

术前中性粒细胞对淋巴细胞比值与晚期胃癌临床病理特点关系的研究

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摘要 目的 探讨中性粒细胞对淋巴细胞比值(N/L 比值)与晚期胃癌临床病理特点的关系。方法 收集 2004 年 4 月至 2007 年 8 月间的 293 名 TNM III、IV 期行手术治疗的胃癌病例的临床病理资料,结合 N/L 比值进行分析。N/L 比值通过术前血常规检查中性粒细胞和淋巴细胞计数计算得出。结果 高 NLR 组 IV 期病例,R2 切除和联合脏器切除的比例更高,肿瘤直径更大,差别具有显著性($P=0.017, 0.007, 0.001$),而年龄、伴随疾病、肿瘤部位、Bormann 分型、病理分级、Lauren 分型、淋巴血管侵犯和术后化疗情况在两组间无明显差异。N/L 比值在 III、IV 期胃癌病例中差别具有显著性($P=0.018$)。结论 术前 N/L 比值跟晚期胃癌分期、手术根治程度相关,N/L 比值升高提示分期偏晚。N/L 比值可以作为一个简单可信的预后指标用来指导胃癌术后风险评估和治疗选择。

关键词 胃癌;中性粒淋巴细胞比值;炎症;预后因素

中图分类号 R735.2 文献标识码 A 文章编号:1673-6273(2012)11-2134-04

Preoperative Neutrophil to Lymphocyte Ratio is Associated with Clinicopathologic Features in Late Stage Gastric Cancer

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ABSTRACT Objective: To investigate the association between Preoperative Neutrophil to Lymphocyte Ratio (N/L ratio) and the clinicopathologic features in Late Stage Gastric Cancer. **Methods:** From April 2004 to August 2007, 293 patients who had undergone gastrectomy with curative intent for the AJCC/UICC TNM Stage III or IV gastric cancer were included. N/L ratio was calculated from lymphocyte and neutrophil counts on routine blood tests taken prior to surgery. **Results:** WBC and neutrophils increased with cancer stage, conversely lymphocytes decreased with stage. The N/L ratios in Stage IV were statistically higher than in Stage III ($P=0.018$). The patients of high NLR group had a more advanced stage (proportion of Stage IV in high NLR group vs. low NLR group, 58.1% vs. 43.5%; $P=0.017$), therefore they received higher rate of R2 resection and combined resection and had a larger tumor size than the patient of low NLR group. **Conclusion:** Preoperative Neutrophil to Lymphocyte Ratio is associated with clinicopathologic features and the elevated preoperative NLR predicts poor prognosis in patients undergoing potentially curative resection for late stage gastric cancer.

Key words: Gastric cancer; Neutrophil to lymphocyte ratio; Inflammation; Prognostic factor

Chinese Library Classification: R735.2 **Document code:** A

Article ID: 1673-6273(2012)11-2134-04

前言

胃癌是世界范围内的常见恶性肿瘤类型,是癌症相关死亡的重要原因^[1]。因此,研究胃癌的预后具有重要意义。目前,此类研究热点主要集中在寻找新的免疫学和组织学标记物。另外,关于宿主炎症反应状态和肿瘤上调炎症反应,因而增加转移倾向,促进血管生成和 DNA 损伤的研究正逐渐成为新的研究热点^[2,3]。有证据表明,肿瘤周围的炎细胞浸润对肿瘤的发展和预后具有重要作用。例如,肿瘤周围淋巴细胞浸润的患者比没有浸润的患者有更好的预后,而中性粒细胞浸润提示预后不良^[4]。

晚期恶性肿瘤全身炎症反应可以引起循环中白细胞水平

的特定改变,表现为中性粒细胞增加、淋巴细胞减少^[5]。数个研究揭示,中心粒细胞增多、淋巴细胞减少或 N/L 比值是预后相关的因素。关于胃癌,Hirashima^[6]等研究指出术前 N/L 比值跟早期胃癌预后相关,Yamanaka^[7]等研究指出 N/L 比值是 IV 期非手术治疗胃癌患者的独立的预后因素。最近,Mohri^[8]等在相对早期可手术治疗的胃癌病例研究中报告了类似的结果。

