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Role of Stereotactic Body Radiotherapy in the Treatment of Liver Metastases: A Systematic Review

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Abstract **Review Article**

Background. Liver metastases are frequent during the course of solid malignancies, particularly colorectal, breast, lung, pancreatic cancers and melanoma. Surgical resection remains the reference local treatment when complete resection is feasible, and thermal ablation is an established option for selected small lesions. Nevertheless, many patients are not suitable candidates for surgery or percutaneous ablation because of tumor location, lesion size, comorbidities, limited hepatic reserve, proximity to vascular or biliary structures, or concomitant extrahepatic disease. In this setting, stereotactic body radiotherapy (SBRT), also referred to as stereotactic ablative radiotherapy (SABR), has emerged as a non-invasive ablative treatment capable of delivering high biological doses in a limited number of fractions while limiting irradiation of uninvolved liver parenchyma. ***Objective.*** This systematic review evaluated the role of SBRT in the treatment of liver metastases between 2015 and 2025, with emphasis on study validity, treatment characteristics, oncological outcomes and toxicity. ***Methods.*** A systematic review was conducted in accordance with PRISMA 2020 recommendations. PubMed/MEDLINE, Scopus, Web of Science and the Cochrane Library were searched for studies published from January 2015 to December 2025. Eligible studies included adult patients treated with SBRT or SABR for liver metastases and reported at least one oncological outcome. Randomized studies were assessed using RoB 2 and non-randomized studies using ROBINS-I. Extracted data included patient and tumor characteristics, treatment schedule, biological effective dose, local control, overall survival, progression-free survival and grade 3 or higher toxicity. Because of substantial clinical and methodological heterogeneity, the synthesis was primarily descriptive. ***Results.*** Thirty-three studies were included. The evidence base consisted mainly of phase I/II trials, retrospective cohorts and multicenter registries. Dose-fractionation schedules were heterogeneous, most commonly ranging from 30 to 75 Gy in 1 to 5 fractions. One-year local control was generally between 75% and 98%, with better outcomes reported when the biological effective dose exceeded 100 Gy. Contemporary pooled data reported local control rates at 1, 2 and 3 years of 85%, 75% and 68%, respectively, and overall survival rates at 1, 2 and 3 years of 79%, 54% and 37%. Severe toxicity was uncommon; with grade 3-4 toxicity estimated at approximately 3%. ***Conclusion.*** SBRT is an effective and safe local treatment option for selected patients with liver metastases, particularly those who are not candidates for surgery or thermal ablation. Its strongest indication is oligometastatic or oligoprogressive disease when an ablative dose can be delivered without exceeding organ-at-risk constraints. However, the current evidence remains limited by the predominance of non-randomized studies and by heterogeneity in patient selection, dose prescription and follow-up definitions.

Keywords: liver metastases; stereotactic body radiotherapy; SBRT; stereotactic ablative radiotherapy; local control; oligometastatic disease.

INTRODUCTION

Liver metastases are among the most common manifestations of metastatic solid tumors, particularly colorectal, breast, lung and pancreatic cancers, as well as melanoma. The liver is a preferential site of metastatic spread because of its dual portal and systemic vascular supply. Prognosis depends on the primary tumor, number and size of hepatic lesions, presence of extrahepatic disease, response to systemic therapy and feasibility of radical local treatment.

Surgical resection remains the standard local approach when complete resection is feasible, especially in colorectal liver metastases. However, only a minority of patients are eligible for curative surgery because of multifocal disease, unfavorable lesion location, insufficient future liver remnant, significant comorbidities or uncontrolled extrahepatic progression. Thermal ablation, including radiofrequency and microwave ablation, is a validated alternative for small lesions, but its efficacy decreases when tumors exceed 3 cm, are adjacent to major vessels, or are technically difficult to access [1,2].

In this context, SBRT has progressively become an important non-invasive local treatment. It allows delivery of ablative radiation doses in a small number of fractions with high spatial precision, image guidance and respiratory motion management. The rationale for SBRT is reinforced by the concept of oligometastatic disease, initially described by Hellman and Weichselbaum, according to which selected patients with a limited metastatic burden may benefit from radical local treatment of all macroscopic sites [3]. This concept was further supported by the SABR-COMET randomized phase II trial, which showed an overall survival benefit for comprehensive SABR in selected patients with oligometastatic cancer, although the trial was not restricted to liver metastases [4,5].

