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·临床研究·

应用经皮氩氦冷冻消融术姑息性治疗恶性实体肿瘤后肿瘤进展的相关因素分析*

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摘要 目的：分析应用经皮氩氦冷冻消融术姑息性治疗恶性实体肿瘤后肿瘤进展的相关因素。**方法**：回顾性搜集 2012 年 8 月-2017 年 6 月上海市第一人民医院收治的因患有恶性实体肿瘤行姑息性经皮氩氦冷冻消融术患者的相关临床资料，并随访至 2017 年 11 月，搜集患者随访结束时的临床资料。将总消融例数根据消融后肿瘤进展情况分为比较肿瘤进展和肿瘤非进展组，比较患者的一般临床特征。将消融后进展的病例列出，比较消融前和进展时相关检验结果差异，探寻肿瘤进展原因。**结果**：共 82 次经皮氩氦冷冻消融术在 2012 年 8 月 -2017 年 6 月间进行，35 名患者所行的 41 次消融被纳入本研究，所有病人接受的经皮氩氦冷冻消融术次数均不大于 2 次，41 次经皮氩氦冷冻消融术共消融 42 枚病灶，其中一次消融术同时消融了 2 枚肝内病灶。35 名患者按照肿瘤全身进展与否分为肿瘤进展组（n=26）及肿瘤非进展组（n=9），有统计学差异的指标包括：消融处为原发肿瘤，随访截止 / 进展时间，消融前至随访截止 / 肿瘤进展时存在化疗相关性粒细胞缺乏，消融前粒细胞与淋巴细胞比值（ratio of peripheral neutrophils to lymphocyte，NLR）>3。对于消融后判定为全身肿瘤进展的 30 次经皮氩氦冷冻消融术，对比消融前及进展时的各项指标，有统计学意义的指标是血浆白蛋白值和 NLR >3。最后，应用上述有统计学意义的计数资料通过 Cox 回归分析评定为肿瘤进展的 30 次消融的无进展生存时间，结果均无统计学意义。**结论**：作为综合治疗的一部分，氩氦冷冻消融术姑息性治疗恶性实体肿瘤后的肿瘤进展因素中，对于原发肿瘤的消融是肿瘤进展的不利因素，化疗相关性粒细胞缺乏、NLR>3、低血浆白蛋白水平是肿瘤进展的有利因素。

关键词：经皮氩氦冷冻消融术；肿瘤姑息治疗；化疗相关性粒细胞缺乏；粒细胞与淋巴细胞比值；血浆白蛋白

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Factors of Tumor Progression after Percutaneous Cryoablation for Non-radical Treatment of Solid Malignant Tumor*

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ABSTRACT Objective: To investigate the influence factors of tumor progression after percutaneous cryoablation for non-radical treatment of solid malignant tumor. **Methods:** We retrospectively analyzed parameters of all patients receiving cryoablation for non-radical treatment from Aug 2012 to Jun 2017, and provided follow-ups until Nov 2017. We separated the cryoablation into two groups by tumor progression to analyze the significance, and analyzed laboratory results before ablations and at the time of progression of the ablations applied to the whole-body tumor progression. **Results:** There were 82 cryoablations performed from August 2012 to June 2017. 41 times (35 patients, 42 lesions) of cryoablations remained according to the following conditions: uncontrolled distance lesions beside the ablation one(s) or a very large lesion which can't be ablated completely. Among the 41 cryoablations, no more than twice of the ablations were performed for one same patient. The two lesions that ablated in one of the cryoablation treatment were both hepatic lesions. 35 patients were separated into two groups by tumor progression of the whole body: progression group (n=26) and non-progression group (n=9). The statistical significant comparisons of the two groups included ablation for primary tumor, time of follow-up/progression, chemotherapy-induced neutropenia until follow-up/progression, neutrophil/lymphocyte>3 at pre-ablation period. We analyzed the lab results of the 30 ablations with the whole-body tumor progression before ablations and at the time of progression, and then separated them into two groups according to the time. The statistical significant comparisons of different times of the two groups included albumin, neutrophil/lymphocyte >3. Then for the progression-free survival of 30 ablations that applied to the whole-body tumor progression, the statis-

