

·讲 座 Lecture·

碘 125 粒子植入联合其它疗法在各期肝癌治疗中的应用

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【摘要】 过去肝癌主要治疗方法为外科手术切除、肝移植和化疗,近年介入治疗在肝癌治疗中得到广泛应用,取得了良好效果。碘 125(^{125}I)放射性粒子植入术产生的 X 射线和 γ 射线可直接杀伤肿瘤细胞,在多种实体肿瘤治疗中效果良好,联合其它疗法治疗早、中期原发性肝癌、肝癌并发症及转移性肝癌效果良好,具有很好的应用前景。该文就 ^{125}I 粒子与其它治疗方法联合治疗肝癌的效果及存在的不足作一介绍,以期能更广泛应用于肝癌或其它实体肿瘤。

【关键词】 碘 125; 肝癌; 联合治疗; 疗效

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【Abstract】 In the past, surgical resection, liver transplantation and chemotherapy were the main treatments for liver cancers. However, interventional therapy has been widely used in clinical treatment of liver cancers in recent years, and excellent results have been achieved in clinical practice. X-rays and γ -rays produced by implanted radioactive ^{125}I particles can directly kill the tumor cells. The use of ^{125}I particles has already achieved good results in the treatment of multiple solid tumors. Combination use of ^{125}I particles and other therapies has been proved to have a good therapeutic effect for the primary hepatocellular carcinoma (HCC) of early and middle stages, the complications of liver cancers and the metastatic liver cancers, indicating that this method has a good clinical application prospect. This paper aims to make a comprehensive review about the efficacy and deficiency of combination use of ^{125}I particles and other therapies in treating liver cancers in order to make this technique more widely used in liver cancers or other solid tumors. (J Intervent Radiol, 2019, 28:910-913)

【Key words】 ^{125}I particle; liver cancer; combination therapy; curative effect

肝细胞癌(HCC)是全球最常发生、有最高致死率的癌症之一^[1]。不同分期肝癌的治疗方法不同,巴塞罗那临床肝癌(BCLC)分期 A 期的早期肝癌患者,主要以外科手术切除、肝移植和经皮局部消融术治疗为主;BCLC 分期 B 期的中晚期肝癌患者,主要以经导管动脉化疗栓塞术(TACE)和分子靶向药物治疗为主^[2]。近年来,碘 125(^{125}I)放射性粒子植入术,特别是联合其它疗法在各期肝癌治疗中取得了良

好效果。

作为一种人工合成的放射性核素, ^{125}I 半衰期为 59.6 d,3 个半衰期后释放约 94% 能量^[3]。其杀伤肿瘤机制为产生 X 射线和 γ 射线直接损伤肿瘤细胞 DNA,并可产生自由基二次损伤肿瘤细胞 DNA,使肿瘤细胞快速死亡或产生突变,同时其射线可使肿瘤血管纤维化和闭塞,肿瘤发生缺血性坏死。有研究认为放射治疗肿瘤可提高体内免疫水平,通过重编程巨噬细胞促进抗肿瘤免疫(使肿瘤脉管系统正常化),增加 CD8⁺T 细胞流入,导致肿瘤缩小;还可使体内产生细胞毒性 T 淋巴细胞(CTL),抑制肿瘤生长^[3-9]。

