·综　述·

激光间质热疗在脑部疾病治疗中的应用现状

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【关键词】激光间质热疗；药物难治性癫痫；脑胶质瘤；脑转移瘤；放射性脑坏死
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激光间质热疗（laser interstitial thermotherapy，LITT）是一种使用激光的热效应破坏靶组织的治疗方式[1]。近年来，LITT在神经外科的应用愈加广泛，使用立体定向技术，可以将纤细的激光光纤直接植入颅内病灶的核心，并使用激光破坏病灶，达到类似于手术切除的效果。对于很多传统需要开颅手术的神经外科疾病，如胶质瘤、转移瘤、放射性脑坏死、药物难治性癫痫等，LITT有一定的优势[2~4]，创伤小，治疗效率高，对病灶周围的皮层破坏小，精准度高。本文就LITT在脑部疾病治疗中的应用现状进行综述。

1 LITT简介

LITT是一种利用激光热消融靶组织的技术，靶点精准，消融过程中出血控制好，很早就应用于全身多种脏器（如肺、肝、前列腺等）疾病的治疗[1,5]。1965年，Fine等[6]报道红宝石激光对动物脑组织有破坏作用。此后，激光逐渐被应用于治疗脑部疾病，但由于激光吸收和散射等问题，使其消融范围并不完全可控，因此没有得到进一步的推广[7]。经过不断摸索，1990年，Sugiyama等[8]在CT引导下使用钇铝石榴石激光消融治疗脑肿瘤5例。随后，Jolesz等[9]报道MRI引导的颅内肿瘤激光热疗，但还无法做到实时监控温度变化和范围。近年来，基于立体定向技术和MRI技术的进步，可以将激光光纤植入脑内指定部位，并在MRI监测下消融，用以监测温度和消融的范围，并开发出成熟的治疗系统[10]。目前，国际上常用的LITT系统有两种，分别使用波长为1 064 nm和980 nm的激光，脑组织穿透范围在2~10 mm[11]。在激光照射靶区时，局部温度升高（周边一般不超过60 ℃），通过蛋白变性，导致靶区细胞的变性和坏死[12]。在治疗前，需要通过MRI制定置入路径，并在麻醉后将激光光纤套筒（有冷却和散射功能，直径约3 mm的圆柱体）使用立体定向技术植入靶区的核心区域。冷却器可以减少激光导致的碳化，延长激光作用的时间，增加组织的热吸收范围[13]。散射器则可以使靶组织得到均匀照射，实现组织内能量均匀和对称的分布[14]。尖端的温度感受器，可以设置指定温度作为安全点，一但超过该温度便触发系统关闭，防止不必要的碳化和重要临近血管、神经等结构的损伤[15]。颅内病变的LITT需要在术中MRI指导下进行。术中MRI快速破坏梯度回波序列[16]，成像约8 s，并在烧蚀过程中重复运行，以形成实时热图，监测手术过程维持足够的热凝时间和估计组织坏死范围[12]。当估计的不可逆损伤扩展到包括整个需要的消融区域时，便可终止手术。相比于其他颅内病变的微创治疗方式（如立体定向放射治疗、聚焦超声、射频热凝毁损等），磁共振引导的LITT具有更大和更精确可靠的消融范围，同时减少并发症[17]。

2 LITT在脑部疾病治疗中的应用

2.1 *脑胶质瘤* 胶质瘤是最常见的脑肿瘤。体积较小的脑胶质瘤（直径小于3 cm）可尝试LITT。特别是对于复发的高级别胶质瘤，全身状态较差，难以接受开颅手术的当然，LITT更有优势[18]。2012年，Carpentier等[15]报道4例复发性胶质母细胞瘤接受LITT后均复发，平均总生存期为10.5个月。2015年，Banerjee等[19]报道WHO分级Ⅲ/Ⅳ级复发胶质瘤LITT治疗后总生存时间平均增加20.9个月，优于化疗和开颅手术。2016年，Patel等[20]报道102例LITT的脑肿瘤，其中约90%为复发病人，当经过一定的学习曲线后，治疗的并发症发生率很低，治疗后1~4 d即可

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出院(平均住院3.6 d),很少出现神经功能缺损。目前,对于胶质瘤而言,LITT并不是首选治疗方式[21],但对于复发性胶质瘤,LITT具有更好的前景[22]。荟萃分析认为,对于复发的高级别胶质瘤,LITT的治疗效率优于开颅手术,而并发症发生率则显著低于开颅手术[23],但这可能和病人选择偏倚相关。因此,仍然需要更多高级别临床研究证实LITT治疗脑胶质瘤的安全性和有效性。

