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## 腹腔镜与开腹宫颈癌根治术对患者血清 IL-4, IL-10, TNF- $\alpha$ 及 IFN- $\gamma$ 水平的影响 \*

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**摘要 目的:**探讨腹腔镜与开腹宫颈癌根治术对患者血清白细胞介素-4(IL-4)、白细胞介素-10(IL-10)、肿瘤坏死因子- $\alpha$ (TNF- $\alpha$ )、 $\gamma$ -干扰素(IFN- $\gamma$ )水平的影响。**方法:**选取2014年3月至2016年9月在我院接受治疗的64例宫颈癌患者作为研究对象,通过随机方式分为腹腔镜组和开腹组。比较两组患者的手术时间、术中出血量、术后通气时间、治疗前后血清IL-4、IL-10、TNF- $\alpha$ 、IFN- $\gamma$ 水平的变化。**结果:**腹腔镜组患者的术中出血量和术后通气时间明显低于或短于开腹组( $P < 0.05$ ),而两组患者的手术时间比较差异无统计学意义( $P > 0.05$ )。术前,两组患者的血清IL-4、IL-10、TNF- $\alpha$ 及IFN- $\gamma$ 水平比较差异均无统计学意义( $P > 0.05$ );术中,腹腔镜组的血清IL-4水平明显低于开腹组( $P < 0.05$ ),其余三组指标水平与开腹组比较差异无统计学意义( $P > 0.05$ );术后1天和7天,腹腔镜组患者的血清IL-4、IL-10、TNF- $\alpha$ 及IFN- $\gamma$ 水平均明显低于开腹组( $P < 0.05$ )。**结论:**腹腔镜宫颈癌根治术在术中失血量更少,安全性更高,且对于患者术后的IL-4、IL-10、TNF- $\alpha$ 和IFN- $\gamma$ 水平抑制效果更加明显,利于患者的术后恢复。

**关键词:**宫颈癌;腹腔镜;白细胞介素-4;白细胞介素-10;肿瘤坏死因子- $\alpha$ ;  $\gamma$ 干扰素

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## Comparison of Effects of Laparoscopic and Open Radical Hysterectomy on Serum IL-4, IL-10, TNF- $\alpha$ and IFN- $\gamma$ Levels of Patients with Cervical Cancer\*

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**ABSTRACT Objective:** To compare of the effects of laparoscopic and open radical hysterectomy on the serum Interleukin-4(IL-4), interleukin-10 (IL-10), tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ) and Interferon- $\gamma$  (IFN- $\gamma$ ) levels of Patients with Cervical Cancer. **Methods:** 64 patients of cervical cancer who were treated from March 2014 to September 2016 in our hospital were selected as research objects. The patients were randomly divided into the abdominal cavity group and open group. The operative time, blood loss, postoperative ventilation time and the levels of IL-4, IL-10, TNF- $\alpha$  and IFN- $\gamma$  in serum before and after treatment were compared between the two groups. **Results:** The intraoperative blood loss and postoperative ventilation time were significantly lower or shorter in the abdominal cavity group than in the open group ( $P < 0.05$ ). There was no statistically significant difference in the operation time between the two groups ( $P > 0.05$ ). There were no significant differences in the levels of serum IL-4, IL-10, TNF- $\alpha$  and IFN- $\gamma$  between the two groups before operation ( $P > 0.05$ ); The serum IL-4 level was significantly lower than that of the open group during the operation ( $P < 0.05$ ). There was no significant difference in the other three index between the other three groups and the laparotomy group ( $P > 0.05$ ). The serum levels of IL-4, IL-10, TNF- $\alpha$  and IFN- $\gamma$  in the abdominal cavity group were significantly lower than those of the laparotomy group on the 1st and 7th day after operation ( $P < 0.05$ ). **Conclusion:** Laparoscopic radical mastectomy in cervical intraoperative less blood loss and more secure. The effect of IL-4, IL-10, TNF- $\alpha$  and IFN- $\gamma$  in the postoperative patients was more obvious. Conducive to the recovery of patients after surgery.