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1 ^{125}I 在早期肝癌中的应用

原发性肝癌起病隐匿,大部分患者确诊时已是中晚期,无法行外科手术切除、肝移植或射频消融(RFA)治疗,部分早期患者可行外科手术或肝移植治疗,但外科手术切除后肝癌 5 年复发率 $>70\%$ ^[10]。外科手术中结合 ^{125}I 粒子植入,可有效减少术后复发,提高患者生存率。Chen 等^[11]选取 68 例肝癌患者(Child A 级,肿瘤数 ≤ 3)进行随机对照试验研究,结果表明治愈性肝切除联合术中切缘 ^{125}I 粒子植入术后患者平均肿瘤复发时间长于单纯肝切除术患者(36.7 个月对 60 个月),术后复发率分别为 70.6%、35.3%,总体生存时间分别为 38.9 个月、63.6 个月,术后 1、3、5 年生存率高于单纯外科手术切除术($P=0.026$)。对于早期肝癌不愿或不能接受外科手术切除的患者可行 RFA 治疗,优点是微创、疗效好,但对肿瘤坏死效果并不理想,治疗肿瘤直径 $<3\text{ cm}$ 患者 3 年复发率达 50%^[12-14],且对早期肝癌患者疗效不优于外科手术切除^[15]。RFA 结合 ^{125}I 粒子植入可取得更好疗效。一项前瞻性随机对照试验研究表明 RFA 联合 ^{125}I 粒子植入与单纯 RFA 治疗直径 $\leq 3\text{ cm}$ 肝癌患者相比,术后 1、3、5 年复发率较低($\text{HR}=0.508$, $95\%\text{CI}=0.317\sim 0.815$, $P=0.004$),术后 1、3、5 年生存率较高($\text{HR}=0.502$, $95\%\text{CI}=0.313\sim 0.806$, $P=0.003$)^[16]。外科手术治疗肝癌创伤大,并发症多,对可行外科手术患者术中行 ^{125}I 粒子植入,可取得更好疗效;RFA 创伤小,RFA 后植入 ^{125}I 不会给患者带来更大的心理和身体负担,也可取得更好疗效。

2 在中晚期肝癌中的应用

TACE 治疗肝癌可导致肿瘤缺血性坏死,减缓肿瘤进展,提高患者生存率,是中期肝癌一线治疗方法。一项研究表明 HCC 患者经 TACE 治疗后 1、2、3、5 年总体生存率分别为 70.3%、51.8%、40.4%、32.4%,同时具有可重复性、创伤小等优点^[17-19]。 ^{125}I 联合 TACE 治疗肝癌可取得更好疗效。张辉等^[20]回顾性分析 27 例 ^{125}I -TACE 治疗肝癌患者,为期 6 个月随访显示患者完全缓解 2 例,部分缓解 16 例,疾病稳定 3 例,总有效率 66.7%。Li 等^[21]回顾性分析 144 例肝癌患者,66 例接受 ^{125}I 联合 TACE 治疗,78 例接受单纯 TACE 治疗,结果显示 ^{125}I 联合 TACE 治疗患者总体生存时间显著长于单纯 TACE 治疗患者($P<0.001$),通过倾向得分匹配后 ^{125}I 联合 TACE 治疗患者 1、3 年生存率仍显著大于单纯 TACE 治疗患者($P<0.001$)。近年 ^{125}I 联合 TACE 越

来越多地应用于肝癌治疗,近期和中期生存率优于单独 TACE 治疗^[22],临床上已逐渐接受 ^{125}I 联合 TACE 治疗中期肝癌患者。

3 在肝癌伴门静脉癌栓中的应用

门静脉癌栓是 HCC 常见并发症,肝癌伴门静脉癌栓患者预后较差,未经治疗患者中位生存期仅为 2.7~4 个月^[23]。目前对肝癌伴门静脉癌栓患者主要以 TACE 联合支架植入术治疗为主,TACE 联合索拉菲尼是治疗 HCC 伴门静脉癌栓的有效方法^[24]。近年 ^{125}I -TACE 治疗肝癌伴门静脉癌栓的效果明显优于单纯 TACE 治疗。一项纳入 25 例接受 ^{125}I 放射性粒子支架植入联合 TACE 治疗的肝癌伴门静脉癌栓患者(Child A 级 15 例,B 级 10 例)研究显示,中位生存期为 12.5 个月(0.6~35.7 个月),高于传统支架治疗或单纯口服索拉菲尼治疗患者^[25-27]。有研究回顾性分析 56 例肝癌伴门静脉癌栓患者,随访 18 个月结果显示 ^{125}I 粒子支架植入联合 TACE 治疗、单纯 TACE 治疗患者中位生存期分别为 8.9 个月、5.7 个月($P<0.05$),中位进展期分别为 7.9 个月、5.3 个月($P<0.05$), ^{125}I 粒子支架植入联合 TACE 治疗短期有效率比单纯 TACE 治疗好^[28]。Huang 等^[29]回顾性分析 210 例肝癌伴门静脉癌栓患者,随访 3.5~43 个月, ^{125}I 粒子植入联合 TACE 治疗、单纯 TACE 治疗患者中位生存期分别为 11 个月、7.5 个月,前者 6 个月和 1、2、3 年生存率均明显高于后者($P<0.001$)。邵海波等^[30]回顾性分析 88 例原发性肝癌伴门静脉癌栓患者,结果表明 ^{125}I 粒子支架植入联合 TACE 治疗与单纯 TACE 治疗相比,延长患者生存期,减缓病情进展。TACE 联合支架植入是目前治疗肝癌伴门静脉癌栓患者常用术式,支架可压迫癌栓,使得血流顺畅通过,降低门静脉压,但随着癌栓生长,癌栓压迫支架会导致支架狭窄,再次引起门静脉高压。在支架上植入 ^{125}I 粒子条,通过粒子条释放射线对癌细胞产生损伤,可使癌栓生长缓慢甚至停止,达到延长患者生存、延缓疾病进展和支架内再狭窄的目的。