本研究的目的是探讨术前外周血 N/L 比值跟晚期胃癌临床病理资料的关系。

1 资料和方法

1.1 研究对象

选取 2004 年 4 月至 2007 年 8 月间在青岛大学医学院附属医院普外科行手术治疗的 381 例 III、IV 期胃癌病例。排除有胃切除手术史、术前放化疗或多发肿瘤的病例,排除开腹和仅行胃空肠吻合的病例,最终 293 例病例入选。

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(收稿日期:2012-01-07 接受日期:2012-01-31)

所有病例都根据肿瘤部位和病变范围行根治性的胃切除。有其他脏器侵犯转移的病例行联合脏器切除,如脾、胰、结肠和肝脏。病理学分期采用 AJCC 分期手册第六版标准。术后是否化疗根据器官功能、活动能力、术后并发症和患者意愿决定。大多数入选病例接受了 5-FU+ 顺铂方案。一半的 IV 期患者采用了多西他赛 / 顺铂 / 5-FU(DCF)方案。

1.2 资料收集

收集病人一般信息、手术方式、组织病理诊断资料。外周静脉血细胞分类计数在术前一周进行。白细胞正常值范围 4000-10000/mm³。N/L 比值通过中性粒细胞计数 / 淋巴细胞计数获得。病人在 N/L 比值中位数处分成两组。本研究经青岛大学医学院附属医院伦理委员会批准通过,所有患者均签署知情同意书。

1.3 统计分析

所有数据采用 spss17.0 进行统计分析。曼 - 惠特尼 U 检验 (The Mann-Whitney U Test)和卡方检验用来分析组间差异。检验水准定为 $P < 0.05$ 。

2 结果

293 例病人的临床病理资料见表 1。男性患者 193 名,女性

100 名,中位年龄 63 岁(范围 21-96 岁)。按照 TNM 分期,III、IV 期病例分别 143 例(48.8%)和 150 例(51.2%)。IV 期病例中 30 例(20%)为局部晚期,80%病例有远处转移,最常见转移部位为远处淋巴结(89 例,74.3%),其次是腹膜(43 例,35.8%)和肝脏(5 例,4.2%)。232 例病人手术为 R0 切除。1 例为胃近端切缘阳性,另外 1 例显微镜下胰腺切缘阳性。剩余的 59 例接受 R2 切除。腹膜是最常见的肿瘤残留部位(36 例,61.0%),其次是主动脉旁淋巴结(20.3%),胰头(13.6%),和区域淋巴结(5.1%)。

N/L 比值的中位数为 2.06(0.47-19.73),第 25 和 75 百分位数为 1.51 和 2.97。本研究中 155 例(52.9%)病例 N/L 比值 ≥ 2.0 ,为高 NLR 组,138 例 N/L 比值 < 2.0 为低 NLR 组。高 NLR 组男性比例更高(72.3%vs.58.7%),IV 期病例更多(58.1%vs.43.5%; $P=0.017$),因此 R2 切除和联合脏器切除的比例更高,肿瘤直径更大,而年龄、伴随疾病、肿瘤部位、Bormann 分型、病理分级、Lauren 分型,淋巴血管侵犯和术后化疗情况在两组间无明显差异(表 1)。比较不同分期中的白细胞、中性粒和淋巴细胞计数(表 2)。随着分期越晚白细胞和中性粒细胞增加,淋巴细胞计数减少。N/L 比值在 IV 期病例中显著高于 III 期($P=0.018$)。

