Low Body Mass Index is An Independent Risk Factor of Locoregional Recurrence in Women with Breast Cancer Undergoing Breast Conserving Therapy

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Background: To investigate the risk factors and prognosis for locoregional recurrence (LRR) after breast conserving treatment (BCT) in women with early breast cancer.

Methods: Women who had undergone BCT from 1998 to 2005 at Chang Gung Memorial Hospital were retrospectively reviewed. LRR was defined as the reappearance of invasive carcinoma in the treated breast and/or ipsilateral axillary lymph node (ALN). The appearance of carcinoma outside this area was defined as distant metastasis (DM). Patient characteristics, tumor characteristics, treatment modality, and follow-up clinical evaluations were analyzed. Survival was estimated by the Kaplan-Meier method and compared with the log-rank test. A multivariate model was built by the Cox regression method.

Results: This study included 858 patients, and the median follow up time was 36 (range 6-193) months. Twenty seven patients developed LRR for a crude LRR rate of 3.1%. The 5-year cumulative incidence of LRR was 5.0%. The mean age of patients at the primary operation was 45 ($\pm$ 9.8) years old. Their median body mass index (BMI) was 23 (range 16-40) kg/m^2. Univariate analysis of locoregional recurrence free survival (LRRFS) revealed that age $\leqq$ 40 years, a low BMI ($\leqq$ 24 kg/m^2) and omission of post-operation radiotherapy were unfavorable factors. Low BMI and young age were independent prognostic factors for LRRFS in multivariate analysis. The five-year overall survival of patients with no recurrence, LRR and DM were 97.4%, 63.2% and 41.6%, respectively ($p < 0.001$).

Conclusions: BCT in a young population can result in good locoregional control after careful preoperative evaluation. Women with a low BMI are at high risk of LRR.
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Key words: breast cancer, breast conserving, locoregional recurrence, body mass index, radiotherapy

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The incidence of female breast cancer in Taiwan has increased recently with a relatively young median age (45-49 years) at diagnosis. Before the 1980s, Taiwan had a low incidence of breast cancer. However, the age-adjusted incidence of female invasive breast cancer increased dramatically from 11.7 per 100,000 women in 1980 to 42.0 per 100,000 women in 2003.[1] Although the breast cancer incidence remains lower in Taiwan than in western countries--the rate is 119.0 per 100,000 women in the United States[2]--the trend has shifted toward that seen in Caucasian Americans.[3] Furthermore, breast cancer patients in Taiwan tend to have a better 5-year survival rate than those in western countries.[4-6]

Breast conserving therapy (BCT) is now well established as a safe and preferred treatment in early-stage disease; many randomized clinical trials have shown no statistically significant difference in patient survival between mastectomy and BCT.[7-12] Most recent evaluations of BCT report locoregional, i.e. the treated breast and ipsilateral axillary lymph node, recurrence free survival at 5 years of 90% to 97%. Local recurrence is associated with a decrease in survival and risk of distant dissemination.[13-15]

BCT is not well accepted in Asian countries including Taiwan, and the relatively thin body figure and risk of local recurrence after BCT are major concerns. An absence of association between BCT and higher recurrence rates has been reported in Japanese and Korean studies.[13,16,17] This study retrospectively analyzed risk factors and prognostic factors for locoregional recurrence (LRR) in Taiwanese women who underwent BCT for early breast cancer.

METHODS

A cohort of 1120 patients that had BCT at Chang Gung Memorial Hospital between Feb 1988 and Feb 2005 was retrospectively reviewed. Patient characteristics, medical comorbidities, location of the tumors, operative details, postoperative outcomes, and follow-up status were collected prospectively and recorded in a breast cancer database. Two hundred and sixty two patients were excluded because of ductal carcinoma in situ, palliative surgery, male breast cancer, phyllodes tumors, leiomyosarcoma, prior operation for the same disease at another hospital, and loss to follow up. Finally, 858 patients were included in this study.

The surgical procedures were chosen with patient consent after thorough discussion of the pros and cons. Selection for BCT was dependent on patient acceptance, patient preference, tumor characteristics, and surgeon's preference. Multicentricity, tumors larger than 3 cm, and tumors located within 2 cm of the nipple were generally considered contraindications to BCT in our practice.