This systematic review aimed to evaluate the role of SBRT in the treatment of liver metastases between 2015 and 2025, focusing on methodological validity, treatment parameters, oncological outcomes and toxicity.

MATERIALS AND METHODS

This systematic review was prepared according to the PRISMA 2020 statement, which provides the current reporting standard for systematic reviews and meta-analyses [6]. The research question was structured according to the PICO framework. The population consisted of adult patients with one or more liver metastases. The intervention was SBRT or SABR. The outcomes of interest were local control, overall survival, progression-free survival and grade 3 or higher toxicity.

A systematic literature search was performed in PubMed/MEDLINE, Scopus, Web of Science and the Cochrane Library for the period from January 1, 2015 to December 31, 2025. The search strategy combined terms related to the hepatic site, stereotactic treatment and outcomes: liver metastases, hepatic metastases, stereotactic body radiotherapy, SBRT, stereotactic ablative radiotherapy, SABR, local control, overall survival, progression-free survival, toxicity, oligometastatic disease and colorectal liver metastases. Boolean operators AND and OR were used to combine the search terms.

Eligible studies were original full-text articles including adult patients treated with SBRT or SABR for liver metastases, with a minimum sample size of ten patients and at least one extractable oncological outcome. Prospective trials, phase I or II studies, retrospective cohorts, multicenter registries and comparative studies were eligible. Studies including both primary liver tumors and liver metastases were retained only when liver metastasis-specific data could be extracted.

Exclusion criteria were narrative reviews, editorials, letters, conference abstracts without complete data, series including fewer than ten patients, pediatric studies, studies exclusively focused on hepatocellular carcinoma or cholangiocarcinoma, conventional non-stereotactic external-beam radiotherapy, exclusive internal radioembolization and publications without follow-up data on oncological outcomes.

Study selection is summarized in the PRISMA 2020 flow diagram (Figure 1). The initial search identified 1,042 records, including 428 from PubMed/MEDLINE, 312 from Scopus, 265 from Web of Science and 37 from the Cochrane Library. After removal of 226 duplicates, 816 records were screened by title and abstract. At this stage, 712 records were excluded because they were not relevant to the research question, did not specifically assess hepatic SBRT, or represented an ineligible publication type. A total of 104 reports were sought for full-text retrieval; 6 could not be retrieved, leaving 98 articles for eligibility assessment. After full-text review, 65 articles were excluded for the following reasons: non-relevant population in 18 cases, absence of specific hepatic SBRT data in 14 cases, insufficient oncological outcome data in 11 cases, sample size below 10 patients in 9 cases, review article/editorial/abstract-only publication in 8 cases, and publication outside the study period in 5 cases. Overall, 33 studies were included in the final synthesis.

Methodological validity was assessed according to study design. Randomized trials were evaluated using the Cochrane RoB 2 tool, which examines bias related to the randomization process, deviations from intended interventions, missing outcome data, outcome measurement and selection of the reported result [7]. Non-randomized studies were assessed using ROBINS-I, which evaluates bias due to confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurement and selective reporting [8].

Data extraction included year of publication, study design, number of patients, number of treated metastases, primary tumor origin, number of lesions, tumor size, prior treatments, dose-fractionation schedule, biological effective dose calculated with an alpha/beta ratio of 10 Gy, radiotherapy technique, respiratory motion management, image guidance, dose constraints,

median follow-up, local control, overall survival, progression-free survival, intrahepatic and extrahepatic recurrence, and acute or late toxicity.

The statistical synthesis was primarily descriptive because of substantial heterogeneity across studies in histology, systemic therapy, lesion size, dose prescription, fractionation, follow-up duration and definitions of local control. Local control and survival outcomes were reported as published, most often by the Kaplan-Meier method. The biological effective dose was calculated using the formula BED = nd [1 + d/(alpha/beta)], with alpha/beta = 10 Gy for tumor tissue. No independent quantitative meta-analysis was performed in this review because individual patient data were unavailable and outcome definitions were inconsistent. When appropriate, pooled estimates from the recent meta-analysis by Franzese *et al.,*were used as a contextual benchmark [9].

