* **79445 Yttrium internal radiation therapy**
* **C2616 Brachytherapy source, non-stranded, yttrium-90, per source, for use in treating primary liver cancer or metastatic cancer to the liver**
* **S2095 Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres**

**Last reviewed at VbBS in March 2018. Minutes indicate that the staff recommendation was accepted without significant discussion. HERC approved the recommendations without change.**

HERC staff summary: The literature on the effectiveness of yttrium 90 radiotherapy for treatment of liver metastases for non-hepatocellular carcinoma/colorectal cancer metastatic to the liver consists solely of small case series. These case series do not show significant improvement in survival compared to conventional chemotherapy for most of the cancers studied. Additionally, yttrium 90 products are not FDA approved for treatment of cancers other than HCC and CRC metastatic to the liver. Yttrium 90 is a much higher cost therapy than traditional chemotherapy.

Evidence

1. **Kuei 2015**, systematic review of yttrium-90 for non HCC/CRC indications (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4507097/pdf/WJG-21-8271.pdf>)
   1. Breast cancer:
      1. 4 retrospective case series (N=75, 21, 40, 77), 3 prospective case series (N=30,44,27) and an additional 37 patients in other studies with discrete response data on the patients with breast primaries
      2. Collective analysis of current literature ranges in response rates between 18%-61% and median overall survival between 6.6 to 13.6 months
         1. baseline historical estimated cumulative survival with metastatic breast cancer at time of diagnosis is 18.5 months. Median survival in patients with unresectable, chemoresistant breast cancer liver metastases (BRCLM) ranges between 3-10 months with standard therapy
      3. The tendency of BRCLM to present with extrahepatic involvement limits SIRT from a prognostic perspective.
      4. Although the number of studies on the effects of SIRT on breast cancer metastasis is gradually increasing, they have so far involved only relatively small, heterogeneous patient cohorts. In order to validate SIRT as a potential first-line adjuvant to chemotherapy, larger multicenter randomized control studies are needed
   2. Cholangiocarcinoma
      1. N=6 prospective case series (N=24, 25, 26, 19, 46, 21) and 1 retrospective case series (N=35)
      2. meta-analysis of 5 of these studies found the highest median overall survival was with hepatic arterial infusion (22.8 months) compared to transarterial radioembolization (13.9 months), transarterial chemoembolization (12.4 months), and drug-eluting transarterial chemoembolization (12.3 months).
      3. In the other 3 studies, overall survival varied between 5.7 months and 16.3 months.
      4. Historical median overall survival for patients with ICC is currently 22 months with standard therapy.
   3. Melanoma
      1. N=4 retrospective case series (N=28, 16, 32, 11) and 3 additional cases extracted from larger studies
      2. Median survival 7.6-10.1 months
      3. Reported median overall survival is 2.4 months with liver involvement with standard therapy
      4. Based on the few small cohort studies so far, SIRT has been demonstrated to be safe and effective at prolonging survival, however without further comparative studies the ideal selection criteria and benefit over other regional therapies remains uncertain.
   4. Pancreatic cancer
      1. N=2 retrospective case series (N=19, 7)
      2. Though the limited available data makes survivability benefits unclear, initial reports as a salvage treatment are encouraging. Median survival with the small cohort is attributed to a roughly 2-4 month improvement over conventional therapy
   5. Renal cell carcinoma:
      1. N=1 retrospective case series (N=6) and 1 case study (N=1)
      2. preliminary data on a handful of patients…are promising for the use of SIRT of hepatic metastases by renal cell carcinoma with a palliative rather than curative intent
   6. Lung cancer
      1. N=1 retrospective case series (N=6) and 1 case study (N=2)
      2. The few cases of yttrium-90 SIRT of lung cancer liver metastases so far demonstrate SIRT’s potential as an effective salvage therapy

HERC staff recommendations:

1. Add the additional HCPCS code for yttrium-90 radioembolization (CPT 79445) to line 500/GN172
   1. S2095 Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres
2. Modify the entry to GN172/line 500 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS as shown below for yttrium-90 for treatment of primary hepatocellular carcinoma, or colorectal cancer metastatic to the liver

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# GUIDELINE NOTE 172, INTERVENTIONS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS

Line 500

The following interventions are prioritized on Line 500 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS:

| Procedure Code | Intervention Description | Rationale | Last Review |
| --- | --- | --- | --- |
| 79445  C2616  S2095 | Radiopharmaceutical therapy, by intra-arterial particulate administration for use in treating primary hepatocellular carcinoma or colorectal cancer metastatic to the liver  Brachytherapy source, non-stranded, yttrium-90, per source, for use in treating primary liver cancer or metastatic cancer to the liver  Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres | Low cost-effectiveness compared to equally effective but less expensive standard chemotherapies; concern for possible harms compared to standard chemotherapy | January, 2018 |

1. Remove CPT 79445 (Radiopharmaceutical therapy, by intra-arterial particulate administration) from all current lines on the Prioritized List
   1. Lines 129,130,160,161,162,165,195,204,214,238,242,262,265,274,279,291,292,299,319, 321, 333,346,376,439,465,533,600,611
   2. Evidence for efficacy is extremely limited; appears experimental; not FDA approved for these indications
2. Add an entry to GN173/line 660 for all non-HCC/CRC metastatic to the liver indications as experimental

GUIDELINE NOTE 173, TREATMENTS THAT HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS; unproven treatments