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tical significant comparisons in Table 2, including ablation for primary tumor, chemotherapy-induced neutropenia until progression and neutrophil/lymphocyte>3 at preablation period, were analyzed by using multivariate analysis with a Cox proportional- hazards model, estimating hazard ratios (HRs) and 95% confidence intervals (CIs), but none of them were statistical significant comparisons. **Conclusions:** For non-radical treatment of solid malignant tumors via percutaneous cryoablation with or without other anti-neoplastic treatments, ablation for primary tumor is a protective factor for tumor progression, and the prognostic factors for tumor progression include: chemotherapy-induced neutropenia, NLR>3, a low level of serum albumin.

Key words: Cryoablation; Non-radical treatment; Chemotherapy-induced neutropenia; Neutrophil to lymphocyte ratio; Serum albumin

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前言

对于大多数恶性实体肿瘤来说,手术切除是唯一可能治愈的治疗方式,但因为肿瘤的大小、位置、转移等原因,只有小部分患者能够接受根治性手术切除治疗。对于进展期恶性实体肿瘤,经皮氩氦冷冻消融术是肿瘤综合治疗的一部分。经皮氩氦冷冻消融术被证实对于多种器官肿瘤的消融均是安全有效的[1-6]。对于转移性恶性实体肿瘤,经皮氩氦冷冻消融术可以降低肿瘤负荷,为后续的化疗或放射治疗打下基础[7]。

有文献报道,对于进展期肝细胞癌患者,年龄、肿瘤直径、肿瘤位于门静脉旁及肝功能分级是氩氦冷冻消融联合肝动脉介入化疗栓塞术后肿瘤进展的影响因素[8]。但目前,只有较少的文章讨论氩氦冷冻消融后患者预后的影响因素,经皮氩氦冷冻消融术姑息性治疗恶性实体肿瘤后肿瘤进展的影响因素尚未完全明确。本研究探讨应用经皮氩氦冷冻消融术姑息性治疗恶性实体肿瘤后肿瘤进展的相关因素。

1 材料与方法

1.1 病例资料

回顾性搜集 2012 年 8 月 -2017 年 6 月上海市第一人民医院收治的因患有恶性实体肿瘤行姑息性经皮氩氦冷冻消融术患者的相关临床资料,并随访至 2017 年 11 月,搜集患者随访结束时的临床资料。纳入本研究的患者均存在未得到有效控制的消融处以外的病灶或无法彻底消融的原发病灶。所有患者消融术前均签署知情同意书。符合以下标准的实体肿瘤患者纳入本研究:存在未得到有效控制的消融处以外的病灶或无法彻底消融的原发病灶。

1.2 治疗方法

所有经皮氩氦冷冻消融术均在 CT 或 B 超引导下应用以氩气和氦气为基础的冷冻消融设备 (Galil Medical Ltd, Cryo-HIT, 以色列)进行。患者取合适体位,CT 或 B 超定位后消毒铺巾,定位点局部麻醉,经定位点应用消融针穿刺进入肿块内,消融针插入的数量和排布根据肿瘤周围血管、重要脏器结构、肿瘤结构、坏死情况等因素综合分析,并按照经验决定。消融针排布满意后,如消融肿块位置较为深在时应用湿纱布包扎穿刺点;如消融位置较为表浅,应用温水袋敷穿刺点,以免皮肤冻伤。按照氩气冷冻 8-15 分钟、氦气复温 3 分钟为一周期进行消融,每一周期预计氩气冷冻即将结束时复查 CT 或 B 超,明确冰球范围及周围情况。消融 2-3 周期后结束消融,逐个拔出消融针,压迫止血,包扎穿刺点。最后复查 B 超或 CT,明确消融范围和临近组织器官等情况。如无特殊处理,结束手术,将病人送回病房。患者术前影像学检查、术中消融情况及术后影像学检查对比如图 1 所示。