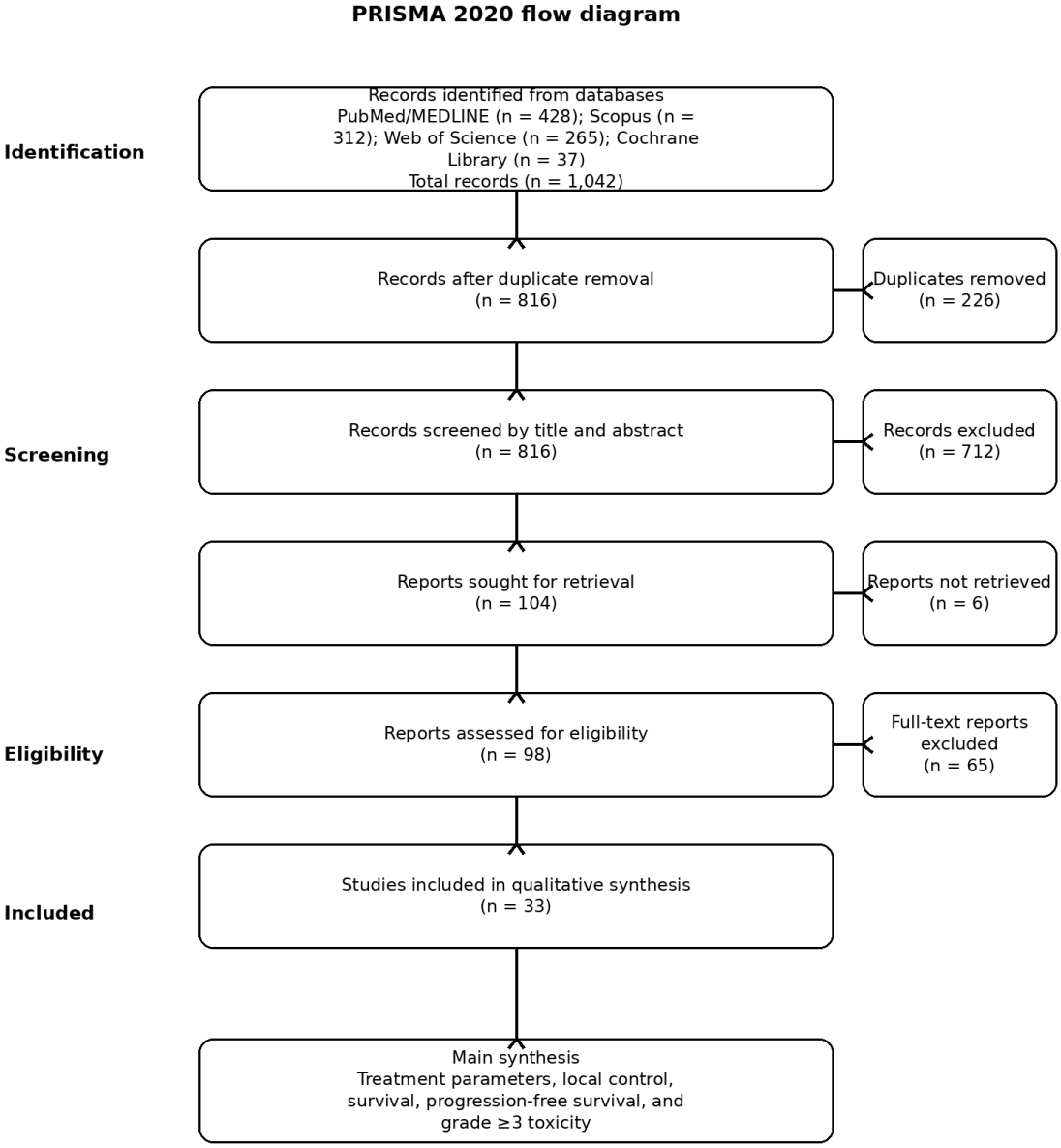

Figure 1: PRISMA 2020 flow diagram of study selection for studies evaluating SBRT in liver metastases between 2015 and 2025

RESULTS

After application of the selection criteria, 33 studies were included in the final analysis. The literature published between 2015 and 2025 was dominated by prospective phase I/II trials, retrospective monocentric or multicenter cohorts and large institutional registries. The overall level of evidence was moderate. The main limitations were selection bias, heterogeneous indications, variability in dose prescription, absence of comparative arms and, in some studies, limited follow-up.

