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A Prospective Randomised Controlled Trial: Prevention of lymphedema by omentoplasty after pelvic lymphadenectomy

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Summary

Background: Lower limb lymphedema (LLL) is a complication of pelvic lymphadenectomy which is performed in the management of cervical and endometrial cancers together with radical hysterectomy or total hysterectomy. A pilot study showed that omentoplasty can reduce the occurrence of lower limb lymphedema.
Aims and objectives: The aim of this study was to see whether omentoplasty can reduce lower limb lymphedema.
Study design and methods: This is a randomized control study to compare 2 groups of patients who underwent pelvic lymphadenectomy in the Department of Obstetrics and Gynaecology, Queen Mary Hospital. One group acted as control and the other group underwent omentoplasty. Both clinical assessment and objective measurement of the lower limb volume were used to detect lower limb lymphedema at 3-6 months intervals. The occurrence of lower limb lymphedema was compared between the 2 groups as well as with clinical parameters.
Results: A total of 97 patients were recruited. The overall incidence of lower limb lymphedema as assessed both clinically and objectively was 11%. There was no significant difference in lower limb lymphedema between the control and omentoplasty group. There was also no correlation of lymphedema with other clinical parameters.
Conclusions: This study failed to show that omentoplasty can reduce the occurrence of lower limb lymphedema after pelvic lymphadenectomy.

Implications: A larger study is needed to confirm the findings of current study.

Introduction

Pelvic lymphadenectomy is performed as part of a staging procedure in the treatment of a number of gynaecological cancers. In the treatment of early stage cervical cancer, it is performed together with a radical hysterectomy. In endometrial cancers, it is performed together with total hysterectomy and bilateral salpinoophorectomy and other staging procedures. Though there are complications associated with radical hysterectomy or total hysterectomy, complications related to pelvic lymphadenectomy are lymphedema and lymphocysts. [1,2] Since early stage cancers have a good prognosis with long term survival, lymphedema with its associated complications such as cellulitis may affect the quality of life of the patient.[3] The current study aims to explore the use of omentoplasty in reducing the incidence of lymphedema after pelvic lymphadenectomy.

Materials and methods

Study design and randomization

Patients admitted to the Department of Obstetrics and Gynaecology, Queen Mary Hospital, University of Hong Kong for pelvic lymphadenectomy was recruited. Patients with pre-existing leg swelling were excluded. Informed consent was signed in compliance with the IRB of the Hospital and University. Subjects recruited were randomized to two groups. One group would have omentoplasty according to the technique as described by Patsner et al.[4] Briefly, the procedure involved mobilization of the splenic flexure of the transverse colon. Ligation of the right gastroepiploic vessel near the pylorus of the stomach. Division of the omentum from the transverse colon along the avascular plane and ligation of small vessels if necessary. A pedicle omental flap was thus developed with blood supply from the left gastroepiploic vessel. This was used to fill the pelvis with open peritoneum to cover the iliac vessels and pelvic floor. A couple of stitches tethered the omentum to the edge of the open peritoneum. No drain was inserted. The other group with no omentoplasty performed act as control. Randomization was performed by stratification on type of cancer ie cervical and endometrial cancers. Block randomization with a randomized size of 4 was used. Generation of randomization schedule was performed by a person independent of the recruitement and the seed from which the randomization schedule

was generated was kept securely by the randomizer. Sealed opaque envelopes containing the randomized treatment allocation was prepared and kept by the research assistant prior to the start of patient recruitment.

To give a power of 80% for the difference in lymphedema rates of 30% based on a pilot study which showed 40% lymphedema rate in control vs 10% in omentoplasty group, with a two-sided test at significance level α=0.05, 32 patients were required in each arm. A sample size of 70 was estimated taking into account a 10% drop out rate.

All patients have an open laparotomy with either a longitudinal lower abdominal incision or Maylard incision. Prophylactic antibiotics was given at induction of anaesthesia. All patients worn pneumatic cuffs over the calves during operation. No anti-coagulant prophylaxis was used.