1.3 肿瘤进展的评价

肿瘤进展的评价按照 RECIST(Response Evaluation Criteria in Solid Tumors)1.1[9]标准进行评价。

1.4 统计学分析

采用 SPSS 20.0 进行统计学分析, 计量资料和计数资料的比较分别采用 t 检验和 x^2 检验,以 $P<0.05$ 为差异有统计学意义。Cox 比例风险回归模型应用风险比(HR)和 95 %可信区间(CI)评价,HR>1 考虑为危险因素。

2 结果

2.1 患者的基本信息

共 82 次经皮氩氦冷冻消融术在 2012 年 8 月 -2017 年 6 月间进行,41 次满足以下条件被纳入本研究:存在未得到有效控制的消融处以外的病灶或无法彻底消融的原发病灶。41 次消融术于 35 名患者中进行, 年龄 59.74± 10.75 岁, 身高 166.83± 1.98 cm,消融时体重 62.71± 11.08 kg,发病至消融时间 37.14± 41.50 个月。所有病人接受的经皮氩氦冷冻消融术次数均不大于 2 次,41 次经皮氩氦冷冻消融术共消融 42 枚病灶,其中一次消融术同时消融了 2 枚肝内病灶。41 次消融术均无围术期死亡及严重并发症发生,如:失血性休克、感染性休克、肠瘘、急腹症等。

41 次消融的消融部位分别为肝脏(n=19)、肺(n=10)、肾上腺(n=3)、胰腺(n=3)、腹腔内肿块(n=2)、体表肿块(n=2)、椎体(n=2)。对于肿瘤全身进展与否, 各消融位置无明显统计学差异。35 名患者肿瘤病理诊断如表 1 所示。

2.2 按照消融后进展与否分类对比

35 名患者按照肿瘤全身进展与否分为肿瘤进展组(n=26)及肿瘤非进展组(n=9),两组间各数据如表 2 所示。在对比的各项数据中,有统计学差异的指标包括:消融处为原发肿瘤,随访截止 / 进展时间, 消融前至随访截止 / 肿瘤进展时存在化疗相关性粒细胞缺乏, 消融前粒细胞与淋巴细胞比值 (ratio of peripheral neutrophils to lymphocyte,NLR)>3。

2.3 消融前与进展时检验结果的对比

对于消融后判定为全身肿瘤进展的 30 次经皮氩氦冷冻消融术,消融前及进展时的相关检验指标如表 3 所示。对比两个时间点的各项指标, 有统计学意义的指标是血浆白蛋白值和 NLR >3。