**Key words:** Cervical cancer; Laparoscopic; Interleukin-4; Interleukin-10; Tumor Necrosis Factor- $\alpha$ ; Interferon- $\gamma$

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### 前言

手术仍是早期宫颈癌的首选,患者术后5年内的存活率在75%以上<sup>[1,2]</sup>。早期手术的主要方式为开腹手术,该种手术方式

虽然能为患者减轻病痛,但容易对患者免疫系统造成破坏,同时也极易产生并发症<sup>[3]</sup>。随着腹腔镜手术的持续发展,不论是技术还是器材,都能为患者提供更好的疗效,该种手术方式最大的特点为并发症少、可减少对患者本身免疫系统的破坏,恢复

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快,尤其是其术口较小广受医生和患者推崇<sup>[9]</sup>。因此,本研究通过对比腹腔镜和开腹宫颈癌根治术对患者血清相关因子水平的影响,旨在探讨两种手术对于患者免疫系统及疗效的影响,从而为治疗宫颈癌提供更多的临床信息,现报道如下。

## 1 资料与方法

### 1.1 一般资料

选取 2014 年 3 月至 2016 年 9 月接受我院治疗的 64 例宫颈癌患者作为研究对象。纳入标准:①符合国际妇产科联盟对于宫颈癌的诊断标准<sup>[9]</sup>;②患者处于宫颈癌 I<sub>a2</sub>~II<sub>a1</sub> 期。排除标准:③患者已经接受过化疗;④患者患有免疫性疾病或病史;⑤患者其他部位患有肿瘤。所有患者以随机方式平均分为开腹组和腹腔镜组,其中开腹组患者,男 18 例,女 14 例,年龄 31~54 岁,平均年龄 (42.31±3.41) 岁,体重 32~55 kg,平均体重 (42.87±3.42)kg, I<sub>a2</sub> 期 3 例、I<sub>b1</sub> 期 20 例、I<sub>b2</sub> 期 7 例、II<sub>a1</sub> 期 2 例,腺癌 5 例、鳞癌 27 例;腹腔镜组患者,男 16 例,女 16 例,年龄 32~55 岁,平均年龄 (43.67±3.29) 岁,体重 33~56 kg,平均体重 (43.17±3.36)kg, I<sub>a2</sub> 期 4 例、I<sub>b1</sub> 期 21 例、I<sub>b2</sub> 期 4 例、II<sub>a1</sub> 期 3 例,腺癌 7 例、鳞癌 25 例。两组患者在性别、年龄、体重、figo 分期及病理类型的差异并无统计学意义 (P>0.05),具有可比性。所有患者及其家属均同意自愿加入本次研究,同时本次研究已经过本院伦理委员会批准同意。

### 1.2 治疗方法

开腹宫颈癌根治术(开腹组患者)按刘新民主编的《妇产科学》<sup>[6]</sup>描述的广泛子宫切除±双附件切除+盆腔淋巴结清扫的手术方式进行手术。腹腔镜下宫颈癌根治术(腹腔镜组患者)按刘新民主编的《妇产科学》描述的腹腔镜下广泛子宫切除±双附件切除+盆腔淋巴结清扫的手术方式进行手术。所有患者在术后进一步接受增强免疫的附属治疗。

### 1.3 观察指标

术前术后分别采取患者 3 mL 外周静脉血,检测肿瘤坏死因子 α(TNF-α)、干扰素 γ(IFN-γ)、IL-4、IL-10,使用双抗体夹心酶标免疫法。采用美国 BD 公司生产的流式细胞仪 FACSCalibur 辅助指标采集。

### 1.4 统计学分析

数据用 spss19.0 软件包进行处理,计量资料用均数±标准差( $\bar{x} \pm s$ )表示,并采用 t 检验, P<0.05 表示差异具有统计学意义。

## 2 结果

### 2.1 两组患者手术中及手术后的情况对比

开腹组患者的手术模式与腹腔镜组手术模式在手术用时上差异较小 (P>0.05),但腹腔镜组患者手术过程中的出血量和术后通气用时均远低于开腹组,差异具有统计学意义 (P<0.05),见表 1。

表 1 两组患者的手术中及手术后的情况对比( $\bar{x} \pm s$ )

