebral body degenerative / distortive changes, atrophy of liver, stomach, intestine, bilateral kidneys and pancreas noted in morbid obese patient compared to the corresponding CT image of same aged non-obese patient with cancer. (Fig. 2A, B, C are axial CT images of morbid obese patient. Remaining i.e. Fig. 2D, E are axial CT images of non-obese patients of same age).

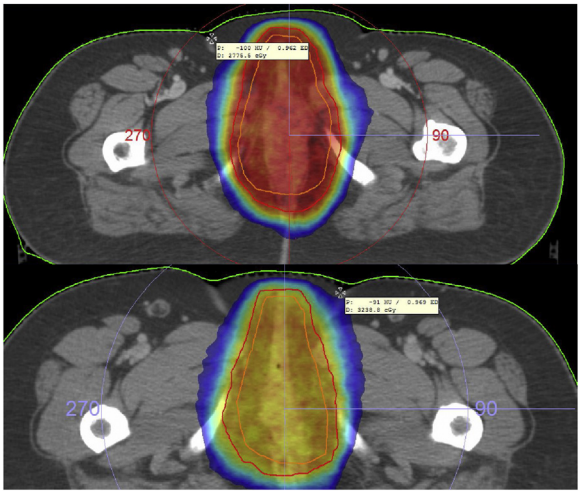

Fig. 3. Dose distribution colour wash at the level of perineum for non-obese (upper picture) and obese (lower picture) patient. Maximum perineal skin radiotherapy dose* by VMAT technique at this level was 27.76 Gy and 32.38 Gy in non-obese and obese patients respectively.
*No constraint was given for perineal skin during radiotherapy planning.

4. Measures to reduce AEs

1 Close monitoring of patients for AEs developing during therapy.
2 Stringent radiotherapy set-up protocol, like a proper position of patients, obviating curved, bent, side-ward inclined position of the body on a treatment couch by utilizing a midline body laser, ascertaining that the immobilization mask is snugly fitting the body surface contour, positioning of the patient appropriately over the base-plate. To summarize, the entire immobilization device for simulation and treatment must be set up with due diligence to reduce daily set-up errors and uncertainties.
3 Radiotherapy treatment planning by exclusively utilizing a higher energy linac beam rather than a lower energy linac or Co-60 beam. 3-D CRT is preferable over IMRT and VMAT as IV and integral dose may be higher in these techniques. Therefore, occasional patients may develop serious toxicities despite the use of VMAT.
4 Adaptive radiotherapy has to be integrated for management of obese patients with carcinoma cervix. Weekly measure of body weight for accurate determination of BSA and correct calculation of dose of chemotherapy has to be attempted.
5 Enrolling over-weight, obese and morbid obese patients into clinical trial for determination of tolerable and effective dose of concurrent cisplatin or carboplatin.

5. Discussion

Obesity per se and other associated conditions impair the quality of life (QoL), increases morbidity and mortality.[4] Obesity and its comorbidity, advanced stage of cervical cancer at presentation and increased rate of weight loss introduces errors and uncertainties, may lead to deviation in physical and clinical radiation dosimetry, pharmacokinetics and pharmacodynamics of chemotherapeutic agents. Such alteration may expose more normal tissue inadvertently to higher dose of chemo-radiotherapy, thereby resulting in higher rates of toxicities.[6–11] Our data both from the table and figure have demonstrated that the radiotherapy target, i.e. primary tumour, cervix, uterus, vagina, fallopian tubes, ovaries and internal, external and common iliac nodes is floating in a surrounding subcutaneous fat bag and increases the risk of inadvertent irradiation of normal tissue. This can happen despite the use of latest technology like IMRT or VMAT.[13] Advanced technology may also increase IV and integral dose and may not reduce normal tissue toxicity.[16,17] Both TV and IV as per ICRU 71 were higher in overweight/obese patients (body AP separation of ≥21 cm) when compared with their

leaner counterparts and may be correlated with increased toxicity observed in clinical studies conducted elsewhere.[12–14] Our study is a retrospective analysis, hence the result of TV and IV is presented in terms of AP separation rather than in terms of BMI.