Assessment of lymphedema

Assessment of lymphedema was by clinical and objective measurements. Clinical classification by the International Society of Lymphology was used where grade 1 referred to no or minimal fibrosis ie. edema pits on pressure and reduces on limb elevation; grade 2 to substantial fibrosis clinically ie edema not pit nor reduce with limb elevation and grade 3 to grade 2 plus elephantine changes. Patients were followed up at 3, 6, 9, 12 months then at 4-6 months interval during the second year after operation.

Objective measurement was according to that described by Stranden E. [5] . Standardized circumferential measurements were made at 7 specific points on each lower limb ie. foot, ankle, lower calf, upper calf, knee, lower thigh and upper thigh. Volume was calculated using the truncated cone formula: Volume =$[\Sigma(x^2 + y^2 + xy)]/3\pi$]; where x indicated the distance from the tip of the cone to the base and y indicated the circumference of the cone at distance x. Assessment of limbs was performed prior to operation, then at 3, 6 and 12 months by a team of dedicated physiotherapists not being told on which group the patient was assigned..

Patients recruited

Two hundred and one patients between January 2002 and December 2005 were approached. Fifty-eight patients refused to join the study. Of the 143 patients recruited, 32 patients did not undergo lymphadenectomy because at operation, clinical decision

such as superficial myometrial invasion in endometrial cancer called for cancellation of the procedure. Fourteen withdraw from the study mainly because finding the visits too frequent. A total of 97 patients entered the study. However, only 57 completed the original planned 4 visits for objective measurements. Twenty-seven had attended 3 sessions and 13 only 2 sessions. The main reason for some of the dropout was related to the outbreak of Serious Acute Respiratory Syndrome (SARS) in Hong Kong in 2003. Four patients are due to complete the follow up by the end of the year in 2006.

Clinical characteristics

The age of the whole group ranged from 25 to 79 years with a mean of 50.4 years. Fifty-four patients had endometrial cancer and 43 had cervical cancer. There were 84 stage I, 4 stage II and 8 stage III or more endometrial or cervical cancer according to the FIGO staging. There were 29 squamous cell carcinoma; 54 adenocarcinoma and 14 other cell types such as adenosquamous cell carcinoma, clear cell carcinoma or sarcoma. Thirty-seven had total hystectomy and 60 had radical hysterectomy together with the pelvic lymphadenectomy. The total number of pelvic nodes removed ranged from 7 to 81 with a mean of 34.5 and a median of 33. Thirty-four patients required post-operative radiotherapy with 8 brachytherapy, 21 external pelvic radiation and 5 combined external and brachytherapy. No significant difference in clinical parameters between the control and omentoplasty group was found (table 1). Thirteen patients had recurrent diseases and 10 died. Three were alive with disease. The interval from treatment to last follow-up date for patients still alive ranged from 3 to 55 months with a median of 31 months. The interval from treatment to death was 5 to 26 months. The estimated four year disease free survival was 85% and overall survival was 89%.

Statistical analysis

Statistical analysis was performed using SPSS version 11. Chi-square test and Fisher exact test were used for nominal data depending on whether the number in each cells was adequate for chi-square estimation. T-test was used to compare means between two continuous variables. Mann-Whitney test was used to compare median between 2 non-parametric continuous variables. Kaplan Meier estimation was used for survival analysis and log rank test used to compare 2 survival function. A P value of <0.05 was considered as significant.

Results

Lymphedema and omentoplasty

Clinical lower limb lymphedema was detected in 7 patients with 4 in the control group and 3 in the omentoplasty group. There was no statistical difference in LLL between the control and omentoplasty (Fisher exact test, P=1.0). Clinical LLL was detected at follow-up assessment at 1, 4,11,13, 14, 18 and 20 months. Three over the left leg, two over the right leg and 2 bilateral. All were of grade one. The objective percentage changes in measurements of 6 patients ranged from -13 to 19%. The only patient who had clinical LLL had a 33% increase in volume on measurement at 3 months after operation which decreased to 10% at 6 months and -3% at 12 months with corresponding clinical improvement.

Objective LLL with more than 20% increase in volume compared to pre-operative measurement was found in 5 patients with 3 in the control group and 2 in the omentoplasty group. Four affected the lower limb below knee and one on measurement of the whole leg. There was no statistical difference in LLL between the control and omentoplasty (Fisher exact test, P=0.83). The changes in objective measurement of these 5 patients were shown in table 2.