Wide excision was applied to achieve a tumor free distance of at least 1 cm grossly, and all surgical margins were confirmed to be negative of malignancy during the operation using frozen sections of residual breast adjacent to the removed tissue. A microscopic distance of less than 1 cm between the tumor and resection margin on histological examination was classified as a close margin. Women with positive margins at histological examination underwent reexcision or mastectomy. Postoperative radiation therapy to the residual breast was administered by a 5000 cGy photon-beam to the whole breast, plus a 1000 cGy electron beam boost to the tumor bed.

Adjuvant chemotherapy and hormonal therapy were applied according to our treatment guidelines based on risk assessment. Briefly, no adjuvant therapy was given to low-risk patients (node negative breast cancer in postmenopausal women with tumor < 1 cm and positive estrogen receptor status). Chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil was given to patients who were node negative and had any risk factor, or patients who older than 40 years of age, had one to three positive nodes and positive estrogen receptor status. Cyclophosphamide, epirubicin and 5-fluorouracil were given to patients with more than three positive axillary nodes. Taxanes were prescribed for high risk patients. Hormonal therapy was given to patients with positive estrogen receptor tumors. A majority of hormonal therapy patients received Tamoxifen; others received oophrectomy and aromatase inhibitors. Patients were followed up at 3-month intervals during the first 2 years, at 6-month intervals in years 3-5, and at 12-month intervals thereafter. The maximum follow-up period was 16 years.

LRR was defined as the reappearance of carcinoma in the treated breast and/or ipsilateral axillary lymph node (ALN). Appearance of carcinoma outside this area was defined as distant metastasis (DM). Concurrent LRR and distant metastasis were viewed as systemic disease and categorized as

metastatic. The body mass index (BMI) was calculated using the following formula: weight (kg)/ height^2 (m^2). BMI was analyzed initially as a continuous factor, and later as a category factor according to criteria published by the Bureau of Health Promotion, Department of Health, Taiwan (underweight and normal range $\leqq$ 24 kg/m^2; overweight and obese > 24 kg/m^2.) A Low BMI was defined as $\leqq$ 24 kg/m^2 and a high BMI as > 24 kg/m^2. Estrogen and progesterone receptors (ER, PR) and HER-2/neu analysis was performed using immunohistochemical staining techniques. Laboratory standards were used to assess hormone receptor positivity according to the Allred score, briefly, total scores more than 3 (weak intensity and positive staining of more than 10% of cells) were considered positive. HER-2/neu analysis was done using the Hercep test (DakoCytomation, Carpentaria, CA, U.S.A.) The staining intensity score was evaluated relative to the provided control slides from 0 to 3+ as follows: 0, no staining or membrane staining observed in < 10% of the tumor cells; 1+, faint, barely perceptible membrane staining in > 10% of the tumor cells and /or cells with only partial membrane staining; 2+, weak to moderate complete membrane staining in > 10% of the tumor cells; 3+, moderate to strong complete membrane staining observed in > 10% of the tumor cells. Specimens staining 3+ were coded as positive.

Patient characteristics, tumor characteristics, treatment modality, and follow-up clinical evaluations were analyzed. The following factors were assessed as risk factors for LRR: age, BMI, cancer stage, tumor histology, ER, PR, HER2/neu overexpression, resection margin, postoperative radiotherapy, hormonal therapy and chemotherapy.

All data are presented as percentages of patients, median with range or mean with SD. Numerical data were compared by independent two-sample *t*-tests. Nominal data were compared by Pearson's chi-square test or Fisher's exact test where appropriate. Survival was estimated according to the Kaplan-Meier method and compared with the log-rank test. A multivariate proportional hazards model was built by Cox regression. Statistical significance was defined as $p < 0.05$.

RESULTS

Characteristics of the 858 patients that were available for analysis of survival and recurrence are summarized in Table 1. The median follow up time was 36 (range 6-193) months. Twenty seven patients developed LRR for a crude LRR rate of 3.1%. The 5-year cumulative incidence of LRR was 5.0%. Sixty-seven (7.8%) patients developed DM. Sixty- seven patients died, including 56 because of breast cancer, in the follow up. Among all 858 patients, the 5-year overall survival (OS), distant metastasis free survival (DMFS) and locoregional recurrence free survival (LRRFS) were 85.4%, 86.1% and 95.0% respectively.

