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Prognostic factors of triple-negative inflammatory breast cancer based on SEER database

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Abstract: Objective To investigate the clinicopathological features and survival prognostic factors of patients with triple negative inflammatory breast cancer (TNIBC). **Methods** The data of patients with TNIBC from 2010 to 2015 were obtained from SEER database, and univariate analysis, multivariate analysis and Kaplan-Meier survival analysis were performed using the "survival" package in R statistical software. **Results** A total of 4 268 cases of inflammatory breast cancer were collected, including 1 023 cases of triple negative subtype. Compared with non-TNIBC patients, TNIBC patients had a lower proportion of whites in ethnic distribution, a higher proportion of histological grade Ⅲ, a higher proportion of AJCC stage Ⅲ, and more patients without distant metastases, and more likely to receive chemotherapy (P<0.05). Univariate Cox analysis showed that laterality, tumor diameter, AJCC stage, M stage, surgery and chemotherapy may be the influencing factors of overall survival (OS) (P <0.05). Multivariate Cox analysis showed that laterality, tumor diameter and surgery were independent influencing factors for survival and prognosis of TNIBC patients, and the smaller the tumor [28-989 mm, HR= 1.565, 95%CI:1.061-2.309, P=0.024;>989 mm, HR= 1.911, 95%CI:1.205-3.030, P=0.006], locating in the right side (HR=0.719, 95%CI:0.560-0.923, P=0.010), and the surgical treatment (HR=0.609, 95%CI:0.423-0.876, P=0.008) were associated with better prognosis. **Conclusion** Laterality, tumor diameter, and surgery are independent influencing factors for survival prognosis in patients with TNIBC, and the smaller the tumor, locating in the right side, and surgery are associated with better prognosis.

Keywords: Inflammatory breast cancer; Triple-negative breast cancer; SEER database; Prognostic factor; Laterality; Tumor diameter; Surgery

Inflammatory breast cancer (IBC) is a rare and aggressive disease, accounting for 2% to 4% of new cases. IBC is highly invasive, progresses rapidly, and has a mortality rate of 8% to 10% [1]. Breast cancers are categorized into different subtypes based on the status of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2), and the subtypes are related to treatment and prognosis [2]. Among these, the triple-negative subtype lacks ER, PR, and HER2, resulting in limited treatment options, significantly reduced survival time, and a higher likelihood of early recurrence and metastasis [3].

Current treatment guidelines for IBC recommend sequential triad therapy, which includes preoperative chemotherapy based on anthracyclines (including targeted therapy based on HER2 receptor status), followed by surgical excision, level I/II axillary lymph node dissection, and postoperative radiotherapy [4-5]. Hormonal therapy is administered based on the status of ER and PR [6]. Previous studies on IBC patients have shown that molecular subtypes can clinically predict survival outcomes in IBC, with the triple-negative subtype associated with the worst survival prognosis [7-9]. Triple-negative inflammatory breast cancer (TNIBC) represents a special group within breast cancer, and there is limited information on optimal treatment and clinical outcomes. This study aims to analyze TNIBC patients in the Surveillance, Epidemiology, and End Results (SEER) database to identify high-risk populations and develop targeted treatment strategies.

1 Data and Methods

1.1 General Data

This study utilized SEER*Stat software (version 8.4.0.1) to obtain data on TNIBC from the SEER database (https://seer.cancer.gov/) for the years 2010 to 2015.

Inclusion criteria: (1) diagnosis years from 2010 to 2015; (2) female; (3) breast cancer as the first and only cancer diagnosis; (4) T_{4d} staging; (5) negative for ER, PR, and HER2.

Exclusion criteria: (1) missing information; (2) cases

identified solely through death certificates or autopsies; (3) concurrent other tumors.

The endpoint was overall survival (OS), defined as the time from the date of diagnosis to the date of death from any cause or the date of the last follow-up.

1.2 Statistical Analysis

Data analysis was performed using R 4.2.1. Categorical data were expressed as cases (%), and inter-group comparisons were made using the chi-square test. Univariate and multivariate Cox regression risk models were used to analyze prognostic factors for TNIBC. Kaplan-Meier survival curves were plotted to assess the correlation between different clinical features and OS. P<0.05 was considered statistically significant.