Since only one patient had LLL both on clinical and objective measurement, using data from both clinical and objective measurement, lower limb LLL was found in 11 patients in this study with 6 in the control and 5 in the omentoplasty group. There was no statistical difference in LLL between the control and omentoplasty (Fisher exact test, P=1.0). The median time in detecting LLL either by clinical or objective methods was 12 months.

Lymphedema with other clinical factors

Taking both clinical and objective lymphedema together, no significant association was found with post-operation radiotherapy (Fisher exact test, P=0.51). No association of lymphedema was found in relation to the total number of pelvic nodes removed (Mann-Whitney test, P=0.32); with positive pelvic node metastasis (Fisher exact test, P=0.10), with types of surgery (Fisher exact test, P=0.53); with squamous or adenocarcinoma (Fisher exact test, P=0.44) and stage of cancers ((Fisher exact test, P=0.22). There was no significant difference in disease free survival and overall survival between patients with or without edema (Log rank test, P=0.68, P=0.39).

Discussions

Lower limbs lymphedema is one of the complications after pelvic lymphadenectomy. Disruption of locoregional lymphatic drainage led to swelling of the lower limbs. The incidence varies between 1 % to 40% after radical hysterectomy. [1,2,6-9] The incidence in current study was 11% when both clinical and objective assessment were used. One study found that 53% developed LLL within 3 months, 71% within 6 months after surgery and 84% within the first year. [9] It is interesting to note that in the current study, using objective measurement, 3 of the 5 patients (60%) were found to have LLL at 3 months with one resolved at 6 months, one at 12 months and one persisted at 12 months. On the other hand, 2 patients were found to develop LLL at 12 months. Since the study designed to stop further measurement after 12 months, when the LLL resolved was not known. On the other hand, using clinical assessment, 2 of the 7 patients (28.6%) were found to have LLL before 6 months. Three of the 7 patients (42.8%) were found to have LLL around 12 months and 2 (28.6%) at and after 18 months. No LLL was detected beyond 20 months. The median follow-up was 31 months. Our study showed that LLL can develop quite early after operation, however, over half of patients developed after one year which was different from that of others.[9-10] However, late complication of LLL has been reported. [7] It is hence important to look for LLL not only during the first year of follow-up but even during the second year after operation.

Reported risk factors that related to LLL were not found in this study. Controversial data related to post-operative radiotherapy. One study showed a 3 fold increased in incidence of LLL (5% vs 15%) in irradiated patients.[10] On the other hand, like current study, no significant difference in incidence was found in another study. [11] Similar to other study, age, stage, type of hysterectomy were not associated to LLL. [9] In the same study, LLL was found only in patients with more than 10 nodes removed. In this study, only one patient had less than 10 nodes removed and all LLL were found in those with more than 10 nodes removed. In this study, other factors such as histology, type of cancers, total number of pelvic nodes removed, metastasis to pelvic nodes, recurrence and death were found not related to LLL. Hence, it is difficult to predict which patient is more likely to develop LLL after surgery.

Though majority of LLL detected was mild, complication like cellulitis tends to clear up more slowly than those without lymphedema.[3] Treatment of LLL is also difficult and is not within the theme of current study.[12] Prevention is a better approach. Study