2.2 *脑转移瘤和放射性脑坏死* 部分脑转移瘤病人因为原发肿瘤或多发转移,全身状态较差,难以接受开颅手术,LITT便成为一种很好的替代疗法[24,25]。目前,已有文献报道,肺癌、乳腺癌、结肠癌等恶性肿瘤脑转移的LITT治疗,并发症发生率较低[26]。但与开颅手术、立体定向放射治疗和全脑放疗相比,其手术有效性还需要进一步研究。

放射性脑坏死是放疗的一种并发症,是在放疗后产生的不可逆的脑坏死,持续数月到数年,进行性加重[27]。放射性坏死的发生率在3%~24%[28]。由于放射性坏死与肿瘤复发难以区分,文献可能不能反映实际的放射性坏死发生率。另外,放射性脑坏死和脑肿瘤复发鉴别困难,通常并不会采取开颅手术治疗,而LITT则可以消融这部分病灶,但其预后仍与消融范围有关[29]。

2.3 *药物难治性癫痫*

2.3.1 *颞叶内侧癫痫* 颞叶癫痫是成人最常见的药物难治性癫痫类型,其中海马硬化导致的内侧颞叶癫痫最常见。对于这种类型癫痫,治疗的金标准为前颞叶切除术(anterior temporal lobectomy, ATL)。由于颞叶新皮层具有语言整合、情绪、认知、视觉传导等功能,因此,人们也在不断探索新的治疗方式以取代ATL。LITT可以将激光探头植入海马,并在MRI监控下进行,是一种治疗海马硬化导致内侧型颞叶癫痫的新方式。Drane等[30]比较LITT(21例)和标准ATL(39例)治疗后的癫痫发作情况,6个月随访显示,LITT治疗的21例者中,11个无发作;标准ATL治疗39例中,24例无发作。Willie等[31]报道接受LITT治疗的13例内侧颞叶癫痫中,7例无癫痫发作,3例改善(随访5~26个月);既没有发现消融的容积或长度与癫痫预后之间的相关性,也没有发现海马硬化对癫痫预后的影响。荟萃分析指出,LITT治疗颞叶癫痫的无发作率为59%,伴有海马硬化者可达66%[18,32]。另有篇荟萃分析指出,LITT治疗颞叶癫痫的无发作率为59%,优于SEEG引导的射频毁损治疗[17]。

2.3.2 *痴笑样癫痫* 痴笑样癫痫是下丘脑错构瘤的主要表现,开颅手术创伤大,对发作控制不理想。射频热凝毁损对于较大体积的错构瘤效果不理想。LITT因其精准毁损因而近年被用于下丘脑错构瘤的治疗。Wilfong和Curry[33]报道LITT治疗下丘脑错构瘤14例,术后随访9个月,86%的病人无发作。目前,LITT治疗下丘脑错构瘤最大宗病例报道纳入71例,93%的病人术后1年无发作,23%的病人接受二次LITT,1例出现记忆减退,1例出现血糖增高[34]。

2.3.3 *其他类型的药物难治性癫痫* 其他致痫灶相对局限的药物难治性癫痫也可以尝试LITT。Esquenazi等[35]报道2例脑室旁结节性灰质异位经过LITT治疗后,癫痫缓解。另有关于结节性硬化症[36]、局灶皮层发育不良[37]、海绵状血管瘤[38]等LITT治疗的报道,因为报道病例数量有限,其安全性和有效性尚无法证实。

3 LITT的安全性

因为立体定向植入的精准性和激光消融范围和出血的良好控制,与开放手术相比,LITT并发症发生率更低。文献报道的LITT的并发症包括血管损伤引起的颅内出血、脑水肿、颅内其他结构的意外损伤、永久性神经功能缺损、一过性局灶性神经功能缺损、癫痫发作和脑脊液漏等,总发生率在3%~24%[39,40]。值得注意的是,Patel等[20]报道3例LITT治疗后死亡的病例(共103例),1例死因为顽固性脑水肿,另2例为原发疾病的快速进展而死亡。降低风险的措施包括:设计更加安全合理的通道、对于较大病灶采取多通道消融、术前激素使用等方法[41]。

综上所述,对于符合LITT适应证的脑部疾病,与开颅手术相比,LITT更加微创、操作更加便捷、并发症发生率更低。整体而言,LITT的治疗效果相比开颅手术稍差,但在某些疾病中则优于开颅手术,例如下丘脑错构瘤引起的药物难治性癫痫。未来需要进行更多前瞻性随机对照临床试验,以确定病人的结局和评估该治疗方式的长期有效性。

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