2 Results

2.1 Clinical and Pathological Characteristics of Patients with TNIBC

A total of 4,268 patients with inflammatory breast cancer were identified from the SEER database from 2010 to 2015, among which 1,023 were TNIBC cases. Among TNIBC patients, 363 cases (35.5%) did not receive surgery, 514 cases (50.2%) did not receive radiotherapy, and 102 cases (10.0%) did not receive chemotherapy. TNIBC histological grades included 162 cases of grade I-II and 723 cases of grade III-IV. There was no difference between the two groups in terms of age, marital status, laterality, tumor diameter, N staging, surgery, and radiotherapy (P>0.05). Compared with non TNIBC patients, TNIBC patients have a lower proportion of Caucasians, a histological grading tendency towards grade III, a higher proportion of AJCC stage III, and more patients without distant metastasis, making them more likely to receive chemotherapy (P<0.05). **See Table 1.**

Tab.1 Clinicopathologic characteristics of patients with TNIBC [case (%)]

Indicators	Non-TNIBC (n = 3,245)	TNIBC (n = 1,023)	χ^2 value	P value
Age				
<56 years	1,428(44.0)	439(42.9)		
56-59 years	1,137(35.0)	363(35.5)	0.411	0.814
>69 years	680(21.0)	221(21.6)		
Race				
White	2,504(77.2)	713(69.7)		
Black	504(15.5)	244(23.9)	39.661	<0.001
Asian	201(6.2)	61(6.0)		
Others	36(1.1)	5(0.5)		
Marital status				
Married	2,353(72.5)	725(70.9)		
Unmarried	737(22.7)	242(23.7)	1.358	0.507
Others	155(4.8)	56(5.5)		
Laterality				
left	1,665(51.3)	534(52.2)	0.247	0.62
right	1580(48.7)	489(47.8)		
Histological grade				
I	106(3.3)	5(0.5)		
II	955(29.4)	157(15.3)		
III	1,687(52.0)	705(68.9)	103.344	<0.001
IV	37(1.1)	18(1.8)		
Others	460(14.2)	138(13.5)		
Diameter of tumor				
<28 mm	474(14.6)	136(13.3)	4.313	0.116
28-989 mm	1,857(57.2)	623(60.9)		
>989 mm	914(28.2)	264(25.8)		
AJCC Stage				
III	2,050(63.2)	705(68.9)	10.953	0.001
IV	1,195(36.8)	318(31.1)		
N Stage				
N_0	439(13.5)	143(14.0)		
N_1	1,482(45.7)	445(43.5)		
N_2	584(18.0)	164(16.0)	7.275	0.122
N_3	657(20.2)	243(23.8)		
Nx	83(2.6)	28(2.7)		
M Stage				
M_0	2,050(63.2)	705(68.9)	10.953	0.001
M_1	1,195(36.8)	318(31.1)		
Surgery	2,090(64.4)	660(64.5)	0.004	0.949
Radiotherapy	1,675(51.6)	509(49.8)	1.08	0.299
Chemotherapy	2,676(82.5)	921(90.0)	33.586	<0.001

Note: Nx indicated lymph node metastasis was unknown.

2.2 Univariate and Multivariate Cox Analysis of Prognostic Factors Affecting TNIBC Patients

Univariate Cox regression analysis showed that laterality, tumor diameter, AJCC staging, M staging, surgery, and chemotherapy may be influencing factors for OS (P<0.05). **See Table 2.** Multivariate Cox analysis revealed that laterality, tumor diameter, and surgery were independent risk factors affecting the survival prognosis of TNIBC patients, with smaller tumors, right-sided tumors, and surgical treatment associated with better prognosis (P<0.05). **See Table 3.**

2.3 Survival Comparisons of Independent Prognostic Factors in TNIBC Patients

Based on the independent prognostic factors obtained from multivariate Cox analysis, Kaplan-Meier survival curves were drawn for the population in this study. Smaller tumor size (P=0.011), right-sided tumors (P=0.004,7), and surgical treatment (P=0.000,25) were associated with better prognosis. **See Figure 1.**

Tab. 2 Univariate analysis of risk factors for TNIBC patient

Indicators	OS (mons)[a]	*HR* (95% *CI*)	*P* value	Indicators	OS (mons)[a]	*HR* (95% *CI*)	*P* value
Age				**Diameter of tumor**			
<56 years	75(66-82)	1	-	**<28 mm**	85(80-99)	1	-
56-69 years	68(62-81)	1.064(0.820-1.380)	0.643	**28-989 mm**	71(63-79)	1.491(1.022-2.175)	0.038
>69 years	67(49-94)	1.392(0.934-2.074)	0.104	**>989 mm**	61(53-69)	1.948(1.245-3.048)	0.003
Race				**N Stage**			
White	68(63-76)	1	-	**N_0**	75(66-85)	1	-
Black	78(61-83)	1.086(0.775-1.522)	0.630	**N_1**	74(63-83)	1.021(0.744-1.402)	0.897
Asian	75(63-NA)	0.796(0.477-1.329)	0.383	**N_2**	68(58-87)	1.050(0.693-1.589)	0.819