4 在肝转移瘤中的应用

^{125}I 在原发性肝癌治疗中取得了良好效果,但肝脏是其它部位肿瘤转移的好发部位之一,特别是结直肠癌,更易转移至肝脏。肝转移瘤治疗,目前主要以手术切除、化疗或介入治疗为主。对于肝多发性转移瘤患者,外科手术很难达到治愈性切除或切除

不彻底,导致肿瘤复发;化疗对部分患者可取得良好效果,但化疗药物不良反应大,部分患者不愿接受化疗; ^{125}I 粒子植入在肝转移瘤治疗中取得了良好效果。一项纳入 64 例肝转移瘤患者研究显示, ^{125}I 治疗后患者 1、3、5 年肝内肿瘤控制率分别为 44%、22%、22%,中位复发时间为 9 个月(95%CI=6~12);1、3、5 年总体生存率分别为 73%、23%、5%,中位生存期为 20 个月(95%CI=16~24);手术不完全切除后 3 年生存率仅为 3%~7%,大部分患者在术后 1 年内死亡^[31-35]。癌症转移是威胁患者生命的重要疾病进展, ^{125}I 联合肝切除术治疗肝转移瘤是一种转型治疗方式,临床疗效值得肯定。

5 存在不足

^{125}I 治疗体内实体肿瘤取得了显著疗效,特别是治疗前列腺癌的效果令人满意。 ^{125}I 治疗具有创伤小、可重复性、效果好的特点,越来越多地应用于治疗其它实体肿瘤。 ^{125}I 植入治疗肝癌效果也逐渐凸显。 ^{125}I 粒子植入后常见并发症是粒子移位,最常见移位于肺和心脏。粒子植入数量>22 或植入次数>2 次时,会明显增加粒子移位率^[36]。因此,肝癌治疗过程中应充分评估患者病情、肿瘤大小及合适的粒子植入数,CT 或超声引导下通过计算机立体治疗计划系统(TPS)评估后进行手术。 ^{125}I 粒子表观放射性活度为 0.8 mCi,植入肿瘤后放射性活度随着距离增加而减少,若在肿瘤内分布不均,可导致其产生的射线对肿瘤杀伤效果随着距离增加而降低。动物实验结果显示距离 0.5 mCi 活度 ^{125}I 粒子 0~2 mm 处小鼠肿瘤内组织氧分压和灌注未增加,距离粒子 2~4 mm 处肿瘤组织氧分压和灌注增加,表明随着离粒子距离增加,射线对肿瘤杀伤效果变差^[37]。因此,粒子植入时应尽量使其在肿瘤内均匀分布。由于 ^{125}I 为放射性粒子,很多患者在进行 ^{125}I 粒子植入时对射线辐射存在忧虑,产生放射性恐惧,但 ^{125}I 粒子射线在组织中辐射距离为 1.7 cm^[38],故对患者病灶周围组织不产生或产生很小伤害,对患者周围家属产生的辐射微乎其微。

6 结语

^{125}I 联合其它疗法在各期肝癌治疗中取得了很好疗效,有助于延长患者生存期、减缓肿瘤进展、降低肿瘤复发率。近年很多新兴药物应用于肝癌治疗或临床试验,未来对 ^{125}I 联合新兴药物治疗肝癌值得探究。 ^{125}I 粒子治疗肝癌尚缺乏大数据前瞻性对照

研究,期望未来能有多中心前瞻性研究进一步表明 ^{125}I 粒子治疗肝癌的疗效,推动 ^{125}I 粒子临床治疗肝癌或其它实体肿瘤。

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