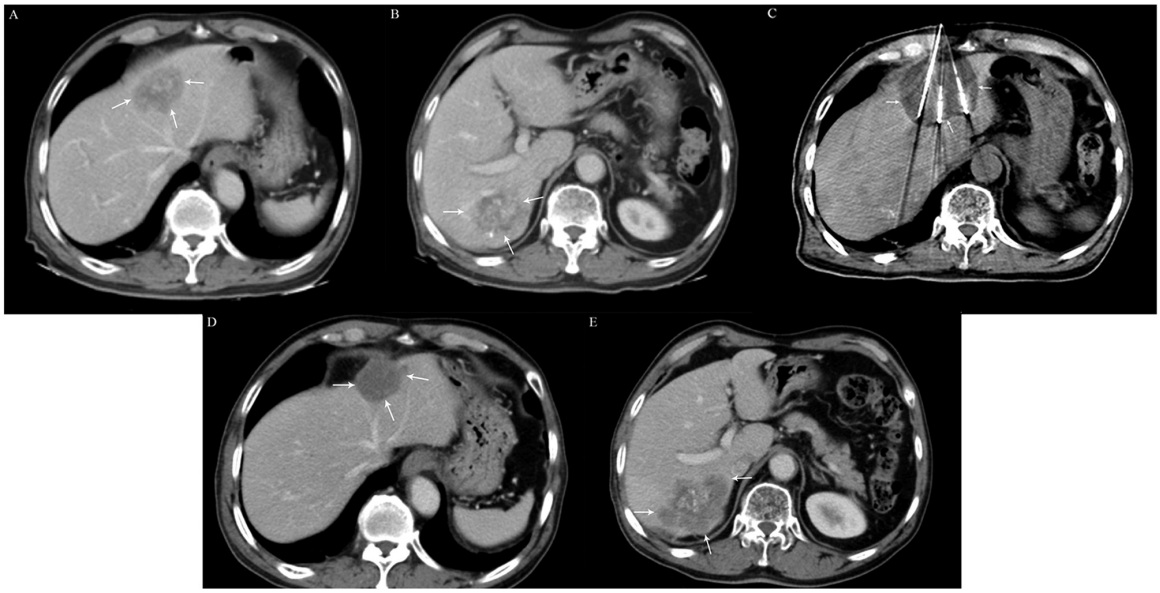

Fig.1 A patient with multiple metastatic liver adenocarcinoma from sigmoid colon received percutaneous cryoablation for the lesion of left lobe liver. several times of TACE were received previously. Axial contrast-enhanced CT image in the portal venous phase demonstrates the metastatic lesion of left lobe liver (a, arrow) which intended to received percutaneous cryoablation and another metastatic lesion of right lobe liver (b, arrow) which intended to handle afterward. Axial CT image (c) during cryoablation demonstrates a suitable position of cryoprobes and a big enough ablated rang. But this patient experienced agnogenic thrombocytopenia after cryoablation, and he refused to receive cryoablation once more for the lesion of right lobe liver. After one time of microwave ablation for the lesion of right lobe liver and one time of TACE, during 203 days from cryoablation to CT reexamination, axial contrast-enhanced CT image in the portal venous phase demonstrates a stable condition for the ablated lesion of left lobe liver which received cryoablation (d, arrow) and a tumor progression condition for the ablated lesion of left lobe liver which received microwave ablation (e, arrow).

表 1 病理诊断及对比

Table 1 Histological diagnosis and comparison

Diagnosis of primary tumor	Frequency	Recurrence	Recurrence rate
Colorectal adenocarcinoma	13	11	84.6 %
Hepatocellular carcinoma	3	1	33.3 %
Hepatic adenocarcinoma	2	1	50.0 %
Pulmonary adenocarcinoma	4	4	100.0 %
Pulmonary squamous cell carcinoma	1	1	100.0 %
Pancreatic carcinoma	3	1	33.3 %
Ureteral carcinoma	2	2	100.0 %
Endometrial cancer	2	2	100.0 %
Renal clear cell carcinoma	2	1	50.0 %
Chordoma	1	0	0.0 %
Malignant melanoma	1	1	100.0 %
Urachal carcinoma	1	1	100.0 %
Total	35	26	74.3 %

表 2 肿瘤进展组与肿瘤非进展组各项指标的对比

Table 2 Comparison of the parameters of progression group and non-progression group (separated by tumor progression of the whole body)

	Progression group (n=26)	Non-progression group (n=9)	P value
Sex (male)	16	6	0.783
Age (years)	60.58± 9.66	57.33± 13.82	0.444
Height at pre-ablation period (cm)	166.35± 8.81	168.22± 4.94	0.439
Body weight at pre-ablation period (kg)	62.54± 11.56	63.22± 10.20	0.876