Others	69(61-NA)	1.302(0.415-4.084)	0.650	**N_3**	60(58-78)	1.181(0.766-1.820)	0.452
Marital status				**Nx**	44(44-NA)	3.684(1.320-10.277)	0.013
Married	73(64-79)	1	-	**M Stage**			
Unmarried	67(61-83)	0.958(0.717-1.281)	0.772	**M_0**	73(66-80)	1	-
Others	71(59-100)	1.207(0.733-1.986)	0.460	**M_1**	54(51-74)	1.563(1.036-2.356)	0.033
Laterality				**Surgery**			
left	66(60-71)	1	-	**No**	61(54-69)	1	-
right	77(70-85)	0.700(0.546-0.897)	0.004	**Yes**	74(67-82)	0.542(0.389-0.755)	<0.001
Histological grade				**Radiotherapy**			
I	73(NA)	1	-	**No**	67(61-75)	1	-
II	74(61-91)	0.680(0.093-4.982)	0.705	**Yes**	74(66-82)	0.783(0.610-1.011)	0.061
III	71(66-80)	0.769(0.107-5.506)	0.794	**Chemotherapy**			
IV	62(28-NA)	1.434(0.172-11.946)	0.739	**No**	44(42-NA)	1	-
Others	67(54-93)	0.866(0.118-6.364)	0.887	**Yes**	71(66-78)	0.446(0.228-0.874)	0.019
AJCC Stage							
III	73(66-80)	1	-				
IV	54(51-74)	1.563(1.036-2.356)	0.033				

Note: [a] meant the data was represent in the form of $M(P_{25}, P_{75})$. Nx indicated lymph node metastasis was unknown.

Tab.3 multivariate analysis of risk factors for TNIBC patients

Pathological features	*HR*(95%*CI*)	*P* value	Pathological features	*HR*(95%*CI*)	*P* value
Laterality			**M Stage**		
Left	1	-	**M_0**	1	-
Right	0.719(0.560-0.923)	0.010	**M_1**	1.299(0.849-1.987)	0.228
Diameter of tumor			**Surgery**		
<28 mm	1	-	**No**	1	-
28-989 mm	1.565(1.061-2.309)	0.024	**Yes**	0.609(0.423-0.876)	0.008
>989 mm	1.911(1.205-3.030)	0.006	**Chemotherapy**		
AJCC Stage			**No**	1	-
III	1	-	**Yes**	0.581(0.280-1.202)	0.143
IV	1.299(0.849-1.987)	0.228			

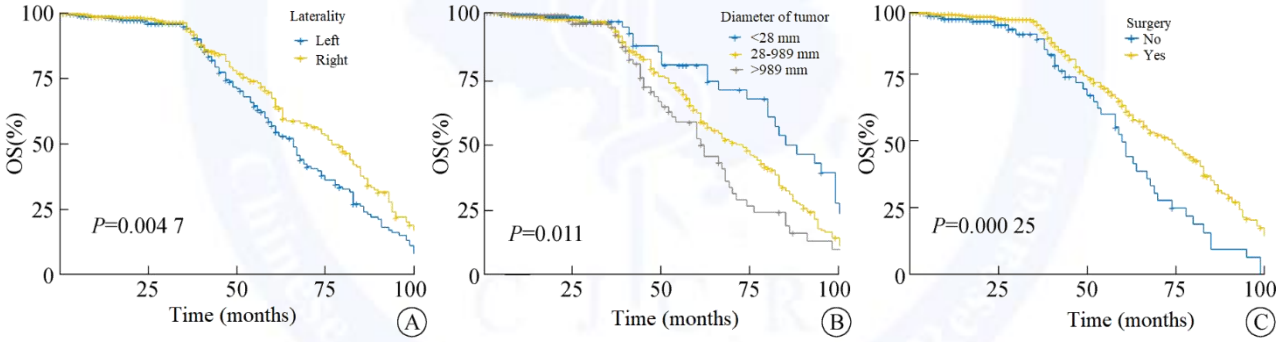

Fig. 1 Survival curves of TNIBC patients with different clinical characteristics

3 Discussion

The treatment methods for Inflammatory Breast Cancer (IBC) are multimodal, including systemic chemotherapy, mastectomy, and radiation therapy. Historically, patients with IBC have primarily received mastectomy. This study showed that surgery could help TNIBC patients to improve the survival. Research indicated that surgical resection can enhance the 5-year OS for IBC patients and reduce tumor-specific mortality rates [8-10]. Considering the cortical lymphatic vessel cancer thrombus and the high recurrence rate of IBC, surgically removing the tumor will undoubtedly lower the recurrence rate [7], which also supports the conclusions of this study. A retrospective analysis of hormone receptor-positive HER2-negative advanced breast cancer found that patients who received resection of the primary tumor had better survival outcomes, and those with isolated bone metastases tended to favor breast-conserving surgery [11].