Prospective studies, including those by Scorsetti *et al.,* Meyer *et al.,* and Hong et al., provided relevant data on feasibility, safety and local efficacy after hepatic SBRT [10-12]. However, their sample sizes were limited and their populations highly selected. Large cohorts and registries, such as those reported by Mahadevan et al., Andratschke *et al.,* and Mendez Romero et al., improved the description of real-world practice but were more exposed to selection bias, missing data and technical heterogeneity [13-15].

In the DEGRO cohort reported by Andratschke *et al.,* 474 patients and 623 liver metastases were analyzed, making it one of the largest multicenter series available. Local control was influenced by the biological dose, tumor volume, histology and respiratory motion management [14]. Although the multicenter design strengthened external validity, heterogeneity in irradiation technique and fractionation limited direct comparison with prospective trials.

Treatment Characteristics

Treatment parameters varied substantially across studies. The most common regimens used 1 to 5 fractions, with total doses ranging approximately from 30 to 75 Gy. Highly ablative schedules, such as 75 Gy in 3 fractions, were mainly reported in selected patients with limited lesions located at a safe distance from gastrointestinal organs at risk [10,16]. Five-fraction regimens, such as 50 Gy in 5 fractions, were frequently used when lesions were close to the stomach, duodenum, colon, bile ducts or chest wall [17].

The biological effective dose emerged as a major determinant of local control. Several studies reported improved tumor control when BED10 exceeded 100 Gy [18-20]. This dose-response relationship is particularly relevant for colorectal liver metastases, which appear less radiosensitive than breast or lung metastases [14,21].

Modern SBRT techniques relied on intensity-modulated radiotherapy, volumetric modulated arc therapy, onboard image guidance, abdominal compression, respiratory gating, tumor tracking or magnetic resonance-guided radiotherapy. MR-guided approaches, particularly those reported by Weykamp *et al.,* improve visualization of liver lesions and organs at risk and allow online plan adaptation in selected cases [22].

Table 1: Treatment parameters in key studies published between 2015 and 2025

Study	Design / population	Main histologies	SBRT/SABR schedule	Approximate BED10 / technique
Scorsetti *et al.,* 2015 [10]	Prospective phase II; inoperable colorectal liver metastases	Colorectal	75 Gy in 3 fractions	262.5 Gy; VMAT/RapidArc
Meyer *et al.,* 2016 [11]	Phase I; selected liver metastases	Mixed	Single fraction 18-40 Gy	Variable; single-fraction SABR
Hong *et al.,* 2017 [12]	Prospective phase II	Mixed	Individualized proton-SBRT	Variable; proton therapy
Klement *et al.,* 2017 [21]	Multicenter cohort; oligometastatic liver disease	Colorectal, breast, lung	Variable schedules	Variable; modern SBRT
Mahadevan *et al.,* 2018 [13]	International registry; 427 patients, 568 metastases	Mixed	1 to 5 fractions	Variable; multicenter SBRT
Scorsetti *et al.,* 2018 [16]	Phase II long-term follow-up; 61 patients, 76 lesions	Mixed	75 Gy in 3 fractions	262.5 Gy; VMAT
Andratschke *et al.,* 2018 [14]	DEGRO registry; 474 patients, 623 metastases	Colorectal, breast, lung, pancreas	Variable schedules	Variable; CBCT, gating, tracking
Kok *et al.,* 2020 [18]	Retrospective cohort	Mixed	BED10 ≤100 Gy vs >100 Gy	Threshold 100 Gy; image-guided SBRT
Mendez Romero *et al.,* 2021 [15]	Dutch-Belgian registry; 515 patients, 668 metastases	Mostly colorectal	3×18-20 Gy, 5×11-12 Gy, 8×7.5 Gy, 12×5 Gy	Variable; multicenter SBRT
Weykamp *et al.,* 2023 [22]	Prospective registry; 40 patients, 54 lesions	Colorectal, breast, others	Median 50 Gy in 5 fractions	Approx. 100 Gy; MR-guided SBRT
Chen *et al.,* 2024 [20]	Retrospective cohort	Colorectal	Variable schedules	Variable; modern SBRT
Franzese *et al.,* 2025 [9]	Systematic review and meta-analysis; 3,101 patients, 4,437 metastases	Mixed	Mostly 1 to 5 fractions	Variable; contemporary SBRT techniques