The mean age of patients at the primary operation was 45 ($\pm$ 9.8) years old. The median BMI was 23 (range 16-40) kg/m^2. Premenopausal and postmenopausal women accounted for 54.4% and 20.0% of all patients. Two hundred and twenty (25.6%) women were in their perimenopausal years or had undergone hysterectomy before the time of operation. The medium tumor size was 1.8 (range 0.3-7.3) cm. Two hundred and seventy six (32.2%) patients had pathological ALN involvement, and the median number of positive lymph nodes was 2 (range 1-34). Distribution by stage was as follows: I, 46.8% (n = 401), II, 41.8% (n = 359), and III, 11.4% (n = 98). Two hundred and twenty six (26.3%) patients avoided postoperative radiotherapy, and 618 (72.0%) patients underwent adjuvant chemotherapy.

Five hundred twenty eight (61.5%) patients were classified as having a low BMI. The mean ages of patients with low and high BMI were 43 ($\pm$ 9.4) and 48 ($\pm$ 9.3) years old respectively ($p < 0.001$), and the resection margins of women with low BMI were more often classified as close margins ($p = 0.018$) than those of women with high BMI. Pre-menopausal women accounted for 61.4% and 43.3% of patients with low and high BMI respectively ($p < 0.001$). There were no other significant differences between women with low and high BMI, including tumor size, lymph node status, cancer stage, hormonal receptor and treatment modalities.

Twenty seven patients developed LRR, including 15 (55.6%) who had LRR within 2 years after the primary surgery. In patients with LRR, 19 (70.4%) had tumor recurrence only on the treated breast, 3 (11.1%) had isolated ALN recurrence, and 5 (18.5%) had synchronous breast and ALN recurrence. Of the 27 LRR patients, 12 (44.4%) developed sequential DM, and one had ipsilateral ALN recurrence fol-

Table 1. Patients Characteristics and Treatment

Characteristic	Low BMI* (n = 528) No. (%)	High BMI† (n = 330) No. (%)	*p*
Age (years)			
≦ 40	191 (36.2)	70 (21.2)	< 0.001
> 40	337 (63.8)	260 (78.8)	
Menopausal status			
Pre-menopausal	324 (61.4)	143 (43.3)	< 0.001
Menopausal	72 (13.6)	99 (30.0)	
Others	132 (25.0)	88 (26.7)	
Tumor size (cm)			
≦ 2	345 (65.3)	221 (67.0)	0.621
> 2	183 (34.7)	109 (33.0)	
Lymph node status			
Negative	354 (67.0)	233 (70.6)	0.307
Positive	174 (33.0)	97 (29.4)	
Stage			
I	244 (46.2)	163 (49.4)	0.246
II	231 (43.8)	125 (37.9)	
III	53 (10.0)	42 (12.7)	
Estrogen receptor			
Negative	250 (47.4)	168 (50.9)	0.278
Positive	235 (44.5)	145 (43.9)	
Unknown	43 (8.1)	17 (5.2)	
Progesterone receptor			
Negative	257 (48.7)	176 (53.3)	0.131
Positive	224 (42.4)	136 (41.2)	
Unknown	47 (8.9)	18 (5.5)	
HER2/neu over-expression			
Negative	258 (48.9)	167 (50.6)	0.684
Positive	83 (15.7)	45 (13.6)	
Unknown	187 (35.4)	118 (35.8)	
Resection margin (cm)			
≧1	437 (82.8)	294 (89.1)	0.018
<1	91 (17.2)	36 (10.9)	
Chemotherapy			
No	137 (25.9)	90 (27.3)	0.656
Yes	391 (74.1)	240 (72.7)	
Radiotherapy			
No	139 (26.3)	79 (23.9)	0.431
Yes	389 (73.7)	251 (76.1)	
Hormonal therapy			
No	284 (53.8)	183 (55.5)	0.639
Yes	244 (46.2)	147 (44.5)	

*: Low body mass index (≦ 24 kg/m^2); †: High body mass index (> 24 kg/m^2).

lowed by DM. Eleven of the 27 patients with LRR died during the follow-up period, 10 because of cancer progression and one from unrelated causes.