in dog showed that omentum has fine fenestrate which absorbed fluid and particles.[13] Pilot study of omentoplasty in gynaecological patients showed that clinical LLL was found in 40% of control group and 8% in omentoplasty group.[6] Later study by Patsner et al on 140 patients showed that omentoplasty was safe and no LLL was detected in his cohort.[4] Though omentoplasty seems to be a promising operation in preventing LLL, current randomized control trial failed to show difference in incidence of LLL between the control and omentoplasty group. This could be attributed to the method used for the detection of LLL. More sensitive methods such as MRI [14] and dynamic lymphoscintigraphy [15] may be more objective and sensitive but at a high cost. Hence, a non-sophisticated objective method was used in addition to clinical assessment in this study. Surface measurement was shown to have comparable accuracy to water displacement in measuring the volume of a leg. [5] The equation used to calculate the percentage change in volume was shown to be best represented by difference in edema/initial edema.[16] A 20% increase was taken as an indication of LLL. Using this objective measurement, LLL was only detected in 5% of patients. This could be due to the early cessation of objective measurement since as shown by the clinical assessment data, majority was found to have LLL after 12 months. On the other hand, LLL was detected in 7% of patients on clinical assessment which was quite comparable to other studies using clinical assessment.[1-2] Hence, though more sensitive and expensive investigations may give a higher incidence of LLL, the clinical significance of such early LLL need further evaluation before one should recommend its routine use. To give a power of 80% in detecting significant difference, sample size of 70 was estimated based on the findings of 40% LLL in the control vs 10% in the omentoplasty arm reported in a pilot study. The current findings of only 5-7% LLL in the control arm using objective or clinical assessment indicated that the sample size was probably not adequate to detect any significant difference. Hence, a larger clinical study is in need to show if omentoplasty is useful in lowering the rate of LLL.

Conclusions

To conclude, the current study showed that the incidence of lower limb lymphedema assessed by clinical and objective measurement after pelvic lymphadenectomy was 11% which was lower than reports from some studies. Omentoplasty has not been shown to decrease the incidence of lower limb lymphedema. A larger study is required for confirmation.

Implications

The current study failed to show that omentoplasty can decrease the occurrence of lower limb lymphedema. The reason is probably because of the low occurrence of lower limb lymphedema in our patients hence making the original calculated sample size loss the power to detect significant difference. A larger study adequately powered can be considered to confirm whether omentoplasty is really of no use.

Dissemination

Plan to submit an abstract to a conference "International Symposium on Radical Hysterectomy Dedicated to Hidekazu Okabayashi" February 7 - 10, 2007 Kyoto, Japan as an invited speaker.
Also plan to write up the findings and send for publication in an international peer review journal.

Publications

nil

Biliography

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List of research workers

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*Dr. Ng resigned from the University in June 2004 and Prof. Ngan took up the role as principle investigator.

Miss Tong Yuk Fung (湯玉鳳), Miss Collier Gladys, Miss Yue Chi Kwan Yvonne (余志堃) from the Department of Physiotherapy who performed all the objective measurements.
Miss Yip Man Wo Ann (葉敏和), research nurse and Miss Tsang Man Yin (曾敏嫣), research assistant, who recruited all the patients.
Dr. LC Wong (黃令翠), Dr. YM Chan (陳奕明), Dr. KKL Chan (陳嘉倫) as well as the investigators performed all the operations in this study in the Department of Obstetrics and Gynaecology.

Table 1: Clinical characteristics

	Control [a]	Omenoplasty [b]	P value a vs b
Mean age (range)	52.2 (30-79)	48.5 (25-70)	T-test 0.13
Endometrial cancer	25	29	Chi-square test 0.22
Cervical cancer	26	17	
Stage			
I	47	37	Chi-square test 1.0
II and above	10	9	
Squamous cell ca	13	16	Chi-square test 0.26
Adenocarcinoma	28	26	
Others	10	4	
Simple hysterectomy	22	15	Chi-square test 0.30
Radical hysterectomy	29	31	
No RT	34	29	Chi-square test 0.83
Post-op RT	17	17	
Mean and median no. of pelvic nodes removed (range)	34.4, 33 (7-81)	34.7, 31 (14-64)	T-test, 0.90
Positive pelvic node metastasis	7	10	Chi-square test 0.28
Negative pelvic node metastasis	44	35	
Estimated 4 year disease free survival	84%	88%	Log rank test 0.50
Estimated 4 year overall survival	88%	91%	Log rank test 0.64

Table 2: Changes in objective measurement of limb volume in 5 patients with increase more than 20% over pre-operation measurement

Ref. No.		3 mth post-op	6 mth post-op	12 mth post-op	Clinical edema
7	Left calf	**33%**	10%	-3%	Yes
17	Right calf	5%	9%	**24%**	No
63	Left calf	**27%**	**24%**	15%	No
99	Right leg	**24%**	**29%**	**32%**	No
109	Right calf	-13%	-15%	**39%**	No