Statistical Synthesis and Oncological Outcomes

Local control was the most frequently reported endpoint. Overall results were favorable, with 1-year local control rates generally ranging from 75% to 98%, depending on dose, lesion size, histology and selection criteria. The best outcomes were reported in studies using high ablative doses, particularly when BED10 exceeded 100 Gy [10,16,18,22].

In the prospective study by Scorsetti *et al.,* evaluating inoperable colorectal liver metastases treated with 75 Gy in 3 fractions, 2-year local control was high and median overall survival approached 29 months [10]. Long-term follow-up confirmed durable control, with local control rates at 1, 3 and 5 years of 94%, 78% and 78%, respectively [16].

In the DEGRO cohort, treated-metastasis control rates were 76.1%, 63.8% and 55.7% at 1, 2 and 3 years, respectively. Overall survival was 70%, 29% and 15% at 1, 3 and 5 years [14]. These outcomes were lower than those reported in highly selected prospective trials, probably reflecting a more heterogeneous population, variable treatment schedules and a higher proportion of heavily pretreated patients.

The Dutch-Belgian registry reported by Mendez Romero *et al.,* included 515 patients and 668 liver metastases. Actuarial 1-year local control was 87% and 1-year overall survival was 84%, confirming the feasibility and efficacy of SBRT in contemporary multicenter practice [15].

The meta-analysis by Franzese *et al.,* including 33 studies, 3,101 patients and 4,437 liver metastases, reported pooled local control rates at 1, 2 and 3 years of 85%, 75% and 68%, respectively. Pooled overall survival rates at 1, 2 and 3 years were 79%, 54% and 37%. Grade 3 or 4 toxicity was low, estimated at approximately 3% [9]. These data support the ability of SBRT to provide high local control with acceptable toxicity, although overall survival remains driven mainly by systemic disease progression.

Table 2: Oncological outcomes of key studies

Study	Median follow-up	Local control	Overall survival	Progression / toxicity
Scorsetti *et al.,* 2015 [10]	Approx. 24 months	High 2-year LC, around 90%	Median OS approx. 29 months	Frequent systemic progression; low severe toxicity
Meyer *et al.,* 2016 [11]	Variable	Favorable with higher doses	Not homogeneously reported	Acceptable safety
Hong *et al.,* 2017 [12]	Prospective follow-up	Favorable control	Variable	Failures influenced by KRAS; no major severe toxicity reported
Klement *et al.,* 2017 [21]	Variable	Better control in non-colorectal tumors	Heterogeneous	Heterogeneous
Mahadevan *et al.,* 2018 [13]	Variable	Prolonged median local control	Median OS approx. 22 months	Frequent extrahepatic progression; low severe toxicity
Scorsetti *et al.,* 2018 [16]	6.1 years	LC at 1, 3, 5 years: 94%, 78%, 78%	Median OS 27.6 months	PFS limited by systemic progression; no major RILD
Andratschke *et al.,* 2018 [14]	15 months	LC at 1, 2, 3 years: 76.1%, 63.8%, 55.7%	OS at 1, 3, 5 years: 70%, 29%, 15%	Frequent out-of-field progression; rare grade 3 toxicity
Kok *et al.,* 2020 [18]	Variable	Better LC if BED10 >100 Gy	Better OS in high-BED group	No major excess toxicity
Mendez Romero *et al.,* 2021 [15]	Variable	1-year LC: 87%	1-year OS: 84%	Heterogeneous recurrence; low severe toxicity
Ohri *et al.,* 2021 [19]	Variable	LC at 1, 2, 3 years: 90%, 79%, 76%	Variable	Variable
Weykamp *et al.,* 2023 [22]	22 months	LC at 1 and 2 years: 98%, 75%	OS at 1 and 2 years: 83%, 57%	PFS at 1 and 2 years: 21%, 5%; no grade ≥3 toxicity
Chen *et al.,* 2024 [20]	Variable	Dose associated with LC	Survival influenced by systemic therapy	Low severe toxicity
Franzese *et al.,* 2025 [9]	Variable	Pooled LC at 1, 2, 3 years: 85%, 75%, 68%	Pooled OS at 1, 2, 3 years: 79%, 54%, 37%	Grade 3-4 toxicity approx. 3%