Univariate analysis of LRRFS revealed that age ≦ 40, low BMI and omission of post-operation radiotherapy were unfavorable factors. The five-year LRRFS of patients with low BMI and high BMI were 93.0% and 98.9% respectively (p = 0.021) (Fig. 1). The five-year LRRFS of those with surgical margins ≧ 1 cm and < 1 cm were 96.2% and 92.6% respectively (p = 0.568). A low BMI [hazard ratio (HR), 6.24; 95% confidence interval (95% CI): 1.33 - 29.27] and young age (HR, 6.83; 95% CI: 1.48 – 31.54) were poor prognostic factors of LRR in multivariate analysis (Table 2). The five-year overall survival of patients with no recurrence, LRR and DM was 97.4%, 63.2% and 41.6% respectively (p < 0.001).

DISCUSSION

Good local control of BCT had been demonstrated in this study as the recurrence rate was similar to recent reports from Japan, Korea and Hong Kong.[16-18] Since young age was considered an important risk factor for local recurrence after BCT,[19-22] the risk of LRR was assumed to be higher in Taiwan than in western countries. Surprisingly, BCT results in low LRR. Racial differences could be one expla-

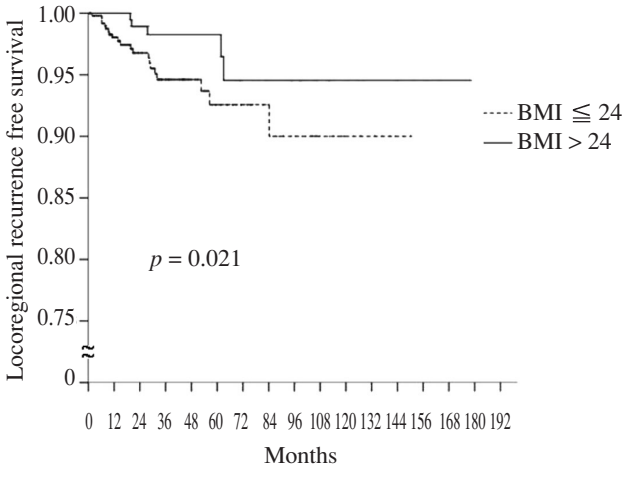

Fig. 1 Locoregional recurrence free survival of women with low (≦ 24) and high BMI (> 24).

Table 2. Prognostic Factors for Locoregional Recurrence Free Survival

Characteristics (No)	Univariate analysis		Multivariate analysis		
	5y-LRRFS (%)	*p*	HR	95% CI	*p*
Age (years)		0.040			0.014
≦ 40 (261)	92.1		6.83	1.48 – 31.54	
> 40 (597)	96.6		–	–	
Menopausal status		0.497			NS[§]
Pre-menopausal (467)	94.7	–	–	–	
Menopausal (171)	94.4		4.21	0.66 – 26.83	
Others (220)	96.3		1.65	0.28 – 9.58	
Body mass index (kg/m^2)		0.021			0.020
≦ 24 (528)	93.0		6.24	1.33 – 29.27	
> 24 (330)	98.9		–	–	
Tumor size (cm)		0.930			
≦ 2 (566)	94.9		–	–	NS
> 2 (292)	95.2		0.24	0.042 – 1.40	
Lymph node status		0.078			NS
Negative (587)	96.7		–	–	
Positive (271)	92.8		0.64	0.08 – 5.11	
TNM Stage		0.235			NS
I (407)	96.7		–	–	
II (356)	94.0		4.52	0.51 – 40.36	
III (95)	91.6		9.81	0.61 – 159.15	
Estrogen receptor		0.424			NS
Negative (418)	94.3		–	–	
Positive (380)	96.2		0.28	0.06 – 1.34	
Progesterone receptor		0.737			NS
Negative (433)	94.6		–	–	
Positive (360)	95.9		1.38	0.35 – 5.40	
HER2/neu over-expression		0.135			NS
Negative (425)	98.2		–	–	
Positive (128)	92.7		5.33	0.90 – 31.54	
Resection margin (cm)		0.568			NS
≧ 1 (731)	96.2		0.58	0.16 – 2.09	
< 1 (127)	92.6		–	–	
Chemotherapy		0.673			
No (227)	92.9		–	–	NS
Yes (631)	95.8		0.48	0.12 – 1.91	
Radiotherapy		0.021			NS
No (218)	92.7		–	–	
Yes (640)	95.7		0.60	0.20 – 1.84	
Hormonal therapy		0.636			
No (467)	95.4		–	–	NS
Yes (391)	93.1		1.93	0.47 – 7.90	