Table 1 Comparison of the intraoperative and postoperative index between two groups of patients( $\bar{x} \pm s$ )

| Groups                 | n  | The amount of bleeding during the procedure(mL) | Surgery time(h) | Postoperative ventilation time(h) |
|------------------------|----|-------------------------------------------------|-----------------|-----------------------------------|
| Open group             | 32 | 331.57±93.81                                    | 3.27±0.42       | 72.36±10.38                       |
| Abdominal cavity group | 32 | 269.49±83.77                                    | 3.31±0.41       | 50.16±11.25                       |
| P Value                |    | P<0.05                                          | P>0.05          | P<0.05                            |

### 2.2 两组患者治疗前后血清 IL-4 水平的比较

两组患者术前血清 IL-4 水平比较差异无统计学意义 (P>0.

05),但术中、术后 1 天、7 天,腹腔镜组的血清 IL-4 水平明显低于开腹组,且差异具有统计学意义 (P<0.05),见表 2。

表 2 两组患者治疗前后血清 IL-4 水平的对比( $\bar{x} \pm s$ , pg/mL)

Table 2 Comparison of the serum IL-4 level between two groups of patients before and after treatment ( $\bar{x} \pm s$ , pg/mL)

| Groups                 | n  | Before surgery | In surgery | 1 day after surgery | 7 days after surgery |
|------------------------|----|----------------|------------|---------------------|----------------------|
| Open group             | 32 | 13.31±4.78     | 19.04±9.36 | 43.50±22.37         | 47.38±18.19          |
| Abdominal cavity group | 32 | 13.19±4.14     | 14.32±7.05 | 26.93±8.82          | 16.27±8.32           |
| P Value                |    | P>0.05         | P<0.05     | P<0.05              | P<0.05               |

### 2.3 两组患者治疗前后血清 IL-10 水平的比较

两组患者在术前及术中的血清 IL-10 水平比较差异均无统计学意义 (P>0.05),但在术后 1 天及 7 天,腹腔镜组血清 IL-10 水平明显低于开腹组 (P<0.05),见表 3。

### 2.4 两组患者治疗前后血清 TNF-α 水平的对比

两组患者在术前及术中的血清 TNF-α 水平比较差异无统计学意义 (P>0.05),而在术后 1 天和 7 天的,腹腔镜组血清 TNF-α

水平远低于开腹组 (P<0.05),见表 4。

### 2.5 两组患者治疗前后血清 IFN-γ 水平的对比

两组患者在术前及术中的血清 IFN-γ 水平比较差异无统计学意义 (P>0.05),而在术后 1 天和 7 天,腹腔镜组血清 IFN-γ 水平远低于开腹组 (P<0.05),见表 5。

## 3 讨论

宫颈癌指在子宫颈上皮处产生恶性肿瘤,近年来该病发病

表 3 两组患者治疗前后血清 IL-10 水平的对比( $\bar{x} \pm s$ , pg/mL)

Table 3 Comparison of the serum IL-10 level between two groups of patients before and after treatment ( $\bar{x} \pm s$ , pg/mL)

| Groups                 | n  | Before surgery | In surgery   | 1 day after surgery | 7 days after surgery |
|------------------------|----|----------------|--------------|---------------------|----------------------|
| Open group             | 32 | 12.46± 4.62    | 17.29± 10.16 | 34.28± 18.86        | 38.43± 20.57         |
| Abdominal cavity group | 32 | 13.01± 4.74    | 17.10± 9.42  | 25.11± 8.07         | 20.46± 7.22          |
| P Value                |    | P>0.05         | P>0.05       | P<0.05              | P<0.05               |

表 4 两组患者治疗前后血清 TNF- $\alpha$  水平的对比( $\bar{x} \pm s$ , pg/mL)

Table 4 Comparison of the serum TNF- $\alpha$  level between two groups of patients before and after treatment ( $\bar{x} \pm s$ , pg/mL)

| Groups                 | n  | Before surgery | In surgery   | 1 day after surgery | 7 days after surgery |
|------------------------|----|----------------|--------------|---------------------|----------------------|
| Open group             | 32 | 12.54± 6.77    | 19.01± 11.96 | 39.04± 21.49        | 38.32± 11.26         |
| Abdominal cavity group | 32 | 12.45± 8.23    | 17.31± 9.19  | 18.68± 9.92         | 13.36± 7.06          |
| P Value                |    | P>0.05         | P>0.05       | P<0.05              | P<0.05               |