In this study, chemotherapy was shown to improve the survival prognosis of patients with TNIBC. IBC is a systemic disease, and local regional treatment is insufficient to prevent distant metastasis. Therefore, systemic chemotherapy has been combined with surgery, radiotherapy, hormonal therapy, and molecular targeted therapy. A single-arm study that included 19 patients with TNIBC reported that the pathological complete response (pCR) rate reached 42% with treatment using panitumumab, carboplatin, paclitaxel, docetaxel, and cyclophosphamide [12]. Currently, there is no data from large randomized controlled trials specifically for IBC. Based on the international consensus on IBC [4], it is generally recommended that preoperative systemic treatment should be administered. This includes sequential therapy based on anthracycline and taxane chemotherapy, with or without carboplatin. The MD

Anderson Cancer Center has adopted a regimen of weekly paclitaxel or dose-dense paclitaxel followed by standard anthracycline and cyclophosphamide (AC) therapy (or dose-dense AC regimen) for TNIBC [13]. Reports from within the country have also demonstrated the efficacy of this chemotherapy regimen [14].

Data from the SEER database show that the combination of surgery and radiotherapy significantly improves the 5-year OS of 15% of IBC patients [15]. However, in this study, radiotherapy was not an independent prognostic factor for TNIBC patients. The impact of radiotherapy on breast cancer prognosis remains controversial. Incorporating radiotherapy as part of the "tri-modality treatment" for IBC has been shown to provide survival advantages. Patients completing tri-modality treatment had a 10-year OS of 37.3%, compared to 28.5% for those who only underwent surgery/chemotherapy [16]. Several retrospective studies have evaluated the role of definitive local treatment in newly diagnosed metastatic IBC patients, suggesting that this approach may be associated with improved overall survival and local disease control [17-18]. However, some studies do not support the positive impact of radiotherapy on breast cancer patients. Data from a large randomized trial indicated that the OS of newly diagnosed stage IV breast cancer patients was not improved after the local regional treatment. Although local regional treatment improved local disease control, it did not have an overall impact on patients' quality of life [19].

Previous studies have pointed out that radiation-related cardiac toxicity may diminish the survival benefits associated with improved local disease control, and this negative effect is related to the radiation dose to the heart [20-22]. In this article, laterality was identified as an independent prognostic factor for TNIBC patients, with better prognosis for right-sided tumors; however, the presence or absence of radiotherapy had little effect on overall survival. The speculated reason is that radiotherapy for left breast tumors increases cardiac toxicity. Thus, minimizing incidental cardiac exposure while ensuring adequate coverage of the target volume remains a challenging issue to enhance the efficacy of radiotherapy.

Due to its aggressiveness and the ineffectiveness of endocrine and anti-HER2 therapies, TNIBC is particularly challenging to treat. The search for specific kinase inhibitors has become a new approach in treating the current triple-negative subtype. Research has shown that Syndecan-1 is expressed at higher levels in TNIBC tissues compared to non-TNIBC tissues. Syndecan-1 acts as a novel tissue biomarker and a regulator of the tumor stem cell phenotype in TNIBC through the interleukin (IL)-6/signal transducer and activator of transcription (STAT)3, Notch, and epidermal growth factor receptor (EGFR) signaling pathways, thus becoming a promising therapeutic target for TNIBC [23]. Another preclinical study indicated that dasatinib (a p-Src inhibitor) and U0126 (a p-Erk1/2 inhibitor) downregulated the expression of cathepsin B (CTSB) in TNIBC (SUM149 cell line), thereby affecting tumor cell invasion and metastasis [24]. Interestingly, IL-8 and monocyte chemoattractant protein-1 (MCP-1)/chemokine CCL2 could reverse the downregulation effect of dasatinib and U0126, increasing tumor cell invasiveness [25]. Therefore, targeting cytokines IL-8 and MCP-1/CCL2 and related signaling molecules may represent a promising therapeutic strategy for TNIBC patients. These studies provide better treatment prospects for TNIBC patients.

In summary, laterality, tumor diameter, and surgery are independent risk factors affecting the survival prognosis of TNIBC patients, with smaller tumors located on the right side and surgical treatment being associated with better prognosis.

The authors report no conflict of interest

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·论　著·

基于 SEER 数据库分析三阴性炎性乳腺癌的预后因素

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摘要：目的　探讨三阴性炎性乳腺癌（TNIBC）患者的临床病理特征及生存预后因素。**方法**　从 SEER 数据库获取 2010 年至 2015 年 TNIBC 患者的病例，利用 R 统计软件中“survival”包进行单因素分析、多因素分析及 Kaplan-Meier 生存分析。**结果**　共收集炎性乳腺癌病例 4 268 例，其中 TNIBC 1 023 例。与非 TNIBC 患者相比，TNIBC 患者中白人占比较低，组织学分级倾向Ⅲ级，AJCC 分期Ⅲ期占比较高，未发生远处转移者更多，更容易接受化疗（P<0.05）。单因素 Cox 分析显示，偏侧性、肿瘤直径、AJCC 分期、M 分期、手术和化疗可能是总生存期（OS）的影响因素（P<0.05）。多因素 Cox 分析显示，偏侧性、肿瘤直径和手术是 TNIBC 患者 OS 的独立影响因素，且肿瘤直径越小[28～989 mm，HR=1.565，95%CI：1.061～2.309，P=0.024；>989 mm，HR=1.911，95%CI：1.205～3.030，P=0.006]、居于右侧（HR=0.719，95%CI：0.560～0.923，P=0.010）、手术治疗（HR=0.609，95%CI：0.423～0.876，P=0.008）与更好的预后相关。**结论**　偏侧性、肿瘤直径和手术是影响 TNIBC 患者生存预后的独立因素，且肿瘤小、居于右侧、手术治疗与更好的预后相关。