Abbreviations: 5y-LRRFS: 5-year locoregional recurrence free survival; HR: hazard ratio; 95% CI: 95% confidence interval; NS: not statistically significant.

nation for the low LRR rate.[6,23] On the other hand, patient selection and surgeon preference for more radical excision in our practice also could have resulted in a favorable outcome. Despite increasing numbers, BCT accounted for only of 35% all breast cancer operations in our database. A tumor larger than 3 cm is regarded as a relative contraindication for BCT, considering the small breast size of Taiwanese women. With careful selection, good results can be obtained with breast conserving in a young population.

The resection margin has long been considered an important factor influencing local recurrence.[13,19,24] A resection margin > 1 cm did not improve the LRRFS, which was not an unusual finding. Singletary reviewed the published evidence and concluded that a wide margin > 1 cm does not necessarily decrease the local recurrence rate after breast conserving surgery.[25] However, controversy still exists about the adequacy of margins from 1 to 10 mm. When a cut-off point of a negative margin was defined as > 2 mm, good correlation between margin status and local recurrence was demonstrated.[25] Unfortunately, precise information on margin distance could not be assessed as the specimens were not inked in our study. While most (85%) of our patients had generous margins > 1 cm, shaved margins seemed to be a reasonable alternative. More limited resections could be advised, however, further studies are needed to evaluate their safety.

Taiwanese women are thinner than the worldwide standard, and a BMI > 24 kg/m^2 is defined as overweight by the Bureau of health Promotion, Department of Health, Taiwan rather than the value of 25 kg/m^2 used by the World Health Organization.[26] More than sixty percent of our patients were defined as normal or underweight, and the impact of low BMI on breast cancer could be an important issue. BMI has been inversely associated with breast cancer incidence in premenopausal women in many series.[27-29] On the contrary, in post-menopausal women, overweight increases the risk of breast cancer.[30] Two mechanisms have been suggested to explain the protective effect of high BMI on premenopausal breast cancer: sex hormones and detection bias.[31] The strong association between low BMI and pre-menopausal status in Taiwanese women might contribute to the early occurrence of breast cancer. However, detailed epidemiological study is needed to confirm this hypothesis.

A low BMI had not attracted much attention as a risk factor for local recurrence. Compatible with Marret et al's work,[32] a low BMI was an independent predictive factor of LRR after BCT in this study. But the biological rationale for the impact of low BMI on local recurrence has not been well established. We will consider two possibilities. First, the high endogenous estrogen level in pre-menopausal lean women is one possible rationale. Premenopausal lean women were found to have higher estrodiol levels than overweight women,[33] while BMI was positively related to estrodiol in postmenopausal women.[34] The endogenous estrogen level is important in the etiology of breast cancer as well as recurrence. No association between body weight and ER status was found in our series or in others.[32,35] The effect of a high estrogen level might have been significant when 62% of our patients were classified as having low BMI and 80% of them were not menopausal. Another implication of the importance of estrogen could be found in studies of ovarian ablation/suppression. Ovarian ablation/suppression yielded no survival benefits on premenopausal patients as a whole, except for those without adjuvant chemotherapy.[36,37] But in women < 40 years old with ER-positive tumors who had undergone chemotherapy, ovarian ablation/suppression was associated with reduced recurrence and improved survival.[38]