表 5 两组患者治疗前后血清 IFN- $\gamma$  的比较( $\bar{x} \pm s$ , pg/mL)

Table 5 Comparison of the serum TNF- $\alpha$  level between two groups of patients before and after treatment( $\bar{x} \pm s$ , pg/mL)

| Groups                 | n  | Before surgery | In surgery   | 1 day after surgery | 7 days after surgery |
|------------------------|----|----------------|--------------|---------------------|----------------------|
| Open group             | 32 | 51.21± 19.72   | 64.19± 26.07 | 97.67± 40.44        | 126.20± 51.87        |
| Abdominal cavity group | 32 | 49.89± 18.81   | 58.25± 27.56 | 69.88± 28.97        | 51.44± 20.37         |
| P Value                |    | P>0.05         | P>0.05       | P<0.05              | P<0.05               |

率居高不下,尤其是 30 至 55 岁的妇女,更有向年轻化的状态发展的趋势<sup>[7,8]</sup>。早期通过开腹宫颈癌根治术治疗,术后 5 年内生存率较高,但肿瘤产生转移和复发的概率也相当高。此外,其较大的创口和会损伤机体免疫力,也使得医患双方对该种手术方式都较为排斥<sup>[9]</sup>。腹腔镜具有创伤小的优势,在本次研究中,两组患者的手术用时虽然差异不明显,但腹腔镜组的术中出血量和术后通气时间远低于开腹组,这表明了腹腔镜手术模式在术中的安全性更高,而在术后患者恢复得更快,临床效果要明显由于传统的开腹式手术。

IL-4 主要通过调节免疫及适应性免疫从而发挥调节人体免疫系统的功能,主要由 Th2 细胞分泌,通过免疫调节起到缓解病痛的作用<sup>[10,11]</sup>。但过量的 IL-4 会使肿瘤患者体内的 IL-10 过量分泌,使免疫系统产生紊乱,无法控制住肿瘤的生长。IL-10 又称为细胞因子合成的抑制因子,通过抑制 IFN- $\gamma$  间接降低了 NK 细胞活性,进一步抑制抗肿瘤因子的繁殖、生长,从而使肿瘤细胞在患者体内不断发展、转移及扩散<sup>[12]</sup>。适量的 IL-10 也可以抑制炎症介质的活性进而达到抗炎效果,这也是手术过程中 IL-10 会突然升高的原因。

TNF- $\alpha$  由巨噬细胞受到刺激后分泌,可以有效地消灭肿瘤细胞,达到抗肿瘤的效果<sup>[13,14]</sup>。有研究表明其除了拥有抗肿瘤效果外,还会引起白细胞粘连至血管内皮细胞中,使白细胞集中于发生炎症的局部区域,释放炎症细胞且不断消灭掉微生物,导致大量的炎症因子不断生长,最终加重患者的炎症反应<sup>[15,16]</sup>。此外,恶性肿瘤患者体内的 TNF- $\alpha$  水平会高出正常人许多,而在抗肿瘤、抗炎症期间也会升高,过量的 TNF- $\alpha$  水平标志着患者病况的严重程度<sup>[17]</sup>。

IFN- $\gamma$  是有效的抗病毒干扰素,其主要功能是调节免疫系

统<sup>[18,19]</sup>,通过刺激树突状细胞来与 NK 细胞相互作用,使 T 细胞的识别肿瘤抗原功能得到加强,最终使机体对于肿瘤的监控能力得到提升。IFN- $\gamma$  水平的不断提高也可以判断为患者的肿瘤严重程度在不断加大<sup>[20]</sup>。