表 1 按 N/L 比值分组的临床病理资料
Table 1 Clinicopathologic Characteristics According to N/L Ratio

| | Total (N=293) | N/L<2.0 (N=138) | N/L>2.0 (N=155) | P-value |
|--------------------|------------------|--------------------|--------------------|---------|
| Sex | | | | |
| Male | 193(65.9%) | 81(58.7%) | 112(73.3%) | 0.020 |
| Female | 100(34.1%) | 57(41.3%) | 43(27.7%) | |
| Agea | 63(21-96) | 62(27-96) | 64(21-85) | 0.800 |
| Comorbidity | | | | |
| No | 195(66.6%) | 89(65.4%) | 106(68.4%) | 0.561 |
| Yes | 98(33.4%) | 49(35.5%) | 49(31.6%) | |
| AJCC stage | | | | |
| III | 143(48.8%) | 78(56.5%) | 65(41.9%) | 0.017 |
| IV | 150(51.2%) | 60(43.5%) | 90(58.1%) | |
| Radicality | | | | |
| R0 | 232(79.2%) | 120(87.0%) | 112(72.3%) | 0.007 |
| R1 | 2(0.7%) | 1(0.7%) | 1(0.6%) | |
| R2 | 59(20.1%) | 17(12.3%) | 42(27.1%) | |
| Type of operation | | | | |
| Total | 129(44.0%) | 59(42.8%) | 70(45.2%) | 0.815 |
| Subtotal | 157(53.6%) | 75(54.3%) | 82(52.9%) | |
| Whipple | 7(2.4%) | 4(2.9%) | 3(1.9%) | |
| Combined resection | | | | |
| No | 173(59.0%) | 90(65.2%) | 83(53.5%) | 0.056 |
| Yes | 120(41.0%) | 48(34.8%) | 72(46.5%) | |

| | | | | |
|-------------------------|---------------|---------------|---------------|-------|
| Tumor location | | | | |
| U | 56(19.1%) | 29(21.0%) | 27(17.4%) | 0.754 |
| M | 64(21.8%) | 27(19.6%) | 37(23.9%) | |
| L | 161(54.9%) | 76(55.1%) | 85(54.3%) | |
| Whole | 12(4.1%) | 6(4.3%) | 6(3.9%) | 0.001 |
| Tumor size | | | | |
| | 6.0(2.0-20.0) | 5.5(2.0-20.0) | 6.6(2.5-19.0) | |
| Bormann type | | | | |
| Type 1 2 3 | 240(81.9%) | 112(81.2%) | 128(82.6%) | 0.870 |
| Type 4 | 53(18.1%) | 26(18.8%) | 27(17.4%) | |
| Differentiation | | | | |
| Differentiated | 73(24.9%) | 31(22.5%) | 42(27.1%) | 0.435 |
| Undifferentiated | 220(75.1%) | 107(77.5%) | 113(72.9%) | |
| Lauren classification | | | | |
| Intestinal | 126(50%) | 56(46.7%) | 70(53.0%) | 0.377 |
| Mixed diffuse | 126(50%) | 64(53.3%) | 62(47.0%) | |
| Lymphovascular invasion | | | | |
| No | 63(21.6%) | 30(21.7%) | 33(21.6%) | 1.000 |
| Yes | 228(78.4%) | 108(78.3%) | 120(78.4%) | |
| Perineural invasion | | | | |
| No | 51(17.5%) | 21(15.2%) | 30(19.6%) | 0.407 |
| Yes | 240(82.5%) | 117(84.4%) | 123(80.4%) | |
| Postoperative CTx | | | | |
| No | 110(37.5%) | 52(37.7%) | 58(37.4%) | 1.000 |
| Yes | 183(62.5%) | 86(62.3%) | 97(62.6%) | |

Note: a Values are median (range).

表 2 按分期分组的术前白细胞计数结果

Table 2 Results of Preoperative Blood Test According to Stage

| AJCC stage | III(n=143) | IV(n=150) | Total(n=293) | P-value |
|------------------------|------------------|------------------|------------------|---------|
| WBC(/mm ³) | 6900(3400-11900) | 7100(3400-14900) | 7000(3400-14900) | 0.366 |
| N(/mm ³) | 3800(800-8960) | 4240(1450-12420) | 3990(800-12420) | 0.081 |
| L(/mm ³) | 2000(360-4220) | 1900(450-4180) | 1960(360-4220) | 0.254 |
| N/L | 1.88(0.47-18.25) | 2.17(0.68-19.73) | 2.06(0.47-19.73) | 0.018 |