Disease time until cryoablation (month)	39.58± 42.14	30.11± 41.18	0.563
Hypertension	10	1	0.104
Diabetes	4	1	0.747
Active lesions except ablated lesions (yes)	15	7	0.270
Ablation for primary tumor	6	6	0.020*
Oligometastasis	10	6	0.142
Gross tumor volume of ablation lesion(s)a (cm^3)	45.83± 103.03	151.57± 190.12	0.144
Close to big vesselb	8	5	0.190
Ablation for recurrent tumor	6	2	0.958
Number of cryoprobes	3.46± 2.06	3.89± 2.15	0.600
Ablation time (min)	20.88± 5.24	22.22± 4.41	0.498
Time of follow-up/progression (days)	234.42± 156.32	460.78± 301.40	0.006*
Other treatment after ablation within 8 weeks	16	5	0.753
How many types of treatment before ablation	1.23± 0.65	1.44± 0.73	0.416
How many types of treatment after ablation up to follow-up/progression	0.88± 0.52	1.00± 0.71	0.603
Chemotherapy-induced neutropenia a until follow-up/progression	16	2	0.038*
Fasting blood-glucose at pre-ablation period (mmol/L)	5.50± 2.43	5.47± 0.60	0.967
Albumin at pre-ablation period (g/L)	40.24± 4.11	39.63± 3.54	0.695
White blood cell at pre-ablation period (× 10^9/L)	5.01± 1.53	5.44± 1.64	0.473
Neutrophil at pre-ablation period (× 10^9/L)	2.98± 1.44	3.52± 1.44	0.340
Lymphocyte at pre-ablation period (× 10^9/L)	1.51± 0.56	1.40± 0.59	0.624
Neutrophil/lymphocyte at pre-ablation period	2.29± 1.74	3.10± 1.99	0.252
Neutrophil/lymphocyte>3 at pre-ablation period	3	4	0.044*
Prothrombin time at pre-ablation period (s)	11.45± 0.96	11.99± 2.25	0.500
Fibrinogen at pre-ablation period (g/L)	3.35± 0.64	3.59± 0.72	0.358
D-dimer at pre-ablation period (mg/L)	1.00± 0.92	0.81± 0.40	0.420
Abnormal fasting blood-glucose up to follow-up/progression	14	5	0.929
Fasting blood-glucose at endpoint of follow-up/progression (mmol/L)	5.87± 1.81	7.04± 3.30	0.192
Albumin at endpoint of follow-up/progression (g/L)	37.92± 3.93	37.60± 3.80	0.832
White blood cell at endpoint of follow-up/progression (× 10^9/L)	5.35± 1.22	9.19± 7.84	0.181
Neutrophil at endpoint of follow-up/progression (× 10^9/L)	3.49± 1.08	6.28± 4.91	0.128
Lymphocyte at endpoint of follow-up/progression (× 10^9/L)	1.35± 0.56	1.93± 2.17	0.454
Neutrophil/lymphocyte at endpoint of follow-up/progression	1.33± 0.21	1.24± 0.23	0.299
Neutrophil/lymphocyte>3 at endpoint of follow-up/progression	11	4	0.911
Prothrombin time at endpoint of follow-up/progression (s)	11.78± 1.02	12.42± 2.66	0.496
Fibrinogen at endpoint of follow-up/progression (g/L)	3.84± 1.12	3.62± 0.66	0.586
D-dimer at endpoint of follow-up/progression (mg/L)	1.09± 0.97	1.06± 0.62	0.919

Note: the results of likelihood ratio were choosed for x^2 test

* stands for that the comparison was statistically significant (P<0.05).

a volume=π× L× D× H/6

b stands for that the vessel's diameter was greater than 3 mm and the distance between vessel and tumor was less than 3 mm