关键词： 炎性乳腺癌；三阴性乳腺癌；SEER 数据库；预后因素；偏侧性；肿瘤直径；手术治疗

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Prognostic factors of triple-negative inflammatory breast cancer based on SEER database

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Abstract: Objective　To investigate the clinicopathological features and survival prognostic factors of patients with triple-negative inflammatory breast cancer (TNIBC). **Methods**　The data of patients with TNIBC from 2010 to 2015 were obtained from SEER database, and univariate analysis, multivariate analysis and Kaplan-Meier survival analysis were performed using the “survival” package in R statistical software. **Results**　A total of 4 268 cases of inflammatory breast cancer were collected, including 1 023 cases of triple-negative subtype. Compared with non-TNIBC patients, TNIBC patients had a lower proportion of whites in ethnic distribution, a higher proportion of histological grade Ⅲ, a higher proportion of AJCC stage Ⅲ, and more patients without distant metastases, and more likely to receive chemotherapy (P<0.05). Univariate Cox analysis showed that laterality, tumor diameter, AJCC stage, M stage, surgery and chemotherapy may be the influencing factors of overall survival (OS) (P<0.05). Multivariate Cox analysis showed that laterality, tumor diameter and surgery were independent risk factors for OS in TNIBC patients, and the smaller the tumor (28-989 mm, HR=1.565, 95%CI: 1.061-2.309, P=0.024; >989 mm, HR=1.911, 95%CI: 1.205-3.030, P=0.006), locating in the right side (HR=0.719, 95%CI: 0.560-0.923, P=0.010), and the surgical treatment (HR=0.609, 95%CI: 0.423-0.876, P=0.008) were associated with better prognosis. **Conclusion**　Laterality, tumor diameter, and surgery are independent influencing factors for survival prognosis in patients with TNIBC, and the smaller

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the tumor, locating in the right side, and surgery are associated with better prognosis.

Keywords: Inflammatory breast cancer; Triple-negative breast cancer; SEER database; Prognostic factor; Laterality; Tumor diameter; Surgery

炎性乳腺癌(inflammatory breast cancer, IBC)是一种罕见且进展迅速的疾病,占乳腺癌新发病例的2%~4%。IBC 侵袭性高,病程进展快,其死亡人数占乳腺癌的 8%~10%[1]。乳腺癌依据雌激素受体(estrogen receptor, ER)、孕激素受体(progesterone receptor, PR)和人表皮生长因子受体 2 (human epidermal growth factor receptor 2, HER2)状态分为不同亚型,与治疗和预后相关[2]。其中,三阴性亚型缺乏 ER、PR 及 HER2,治疗方法选择有限,生存期较低,并且容易发生早期复发和转移[3]。

目前 IBC 的治疗指南推荐序贯三联治疗,包括术前基于蒽环类药物的化疗(包括根据 HER2 受体状态的靶向治疗),然后进行全乳房切除术和Ⅰ/Ⅱ级腋窝淋巴结清扫术和乳房切除术后放疗[4-5]。根据 ER 和 PR 的状态进行激素治疗[6]。先前对 IBC 患者的研究表明,分子亚型在临床上可用于预测 IBC 的生存结果,三阴性亚型与最差的生存预后相关[7-9]。炎性乳腺癌三阴性亚型(triple-negative subtype of IBC, TNIBC)是乳腺癌一个特殊群体,最佳治疗和临床结局的信息较少。本研究旨在对美国监测、流行病学和结果(The Surveillance, Epidemiology, and End Results, SEER)数据库中的 TNIBC 患者进行分析,识别高危人群并制定针对性的治疗策略。

1　资料与方法

1.1　一般资料　本研究从 SEER 数据库(https://seer.cancer.gov/)获取 2010 年至 2015 年 TNIBC 的数据。纳入标准:(1) 诊断年份为 2010 年至 2015 年;(2) 女性;(3) 乳腺癌作为第一和唯一的癌症诊断;(4) T_{4d}分期;(5) ER、PR 和 HER2 均为阴性。排除标准:(1) 信息缺失;(2) 仅通过死亡证明或尸检获得的病例。事件终点为总生存期(overall survival, OS),OS 被定义为诊断日期与任何原因死亡日期或最后一次随访之间的时间段。