对比两组患者外周血中 IL-4、IL-10、TNF- $\alpha$  以及 IFN- $\gamma$ ,两组患者术前以及术中的差异不明显,而术后 1 天以及术后第 7 天腹腔镜手术模式下的患者明显 4 项指标更低于开腹组患者,其中,IL-4 和 IL-10 两种抑炎因子在术后会逐渐减少,证明了腹腔镜手术有效的减轻了机体炎症症状的发生,从而也使得两类因子在术后分泌相应的下降;TNF- $\alpha$  虽为抗肿瘤细胞因子,但过量的分泌也会促使机体产生炎症,而腹腔镜组患者经过手术后,TNF- $\alpha$  表达下降,也说明了腹腔镜手术模式对于患者术后炎症有抑制作用;而腹腔镜组患者 IFN- $\gamma$  水平表达下降,则客观证明了对于患者的宫颈癌有着明显的疗效。四组指数的下降充分说明腹腔镜组患者体内的肿瘤因子明显减少且未出现转移等状况,而炎症症状也明显优于开腹组。

综上所述,腹腔镜宫颈癌根治术对于患者血清 IL-4、IL-10、TNF- $\alpha$ 、IFN- $\gamma$  水平表达的控制有着优异的效果,较之传统的开腹式手术安全性更高,疗效更加明显,同时也更加利于患者的术后恢复。

#### 参 考 文 献(References)

- [1] Cheng Jing-xing, Yao Li-li, Li He-yue, et al. Clinical Analysis of 5766 Cases of Cervical Cancer [J]. Journal of Practical Obstetrics and Gynecology, 2014, 30(10): 768-772
- [2] Chang L, Ho SY, Yeh SA, et al. An innovative method to acquire the location of point A for cervical cancer treatment by HDR brachytherapy[J]. J Appl Clin Med Phys, 2016, 17(6): 6355

- [3] Lan-Tao TU, Si-yuan Zeng, Mei-rong Liang, et al. Comparative analysis of the complications of laparoscopic and abdominal cervical cancer surgery[J]. China Journal of Endoscopy, 2016, 22(07): 61-65
- [4] Zhao Ji-tong, Zhou Sheng-tao, Bian Ce, et al. Laparoscopy Versus Laparotomy for the Management of Early-stage Cervical Cancer: A Meta-analysis [J]. Journal of Practical Obstetrics and Gynecology, 2016, 32(08): 618-622
- [5] Xiang-qun Wei, Chun-xiu Wu, Hao Feng, et al. Comparative study of laparoscopic and transabdominal radical hysterectomy's impact on the cellular immunity[J]. China Journal of Endoscopy, 2016, 22(03): 1-6
- [6] Deng Kai-xian, Li Wei-li, Chen Chun-lin, et al. Investigation on invasion situation of cardinal ligament in stage I A2~II A2 cervical cancer and it's risk factors analysis[J]. Chongqing Medicine, 2016, 45(12): 1641-1644
- [7] Mo Xiaoliang, Luo Dian-zhong. New Insights into Cervical Cancer Screening Guidelines in the United States 2012 [J]. Cancer Res Prev Treat, 2014, 41(02): 188-192
- [8] Li Y, Huang K, Ji PL, et al. Cervical Infection of Oncogenic Human Papillomavirus (HPV) Types in Beijing, China [J]. Biomed Environ Sci, 2016, 29(10): 734-741
- [9] Wang Feng-di, Yang Hui yun. Comparison of laparoscopic radical laparotomy and laparotomy for cervical [J]. Jiangsu Med J, 2014, 40(22): 2781-2782
- [10] Huang Yan. Influence of Shenqi Fuzheng Injection Combined with Sanshenqi Oral Liquid on Cellular Immunity Function in Cervical Cancer Patients with Postoperative Radiotherapy [J]. Chinese Journal of Experimental Traditional Medical Formulae, 2014, 20(23):209-212
- [11] Xie F, Liu LB, Shang WQ, et al. The infiltration and functional regulation of eosinophils induced by TSLP promote the proliferation of cervical cancer cell[J]. Cancer Lett, 2015, 364(2): 106-117
- [12] Yu Yang, Sun Xiang. Effect of Th1 / Treg cell imbalance on clinical stage of cervical[J]. Journal of Practical Medicine, 2016, 32(06):999-1001
- [13] Ham B, Fernandez MC, D'Costa Z, et al. The diverse roles of the TNF axis in cancer progression and metastasis [J]. Trends Cancer Res, 2016, 11(1): 1-27
- [14] Tanaka T, Imamura T, Yoneda M, et al. Enhancement of active MMP release and invasive activity of lymph node metastatic tongue cancer cells by elevated signaling via the TNF- $\alpha$ -TNFR1-NF- $\kappa$ B pathway and a possible involvement of angiopoietin-like 4 in lung metastasis [J]. Int J Oncol, 2016, 49(4): 1377-1384
- [15] Matucci A, Cammelli D, Cantini F, et al. Influence of anti-TNF immunogenicity on safety in rheumatic disease: a narrative review[J]. Expert Opin Drug Saf, 2016, 15(sup1): 3-10
- [16] Wu L, Yao C, Xiong Z, et al. The effects of a picosecond pulsed electric field on angiogenesis in the cervical cancer xenograft models [J]. Gynecol Oncol, 2016, 141(1): 175-181
- [17] Tan Xi-feng, Xu Huijun, Guo Li-hua, et al. Changes of T lymphocytes immune functions of cervical cancer patients with postoperative infections and analysis of clinical significance [J]. Chin J Nosocomiol, 2015, 25(06): 1270-1272
- [18] Ma Dong, Yang Yan-yan, Zhao Li, et al. Expressions of IL-10 and IFN- $\gamma$  Genes and Their Methylation in Promoter Region in Cervical Tissues[J]. Chinese General Practice, 2014, 17(23): 2718-2721
- [19] Liu Y, Zhang J, Jia ZM, et al. The correlation between HLA-DRB1 and HLA-DQB1 gene polymorphisms and cytokines in HPV16 infected women with advanced cervical cancer[J]. Int J Clin Exp Med, 2015, 8(7): 11490-11495
- [20] Yang H, Cong Y, Wu T, et al. Clinical efficacy of Yingliu mixture combined with metimazole for treating diffuse goitre with hyperthyroidism and its impact on related cytokines [J]. Pharm Biol, 2017, 55(1): 258-263