Second, the relationship between tumor size and breast volume might be another explanation. Although no association between BMI and breast size has been demonstrated, we propose that women with lower BMI have less adipose tissue and a smaller breast volume. Smaller breasts were identified as a risk factor of re-excision lumpectomy in a previous report.[39] Obtaining a wide margin in women with small breasts would result in remarkable deformity, and as a result, women with low BMI had a higher proportion of close margins in our series. The compromise between achieving an adequate margin and acceptable cosmetic outcome could contribute to higher recurrence in thin women. Fortunately, most women (95.2%) were satisfied with their treatment outcomes as presented in our previous study.[40]

In surgical treatment of thin women, special precautions should be taken, as tumors could be close to the skin and underlying fascia layers. Tumors should

not be transected and a secure margin must be obtained. Intra-operative frozen section examinations of shaved margins could reduce the possibility of second operations and lower the recurrence rate.[41,42] Furthermore, "oncoplastic techniques", such as immediate latissimus dorsi flap and breast tissue rearrangement, could allow extensive excision with good cosmetic outcomes.[43,44]

The effect of radiotherapy in decreasing recurrence has been well demonstrated in many previous studies. Some authors focused on margin assessment rather than irradiation; one recent Japanese study reported that after complete tumor resection with meticulous margin assessment, postoperative irradiation could be avoided in as many as 60% of patients without increasing the risk of local recurrence.[45] A low recurrence rate was also confirmed by our study, as a high proportion of patients omitted postoperative irradiation. However, as shown above, omission of radiotherapy was a significant risk factor for LRR. We recommend post-operative irradiation in every women undergoing BCT even if they have a radical resection.

This retrospective series was collected over a 17 year period, and there was some evolution of clinical practice over time. First, hormonal receptors were examined with the detran-charcoal method in the first few years, and HER-2/neu overexpression was not routinely checked until the late 1990s. Shorter follow up times in many patients with HER-2/neu overexpression results in unreliable 5-year survival rates. Second, surgeons preferred more radical resection and more patients omitted post-operative irradiation when BCT was first done. Third, neck lymph nodes are classified as N3 rather than M1 in the American Joint Committee on Cancer 6th edition staging system, which is different from the criteria for this study. The vast majority of patients were treated before 2002 when neck lymph nodes were still defined as distant metastasis, so neck lymph node recurrence was recognized as distant metastasis. However, when studying early breast cancer in an area of low incidence with an annual local recurrence rate of about 1% per year, a long period of case collection could not be avoided.

In conclusion, with careful selection, breast conserving is safe when considering local control in Taiwanese women. Patients with a low BMI and young age are at high risk of LRR.

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低身體質量比爲乳癌婦女接受乳房保留療法後局部再發之危險因子

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背 景： 研究早期乳癌婦女接受乳房保留治療 (breast conserving therapy) 後局部再發 (locoregional recurrence) 之預後因子及危險因子。

方 法： 採取回顧性之世代研究爲研究方法。局部再發定義爲經手術治療之同側乳房及 (或) 腋下淋巴節再度出現侵襲性癌。在乳房或腋下淋巴節以外再度出現侵襲性癌則定義爲遠處轉移 (distant metastasis)。病人統計資料、腫瘤特性、治療模式及後續追蹤皆列入分析。存活率分析使用 Kaplan-Meier 統計方式並以 log-rank 分析比較變異數。多因子存活率分析則採用 Cox regression 方法。

結 果： 本研究包括 858 位病患，中位追蹤時間爲 36 (range 6-193) 個月。27 位病患發生局部再發，粗估再發率爲 3.1%。累計五年再發率爲 5%。病人平均年齡爲 45 (±9.8) 歲，中位身體質量指數 (BMI) 爲 23 (range 16-40) kg/m^2。單變項分析無局部再發存活發現：年齡 ≦40，低 BMI (≦24 kg/m^2) 及術後未接受放射治療皆是危險因子。多變項分析發現：低 BMI 及年齡是獨立之預後因子。無再發、局部再發及遠端轉移三組病患之五年總合存活率 (overall survival) 依序分別爲 97.4%，63.2% 及 41.6% ($p < 0.001$)。

結 論： 乳房保留治療，在審慎的術前評估下，可以在年齡較輕的乳癌群體中提供良好之局部控制。身體質量指數 (BMI) 較低之婦女爲局部再發之高危險群。

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關鍵詞： 乳癌，乳房保留，局部再發，身體質量指數，放射線治療

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