1.2　统计学方法　采用 R4.2.1 软件进行数据分析。计数资料以例(%)表示,组间比较采用χ^2 检验。不符合正态分布的计量资料以 $M(P_{25},P_{75})$表示。采用单因素和多因素 Cox 回归风险模型分析 TNIBC 的预后因素。采用 Kaplan-Meier 法绘制不同临床特征患者的生存曲线。$P<0.05$ 为差异有统计学意义。

2　结　果

2.1　TNIBC 患者的临床病理特征(表 1)　从 SEER 数据库中获得了 IBC 患者 4 268 例,其中 TNIBC 1 023例。TNIBC 患者中分别有 363 例(35.5%)、514 例(50.2%)和 102 例(10.0%)未接受手术、放疗和化疗。

表 1　TNIBC 患者的临床病理特征　[例(%)]
Tab. 1　Clinicopathologic characteristics of patients with TNIBC　[case (%)]

项目	非 TNIBC (n=3 245)	TNIBC (n=1 023)	χ^2 值	P 值
年龄				
<56 岁	1 428(44.0)	439(42.9)		
56~59 岁	1 137(35.0)	363(35.5)	0.411	0.814
>69 岁	680(21.0)	221(21.6)		
种族				
白人	2 504(77.2)	713(69.7)		
黑人	504(15.5)	244(23.9)	39.661	<0.001
亚裔	201(6.2)	61(6.0)		
其他	36(1.1)	5(0.5)		
婚姻状况				
已婚	2 353(72.5)	725(70.9)		
未婚	737(22.7)	242(23.7)	1.358	0.507
其他	155(4.8)	56(5.5)		
偏侧性				
左侧	1 665(51.3)	534(52.2)	0.247	0.620
右侧	1 580(48.7)	489(47.8)		
组织学分级				
Ⅰ	106(3.3)	5(0.5)		
Ⅱ	955(29.4)	157(15.3)		
Ⅲ	1 687(52.0)	705(68.9)	103.344	<0.001
Ⅳ	37(1.1)	18(1.8)		
其他	460(14.2)	138(13.5)		
肿瘤直径				
<28 mm	474(14.6)	136(13.3)		
28~989 mm	1 857(57.2)	623(60.9)	4.313	0.116
>989 mm	914(28.2)	264(25.8)		
AJCC 分期				
Ⅲ	2 050(63.2)	705(68.9)	10.953	0.001
Ⅳ	1 195(36.8)	318(31.1)		
N 分期				
N_0	439(13.5)	143(14.0)		
N_1	1 482(45.7)	445(43.5)		
N_2	584(18.0)	164(16.0)	7.275	0.122
N_3	657(20.2)	243(23.8)		
N_x	83(2.6)	28(2.7)		
M 分期				
M_0	2 050(63.2)	705(68.9)	10.953	0.001
M_1	1 195(36.8)	318(31.1)		
手术	2 090(64.4)	660(64.5)	0.004	0.949
放疗	1 675(51.6)	509(49.8)	1.080	0.299
化疗	2 676(82.5)	921(90.0)	33.586	<0.001

注:N_x 为淋巴结转移情况未知。

TNIBC 组织学分级Ⅰ、Ⅱ级 162 例，Ⅲ、Ⅳ级 723 例。两组患者在年龄、婚姻、偏侧性、肿瘤直径、N 分期、手术和放疗方面差异无统计学意义（$P>0.05$）。与非 TNIBC 患者相比，TNIBC 患者中白种人占比较低，组织学分级倾向Ⅲ级，AJCC 分期Ⅲ期占比较高，未发生远处转移者更多，更容易接受化疗（$P<0.05$）。

2.2　单因素、多因素 Cox 回归分析影响 TNIBC 患者预后的因素　单因素 Cox 回归分析结果显示，偏侧性、肿瘤直径、AJCC 分期、M 分期、手术和化疗可能是 OS 的影响因素（$P<0.05$）。见表 2。多因素 Cox 分析显示，偏侧性、肿瘤直径和手术是 TNIBC 患者 OS 预后的独立影响因素，且肿瘤直径越小、居于右侧、手术治疗与更好的预后相关（$P<0.05$）。见表 3。

2.3　TNIBC 患者独立预后因素的生存比较　基于多因素 Cox 分析得出的独立预后因素，进行 Kaplan-Meier 生存曲线分析，结果显示，肿瘤小（$P=0.011$）、居于右侧（$P=0.004\ 7$）、手术治疗（$P=0.000\ 25$）与更好的 OS 相关。见图 1。

表 2　TNIBC 患者 OS 影响因素的单因素 Cox 分析

Tab. 2　Univariate Cox analysis of influencing factors of OS in patients with TNIBC