DISCUSSION

This systematic review confirms that SBRT is an effective and safe local treatment option for selected patients with liver metastases, particularly when surgery is not feasible, percutaneous ablation is unsuitable, or the clinical situation corresponds to oligometastatic or oligo progressive disease. Its main strength is the ability to deliver an ablative local treatment without an invasive procedure, with high precision and acceptable toxicity in experienced centers.

The most consistent technical prognostic factor is the biological dose delivered. Data from Kok et al., Ohri et al., Chen *et al.,* and Weykamp *et al.,* support a dose-response relationship, with improved local control when BED10 exceeds 100 Gy [18-20,22]. This point has direct clinical implications. A dose-compromised SBRT regimen imposed by proximity to organs at risk may still provide palliation or cytoreduction, but it should not be considered equivalent to fully ablative treatment.

Tumor histology is another major determinant of outcome. Colorectal liver metastases are generally associated with lower local control than breast or lung metastases, suggesting relative radioresistance in a proportion of colorectal lesions [14,21]. In these patients, dose escalation within organ-at-risk constraints is particularly important. Hong *et al.,* also suggested that KRAS mutational status may influence local failure after SBRT, supporting future integration of molecular markers into patient selection and treatment personalization [12].

The toxicity profile of hepatic SBRT is favorable in contemporary series. Severe toxicity is uncommon when dose constraints to uninvolved liver and gastrointestinal organs are respected. The DEGRO cohort reported infrequent grade 3 toxicity and no treatment-related grade 4 or 5 toxicity [14]. The meta-analysis by Franzese *et al.,* confirmed this favorable safety profile, with grade 3 or 4 toxicity estimated at approximately 3% [9]. This low toxicity rate should nevertheless be interpreted with caution because it reflects strict patient selection and dose adaptation according to organ-at-risk constraints.

The position of SBRT relative to surgery and thermal ablation remains clinically important. In operable patients, surgery remains central, particularly for resectable colorectal liver metastases. In patients with small lesions that are technically accessible, radiofrequency or microwave ablation remains an effective option. SBRT becomes especially relevant in cases of surgical contraindication, deep lesions, perivascular or subdiaphragmatic location, proximity to biliary structures, or technical inaccessibility for percutaneous procedures. It is also attractive in oligoprogressive disease during effective systemic therapy, where local control of a progressing lesion may allow continuation of the same systemic treatment line.

This review has limitations. Most included studies were non-randomized, and many were retrospective. Populations were heterogeneous with respect to primary tumor, systemic therapy, lesion number, tumor volume, dose prescription, technique and follow-up. Indirect comparisons between studies should therefore be interpreted cautiously. Overall survival cannot be attributed to SBRT alone because it is strongly influenced by systemic disease control, tumor biology and subsequent systemic therapies. Prospective randomized trials comparing SBRT with other local modalities are required to better define its place in therapeutic algorithms.

CONCLUSION

SBRT has an increasing role in the treatment of liver metastases. Studies published between 2015 and 2025 show that it provides high local control, generally exceeding 80% at 1 year in contemporary series, with low severe toxicity. Its efficacy depends strongly on the biological dose delivered, with BED10 above 100 Gy representing an important target whenever organ-at-risk constraints allow. SBRT does not replace surgery when complete resection is feasible, but it represents a major ablative alternative for patients who are inoperable, unsuitable for ablation, or have oligometastatic or oligoprogressive disease. Future studies should refine indications according to histology, molecular status, tumor volume, sequencing with systemic therapy and direct comparison with surgery or percutaneous ablation.

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