3 讨论

癌症和炎症的关系假说最先由 Rudolf Virchow 在 1863 年提出,他认为淋巴网状内皮细胞浸润反映了肿瘤起源自慢性炎症反应的部位^[2]。近年来,随着对恶变组织炎症微环境的认识不断加深, Virchow 的假说得到了支持,癌症和炎症之间的关系也用来指导肿瘤的预防和治疗。

肿瘤的浸润和转移能力是肿瘤自身特点和环境共同决定的^[3]。肿瘤的异常表型刺激炎细胞浸润,而肿瘤引起的组织破坏和崩解可以引起更广泛的非特异性炎症反应。结果,晚期肿瘤病人中中性粒细胞升高,淋巴细胞减少^[3]。这跟我们的研究结果一致,中性粒细胞和淋巴细胞计数和 N/L 比值同肿瘤分期相关(表 2)。

许多研究指出白细胞亚群的计数改变跟肿瘤预后相关。黑色素瘤、肾细胞癌和非小细胞肺癌的外周血中性粒细胞增多有重要的预后意义^[9-11]。淋巴细胞减少的程度跟晚期胰腺癌和直肠癌的生存率有关^[12,13]。N/L 比值升高在结直肠癌、肝内胆管癌、肝细胞癌和胰腺癌中有重要预后价值。关于胃癌有数个研究报道白细胞亚群的预后意义。Hirashima^[6]等 N/L 比值跟早期胃癌预后有关,但没有进行多变量分析。Yamanaka^[7]等分析 1220 例非手术治疗的 IV 期胃癌病例后指出 N/L 比值升高提示预后不良。最近,有两个研究术后 N/L 比值的预后意义。Aliustaoglu^[14]等的研究侧重于局部晚期胃癌经根治性手术切除和辅助化疗的病例,没有分析跟 TNM 分期的关系。Mohri^[8]等指出 N/L 比值是相对早期胃癌病例的独立预后因素(81%病例为 I、II 期)。本研究中术前 N/L 比值在晚期胃癌经手术切除的

病例中跟预后相关,这跟以前的研究结果相符。

N/L 比值升高患者预后不良的原因可能有以下几个方面:首先,N/L 比值增高反映了中性粒细胞对肿瘤的反应增高。循环中性粒细胞可以释放血管内皮生长因子(VEGF)等促血管生成的因子,因此中性粒细胞升高可能刺激肿瘤细胞血管生成,促进肿瘤进展^[15]。其次,N/L 比值升高患者都有淋巴细胞相对减少,可能影响淋巴细胞介导的抗肿瘤免疫反应。事实上,许多研究指出中性粒细胞升高抑制淋巴细胞,NK 细胞和活化的 T 细胞的细胞溶解活性^[16]。最后,目前研究和临床观察已形成共识,全身炎症反应跟癌症患者进行性的营养状态和器官功能减退相关,使预后不良^[17]。

N/L 比值跟肿瘤预后相关对于在肿瘤的预防和治疗中都有重要意义。实际上,大量正在进行的研究关注抗炎药物对肿瘤进展的效应。例如,许多数据证实,非甾体抗炎药(NSAIDs)减少结肠癌 40-50%的风险,可用来预防肺癌,食道癌和胃癌^[18,19]。促进淋巴细胞抗肿瘤免疫的疫苗的效果也正在评价中^[20]。根据以前的研究,N/L 比值可以作为手术后复发的预测指标。在决定是否对肿瘤病人进行化疗时可以将 N/L 比值升高作为一个参考指标。N/L 比值升高的患者更应该考虑结合化疗、放疗、免疫治疗等的综合治疗方式。

本研究存在一些问题,主要是样本含量较小,和研究的回顾性设计。本研究的对象只包括胃癌晚期病例中可能进行根治性切除的病例,入选的 IV 期病例不能完全代表全部此类病例。总之,本研究提示术前 N/L 比值跟肿瘤的临床分期和手术根治程度相关,N/L 比值升高提示分期偏晚,而 N/L 比值升高是否促进肿瘤的进展,尚需进一步研究。N/L 比值可能成为一个简单可信的预后指标,用来进行胃癌病人的风险分层。需要进一步的多中心研究来证实 N/L 比值的预后作用和临床意义。

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