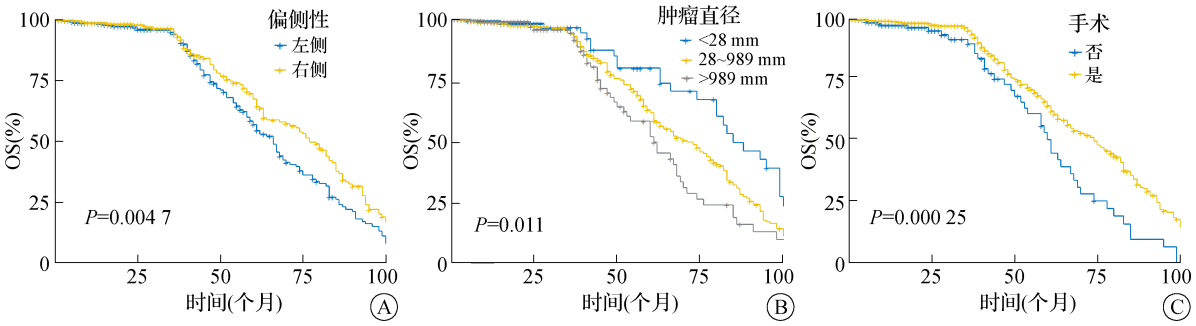
项目	OS[月，$M(P_{25},P_{75})$]	*HR*(95%*CI*)	*P* 值	项目	OS[月，$M(P_{25},P_{75})$]	*HR*(95%*CI*)	*P* 值
年龄				肿瘤直径			
<56 岁	75(66,82)	1	—	<28 mm	85(80,99)	1	—
56~69 岁	68(62,81)	1.064(0.820~1.380)	0.643	28~989 mm	71(63,79)	1.491(1.022~2.175)	0.038
>69 岁	67(49,94)	1.392(0.934~2.074)	0.104	>989 mm	61(53,69)	1.948(1.245~3.048)	0.003
种族				N 分期			
白人	68(63,76)	1	—	N_0	75(66,85)	1	—
黑人	78(61,83)	1.086(0.775~1.522)	0.630	N_1	74(63,83)	1.021(0.744~1.402)	0.897
亚裔	75(63,NA)	0.796(0.477~1.329)	0.383	N_2	68(58,87)	1.050(0.693~1.589)	0.819
其他	69(61,NA)	1.302(0.415~4.084)	0.650	N_3	60(58,78)	1.181(0.766~1.820)	0.452
婚姻状态				N_x	44(44,NA)	3.684(1.320~10.277)	0.013
已婚	73(64,79)	1	—	M 分期			
未婚	67(61,83)	0.958(0.717~1.281)	0.772	M_0	73(66,80)	1	—
其他	71(59,100)	1.207(0.733~1.986)	0.460	M_1	54(51,74)	1.563(1.036~2.356)	0.033
偏侧性				手术			
左侧	66(60,71)	1	—	否	61(54,69)	1	—
右侧	77(70,85)	0.700(0.546~0.897)	0.004	是	74(67,82)	0.542(0.389~0.755)	
组织学分级				放疗			<0.001
Ⅰ	73(NA)	1	—	否	67(61,75)	1	—
Ⅱ	74(61,91)	0.680(0.093~4.982)	0.705	是	74(66,82)	0.783(0.610~1.011)	0.061
Ⅲ	71(66,80)	0.769(0.107~5.506)	0.794	化疗			
Ⅳ	62(28,NA)	1.434(0.172~11.946)	0.739	否	44(42,NA)	1	—
其他	67(54,93)	0.866(0.118~6.364)	0.887	是	71(66,78)	0.446(0.228~0.874)	0.019
AJCC 分期							
Ⅲ	73(66,80)	1	—				
Ⅳ	54(51,74)	1.563(1.036~2.356)	0.033				

注：NA 表示缺失值；N_x 为淋巴结转移情况未知。

表 3　TNIBC 患者 OS 影响因素的多因素 Cox 分析

Tab. 3　Multivariate Cox analysis of influencing factors of OS in patients with TNIBC

病理特征	*HR*(95%*CI*)	*P* 值	病理特征	*HR*(95%*CI*)	*P* 值
偏侧性			M 分期		
左侧	1	—	M_0	1	—
右侧	0.719(0.560~0.923)	0.010	M_1	1.299(0.849~1.987)	0.228
肿瘤直径			手术		
<28 mm	1	—	否	1	—
28~989 mm	1.565(1.061~2.309)	0.024	是	0.609(0.423~0.876)	0.008
>989 mm	1.911(1.205~3.030)	0.006	化疗		
AJCC 分期			否	1	—
Ⅲ	1	—	是	0.581(0.280~1.202)	0.143
Ⅳ	1.299(0.849~1.987)	0.228			