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- [42] Yin RX, Li YY, Wu JZ, et al. Interactions between the apolipoprotein a1/c3/a5 haplotypes and alcohol consumption on serum lipid levels [J]. Alcohol ClinExp Res, 2013, 37(2): 234-243
- [43] Cohen JC, Stender S, Hobbs HH, et al. APOC3, coronary disease, and complexities of Mendelian randomization [J]. Cell Metab, 2014, 20(3): 387-389
- [44] TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute, Crosby J, Peloso GM, et al. Loss-of-function mutations in APOC3, triglycerides, and coronary disease[J]. N Engl J Med, 2014, 371: 22-31
- [45] Pollin TI, Damcott CM, Shen H, et al. A null mutation in human APOC3 confers a favorable plasma lipid profile and apparent cardioprotection[J]. Science, 2008, 322: 1702-1705
- [46] Gibson WT. Beneficial metabolic phenotypes caused by loss-of-function APOC3 mutations[J]. Clin Genet, 2015, 87(1): 31-32
- [47] GeachT.Genetics: APOC3 mutations lower CVD risk [J]. Nat Rev Cardiol, 2014, 11(9): 496-496
- [48] Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG, et al. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease [J]. N Engl J Med, 2014, 371: 32-41
- [49] Tachmazidou I, Dedoussis G, Southam L, et al. A rare functional cardioprotective APOC3 variant has risen in frequency in distinct population isolates[J]. Nat Commun, 2013, 4: 2872
- [50] Atzmon G, Rincon M, Schechter CB, et al. Lipoprotein genotype and conserved pathway for exceptional longevity in humans[J]. PLoSBiol, 2006, 4(4): e113
- [51] Kawakami A, Osaka M, Tani M, et al. Apolipoprotein CIII links hyperlipidemia with vascular endothelial cell dysfunction [J]. Circulation, 2008, 118(7): 731-742
- [52] Caron S, Staels B. Apolipoprotein CIII: a link between hypertriglyceridemia and vascular dysfunction[J]. Circ Res, 2008, 103(12): 1348-1350