As anticipated from the above mentioned dosimetric and clinical studies, incidence of grade III perineal skin toxicity did not completely disappear in our study population and when occurred was associated with dyselectrolytemia, pancytopenia and diarrhoea. However, unlike treatment with a conventional technique, no immediate/sudden death was reported with this toxicity after the introduction of 3-D CRT for management of obese patients with carcinoma cervix. Concern has been raised with respect to the development of a perineal skin reaction in patients with carcinoma cervix as radiotherapy portals do not include perineum unless and until the disease extends to the lower 1/3 of vagina. Literature recommendations with respect to defining lower borders of radiation portals were based on determining the extent of cervical cancer by utilizing clinical examination and Magnetic Resonance Imaging (MRI). However, clinical examination of consecutive patients with cervical cancer in our set-up revealed that the lowest vaginal extent of disease was somewhere between 1 and 3 cm from the vaginal introitus. Despite its limitation to detect accurate extent of disease, Computed Tomography (CT) was the imaging modality of choice in our set-up due to a long MRI scanning time. [Personal Communication] Literature published by Toita T et al. and Bansal A have suggested to include the vagina in radiation portal and concur with our clinical practice.[18,19] Similar to our study, Salvo N et al. has also reported a perineal skin reaction in patients treated by chemo-radiotherapy for carcinoma cervix.[20]

We did not observe increased frequency of a perineal reaction with the introduction of 3-D CRT for management of obese patients with carcinoma cervix. Perineal reaction occurred only occasionally in the obese patients after introduction of high energy radiation beam based 3-D CRT. These reactions were managed on an out-patient basis. However, we encountered a grade III perineal reaction in obese a patient treated by VMAT which was associated with recalcitrant systemic toxicities and prolonged hospitalization. Another obese patient managed by VMAT developed recalcitrant systemic reaction and needed repeated hospitalization. On review of VMAT plans, there was a wide variation in radiation dose over the perineal skin in overweigh/obese patients with carcinoma cervix. In order to reduce morbidity of chemo-radiotherapy, future studies may consider the perineal skin as a critical structure and report the side-effects akin to those demonstrating relationship between radiation dermatitis and breast cancer.[21]

Local failure in obese patients was higher in our study and may be comparable to the observation by Choi Y et al. In their series, they found that the pelvic lymph node recurrence after post-operative radiotherapy of over-weight/obese patients with cervical cancer was higher. Authors of this study concluded that the pelvic lymph node control was closely related to a local tumour control.[8] Obesity in developing countries is usually noted in subjects of higher socio-economic status which, in turn, may influence compliance with therapy and follow-up. Hence, we cannot rule out a bias for the observed increase in disease failure in overweight/obese patients.

With respect to administration of chemotherapy, American Society of Clinical Oncology (ASCO) has recommended the dose of chemotherapy based on actual body weight rather than capping at BSA of 1.75 m^2 or 2.0 m^2 for combination weekly concurrent chemotherapy or chemotherapy in management of recurrent tumours, respectively.[22–24] However, these recommendations were based only on pharmacokinetics studies of limited cycles of cisplatin administered to a very small group of patients. Loos WJ et al. have concluded that their study included all patients with malignant tumours for which cisplatin based therapy was a viable treatment option. Future clinical studies were recommended as the comparison of observed toxicities and efficacy was not feasible in that particular study.[10,11] Therefore, concern of oncologists regarding increased risk of toxicity remains to be answered by determination and administration of cisplatin or carboplatin dose based on actual body weight.

To conclude, obesity, in itself is a risk factor for cervical cancer; it increases toxicity and decreases control. Management of obese patients with carcinoma cervix poses challenges to clinical oncologists.

6. Summary

Obesity in patients of carcinoma cervix may be associated with increased incidence and severity of AEs. Stringent monitoring of these patients during therapy, proper chemotherapy dose adjustment, employment of an appropriate radiotherapy technique may reduce toxicities of anti-cancer therapy. Further research is needed to conclude about an appropriate radiotherapy technique, dose of chemotherapeutic and supportive care agents.

Conflict of interest

None declared.

Financial disclosure

None declared.

Disclaimers

No disclaimers.

Acknowledgments of research support/grants received

Nil.

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