2.4 影响无进展生存时间的因素

对于消融后判定为全身肿瘤进展的 30 次经皮氩氦冷冻消融术，为探寻影响其消融后至全身肿瘤进展的无进展生存时间（Progression-Free Survival，PFS）的因素，将表 2 中有统计学意义的计数资料以 Cox 比例风险回归模型分析，应用风险比（HR）和 95 %可信区间（CI）评价，结果如表 4 所示。消融处为原发肿瘤、消融前至随访截止 / 肿瘤进展时存在化疗相关性粒细胞缺乏、消融前 NLR >3 对于无病生存时间均无明显统计学差异。

表 3 消融前与进展时检验结果的对比

Table 3 Comparison of the parameters at pre-ablation period and progression period (separated by tumor progression of the whole body)

	Pre-ablation period (n=30)	Progression (n=30)	P value
Fasting blood-glucose (mmol/L)	5.40± 2.29	5.63± 1.80	0.674
Albumin (g/L)	40.43± 4.12	37.93± 3.89	0.019*
White blood cell (× 10^9/L)	4.93± 1.49	5.40± 1.20	0.187
Neutrophil (× 10^9/L)	2.93± 1.35	3.51± 1.07	0.068
Lymphocyte (× 10^9/L)	1.47± 0.55	1.37± 0.54	0.446
Neutrophil/lymphocyte	2.28± 1.62	3.16± 1.97	0.063
Neutrophil/lymphocyte>3	3	12	0.007*
Prothrombin time (s)	11.49± 0.92	11.79± 0.99	0.229
Fibrinogen (g/L)	3.40± 0.63	3.77± 1.09	0.111
D-dimer (mg/L)	1.15± 1.10	1.17± 1.09	0.947

Note: * stands for that the comparison was statistically significant (P<0.05).

表 4 应用 Cox 回归分析影响 PFS 因素

Table 4 Results of Multivariate analysis(Cox proportional- hazards model) to determine independent risk factors for disease-free survival (n=30)

	P value	HR	CI 95%
Ablation for primary tumor	0.443	0.681	0.255-1.818
Chemotherapy-induced neutropenia until progression	0.400	0.685	0.284-1.653
Neutrophil/lymphocyte>3 at preablation period	0.330	1.935	0.513-7.301

Note: HR=hazard ratio, CI=confidence interval.

3 讨论

经皮氩氦冷冻消融术是应用极度低温的条件将消融位置蛋白变性、细胞脱水以达到消融目的[10,11]，是抗肿瘤综合治疗的重要部分。但大部分患有进展期或转移性实体肿瘤患者接受包含经皮氩氦冷冻消融在内的综合性抗肿瘤治疗后，都存在肿瘤进展的风险。

一般来说，转移性肿瘤被认为异形性较高并与原发性肿瘤在某些方面存在差异[12]。本研究中，对于原发肿瘤的消融在消融后全身复发与否方面存在统计学差异（表 2 所示）。这表明，转移性病灶在姑息性消融后更加容易发生进展或转移。McDevitt 的研究结论与本研究类似，表明原发性肺癌冷冻消融后，在生存期（Overall Survival，OS）、PFS、局部进展时间方面，均较对于转移性肺癌的消融有明显优势[2]。

白蛋白是人体血浆中最为丰富的蛋白。营养不良和炎症反应能够抑制白蛋白的合成[13]。血浆白蛋白水平也被认为是影响多种恶性肿瘤 OS 的独立危险因素，包括结肠癌、胃癌、乳腺癌和肺癌[14-17]。本研究中，在氩氦冷冻消融后肿瘤进展的患者中，消融前和进展时患者的血浆白蛋白指标有统计学差异（表 3 所示）。这表明低血浆白蛋白水平是恶性实体肿瘤姑息性氩氦冷冻消融后肿瘤进展的有利因素。