注:A 为偏侧性;B 为不同肿瘤直径;C 为是否手术。

图 1　不同临床特征的 TNIBC 患者的生存曲线

Fig. 1　Survival curves of TNIBC patients with different clinical characteristics

3　讨　论

IBC 的治疗方法是多模式的,包括全身化疗、乳房切除术和放射治疗。从历史上看,IBC 患者主要接受乳房切除术治疗。本研究显示,手术有助于提高 TNIBC 患者的生存期。研究表明进行乳房切除术可以改善 IBC 患者的 5 年总生存率,降低肿瘤特异性死亡率[8-10]。考虑到 IBC 真皮层淋巴管大量癌栓和高复发率,手术切除肿瘤肯定会降低复发率[7],本研究也印证了该结论。对性激素受体阳性 HER2 阴性晚期乳腺癌回顾分析发现,原发灶肿瘤切除患者有更好的生存预后,并且单纯骨转移者倾向于保乳术式[11]。

本研究中,化疗能够改善 TNIBC 患者的生存预后。IBC 是一种全身性疾病,局部区域治疗不足以预防远处转移。因此,全身化疗已与手术、放疗、激素治疗和分子靶向治疗相结合。一项纳入 19 例 TNIBC 患者的单臂研究认为,接受帕尼单抗、卡铂、紫杉醇、多西紫杉醇和环磷酰胺治疗,病理完全缓解率(pCR)达到 42%[12]。目前没有针对 IBC 的大型随机对照试验的数据,基于国际上对 IBC 的共识[4],普遍认为应在手术前进行全身治疗,包括基于蒽环类药物和紫杉烷类化疗的序贯治疗,联合或不联合卡铂。美国 MD 安德森癌症中心针对 TNIBC 采用每周 1 次紫杉醇或剂量密集的紫杉醇,然后是标准蒽环类药物联合环磷酰胺方案(AC)(或剂量密集的 AC 方案)[13]。国内也有报道表明了该化疗方案的有效性[14]。

来自 SEER 数据库的数据显示,手术结合放疗显著改善了 15%的 IBC 患者的 5 年生存率[15]。然而,本研究中放疗并不是 TNIBC 患者的独立预后因素。放疗对乳腺癌预后的影响存在争议。将放疗作为 IBC "三模式治疗"的一部分,已被证明可带来生存优势,完成三模式治疗的患者 10 年生存率为 37.3%,而仅接受手术/化疗的患者为 28.5%[16]。多项回顾性研究评估了新诊断的转移性 IBC 患者中确定性的局部治疗作用,并提出这种方法可能与改善 OS 和局部疾病控制有关[17-18]。然而,也有研究不支持放疗对乳腺癌患者带来的积极影响。一项大型随机试验的数据显示,在接受局部区域性治疗后,新诊断的Ⅳ期乳腺癌患者的总生存率没有改善,尽管局部区域性治疗可改善局部疾病控制,但对患者的生活质量没有整体影响[19]。

既往研究指出,辐射相关的心脏毒性可能会降低与局部区域控制改善相关的生存收益,且该负面损害与心脏辐射剂量相关[20-22]。本文中,偏侧性是 TNIBC 患者的独立预后因素,且右侧肿瘤预后较好,但放疗与否对 OS 影响不大。推测原因可能是对左乳肿瘤放疗增加了心脏毒性。因此,尽量减少心脏的偶然照射,同时保持目标体积的充分覆盖仍然是提高放疗有效性需要攻克的难题。

由于其侵袭性以及内分泌和抗 HER2 治疗的无效性,TNIBC 治疗起来特别具有挑战性。寻找特定激酶抑制剂已成为当前三阴性亚型治疗的新思路。研究表明, Syndecan-1 在 TNIBC 组织中的表达高于非 TNIBC 组织,Syndecan-1 通过白细胞介素(IL)-6/信号转导和转录活化因子(STAT)3,Notch 和表皮生长因子受体(EGFR)信号通路充当新型组织生物标志物和 TNIBC 的肿瘤干细胞表型调节剂,有希望成为 TNIBC 的治疗靶点[23]。另一项基础研究表明,达沙替尼(p-Src 的抑制剂)和 U0126(p-Erk1/2 的抑制剂)下调了 TNIBC(SUM149 细胞系)对半胱氨酸蛋白酶 CTSB 的表达,从而影响肿瘤细胞的侵袭和转移[24]。更有意思的是,IL-8 和单核细胞趋化蛋白 1(MCP-1)/趋化因子 2(CCL2)可以逆转达沙替尼和 U0126 的这种下调效应,增加肿瘤细胞侵袭性[25]。因此,靶向细胞因子 IL-8 和 MCP-1 / CCL2 以及相关的信号分子可能

成为 TNIBC 患者的有前途的治疗策略。这些研究给 TNIBC 患者带来了更好的治疗前景。

综上所述，偏侧性、肿瘤直径和手术是影响 TNIBC 患者生存预后的独立因素，且肿瘤越小、居于右侧、手术治疗与更好的预后相关。

利益冲突　无

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