粒细胞缺乏是一种化疗相关的剂量限制性的毒副反应，使患者出现易感体质，甚至威胁生命的感染，导致治疗延迟、疗效降低[18]。也有一些研究表明，对于某些实体恶性肿瘤如非小细胞肺癌、胃癌等，化疗或同步放化疗期间出现粒细胞缺乏患者的 OS 或 PFS 较未出现的患者明显延长[19,20]。本研究中，所有患者在消融前至肿瘤进展 / 随访截止的时间内，均接受过化疗。我们将消融后肿瘤进展的 30 次消融按照出现化疗相关性粒细胞缺乏与否分为两组，将肿瘤进展时间做 t 检验：化疗相关性粒细胞缺乏组（n=19，PFS=268.00± 165.82 天），非化疗相关性粒细胞缺乏组（n=11，PFS=189.91± 100.85 天），P=0.169。虽然无统计学差异，但化疗相关性粒细胞缺乏组的 PFS 较非化疗相关性粒细胞缺乏组长，与上述文献结果类似。

本研究中，化疗相关性粒细胞缺乏在消融后全身复发与否方面存在统计学差异（表 2 所示）。这表明出现化疗相关性粒细胞缺乏是恶性实体肿瘤姑息性氩氦冷冻消融术后肿瘤进展的有利因素。据报道，氩氦冷冻消融术可以激发体内抗肿瘤免疫反应，并在炎症微环境中发挥效果[21,22]。并且发现免疫反应首先由淋巴细胞介导[23]。所以可以认为，淋巴细胞的数量直接影响炎症反应和冷冻消融介导的免疫反应的效果。外周淋巴细胞在抗肿瘤方面起到重要作用，淋巴细胞缺乏被认为在抗肿瘤微环境中有负面作用[24]。淋巴细胞缺乏对于多种恶性实体肿瘤预后

存在负面影响[25-27]。有文章认为,T 细胞功能降低、数量缺乏与化疗相关性粒细胞缺乏直接相关[28]。将 41 次消融按照是否存在化疗相关粒细胞缺乏分为化疗相关粒细胞缺乏组及非化疗相关粒细胞缺乏组，应用 t 检验分析两组间随访截止 / 肿瘤进展时淋巴细胞的数量:化疗相关粒细胞缺乏组(n=21,淋巴细胞 =1.20± 0.51× 10^9/L),非化疗相关粒细胞缺乏组(n=20,淋巴细胞 =2.20± 1.87× 10^9/L),P=0.024,有统计学差异。虽然本研究中无法体现淋巴细胞功能对于肿瘤的影响,但化疗相关性粒细胞缺乏伴随淋巴细胞数量减少,恶性实体肿瘤姑息性氩氦冷冻消融术后肿瘤进展的有利因素。

文献表明，升高的 NLR 对于多种恶性实体肿瘤的预后是一种负面预测因素[29],并且对于 OS 亦存在负面影响[30]。本研究中，在氩氦冷冻消融后肿瘤进展的患者中，消融前和进展时 NLR>3[31]的数量有统计学差异(表 3 所示)。这表明 NLR>3 是恶性实体肿瘤姑息性氩氦冷冻消融后肿瘤进展的有利因素。

但是,我们在表 2 中得到了一个与上述相反的结论:消融前 NLR>3 在消融后全身复发与否方面存在统计学差异，是氩氦冷冻消融术姑息性治疗恶性实体肿瘤后肿瘤进展的不利因素。肿瘤进展组(n=30)中 NLR>3(n=3)对比肿瘤非进展组(n=11)中 NLR>3(n=5)。分析原因考虑,在肿瘤进展组(n=30)化疗相关性粒细胞缺乏患者较多(n=19),淋巴细胞数量亦随之减少,故在消融前 NLR>3 数量较多。

综上所述,作为综合治疗的一部分,氩氦冷冻消融术姑息性治疗恶性实体肿瘤后的肿瘤进展因素中,对于原发肿瘤的消融是肿瘤进展的不利因素,化疗相关性粒细胞缺乏、NLR>3、低血浆白蛋白水平是肿瘤进展的有利因素。本研究仍有不足之处,包括回顾性研究、较少的病例数量、多种肿瘤病理类型、较短的随访时间。

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