The following treatments are prioritized on Line 660, CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; unproven treatments, for the conditions listed here:

|  |  |  |  |
| --- | --- | --- | --- |
| CPT/HCPCS Code | TREATMENT | Rational | Date of Last Review/Link to Meeting Minutes |
| 79445  C2616  S2095 | Radiopharmaceutical therapy, by intra-arterial particulate administration for use in treating cancers other than primary hepatocellular carcinoma or colorectal cancer metastatic to the liver  Brachytherapy source, non-stranded, yttrium-90, per source, for use in treating primary liver cancer or metastatic cancer to the liver  Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres | No evidence of effectiveness | March, 2018 |

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**Last reviewed at VbBS in January 2018. Minutes indicate that the staff recommendation was accepted without significant discussion. HERC approved the recommendations without change.**

* CPT 79445 Radiopharmaceutical therapy, by intra-arterial particulate administration for use in treating primary hepatocellular carcinoma or colorectal cancer metastatic to the liver
* C2616 Brachytherapy source, non-stranded, yttrium-90, per source, for use in treating primary liver cancer or metastatic cancer to the liver

Evidence

*SARAH*

1. **Vilgrain 2017**, Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial
   1. Methods:
      1. multicenter, open label RCT phase 3 trial done in France
      2. Patients were eligible if they were aged at least 18 years with a life expectancy greater than 3 months, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, Child-Pugh liver function class A or B score of 7 or lower, and locally advanced hepatocellular carcinoma (Barcelona Clinic Liver Cancer [BCLC] stage C), or new hepatocellular carcinoma not eligible for surgical resection, liver transplantation, or thermal ablation after a previously cured hepatocellular carcinoma (cured by surgery or thermoablative therapy), or hepatocellular carcinoma with two unsuccessful rounds of transarterial chemoembolisation.
      3. Patients were randomly assigned (1:1) to receive continuous oral sorafenib (400 mg twice daily) or SIRT with 90Y-loaded resin microspheres 2–5 weeks after randomisation.
      4. The primary endpoint was overall survival. Analyses were done on the intention-to-treat population
   2. Results:
      1. N=467 patients (237 were assigned to SIRT and 222 to sorafenib)
         1. In the SIRT group, 53 (22%) of 237 patients did not receive SIRT; 26 (49%) of these 53 patients were treated with sorafenib.
      2. Median follow-up was 27.9 months (IQR 21·9–33·6) in the SIRT group and 28.1 months (20·0–35·3) in the sorafenib group.
      3. Median overall survival was 8.0 months (95% CI 6.7–9.9) in the SIRT group versus 9.9 months (8.7–11.4) in the sorafenib group (hazard ratio 1.15 [95% CI 0.94–1.41] for SIRT *vs* sorafenib; p=0.18).
      4. In the safety population, at least one serious adverse event was reported in 174 (77%) of 226 patients in the SIRT group and in 176 (82%) of 216 in the sorafenib group. 19 deaths in the SIRT group and 12 in the sorafenib group were deemed to be treatment related.
   3. Conclusion: In patients with locally advanced or intermediate-stage hepatocellular carcinoma after unsuccessful transarterial chemoembolisation, overall survival did not significantly differ between the two groups. Quality of life and tolerance might help when choosing between the two treatments.

*FOXFIRE, SIRFLOX, and FOXFIRE-Global*

1. **Wasan 2017** (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5593813/pdf/main.pdf>)
   1. Combined analysis of FOXFIRE, SIRFLOX, and FOXFIRE-Global RCTs for yttrium-90 with chemotherapy compared to chemotherapy alone for colorectal liver metastases to the liver
   2. Combined analysis of 3 trials done in 14 countries for chemotherapy-naive patients with metastatic colorectal cancer (WHO performance status 0 or 1) with liver metastases not suitable for curative resection or ablation
   3. Methods:
      1. Treatment groups: oxaliplatin-based chemotherapy (FOLFOX: leucovorin, fluorouracil, and oxaliplatin) or FOLFOX plus single treatment SIRT concurrent with cycle 1 or 2 of chemotherapy.
      2. Participants and investigators were not masked to treatment.
      3. The primary endpoint was overall survival, analysed in the intention-to-treat population, using a two-stage meta-analysis of pooled individual patient data. All three trials have completed 2 years of follow-up.
   4. Findings:
      1. N=549 FOLFOX alone, 554 FOLFOX plus SIRT
      2. Median follow-up was 43.3 months (IQR 31.6–58.4).
      3. There were 411 (75%) deaths in 549 patients in the FOLFOX alone group and 433 (78%) deaths in 554 patients in the FOLFOX plus SIRT group. There was no difference in overall survival (hazard ratio [HR] 1.04, 95% CI 0.90–1.19; p=0.61). The median survival time in the FOLFOX plus SIRT group was 22.6 months (95% CI 21.0–24.5) compared with 23.3 months (21.8–24.7) in the FOLFOX alone group.
      4. Serious adverse events of any grade occurred in 244 (43%) of 571 patients receiving FOLFOX alone and 274 (54%) of 507 patients receiving FOLFOX plus SIRT. 10 patients in the FOLFOX plus SIRT group and 11 patients in the FOLFOX alone group died due to an adverse event; eight treatment-related deaths occurred in the FOLFOX plus SIRT group and three treatment-related deaths occurred in the FOLFOX alone group.
   5. Interpretation Addition of SIRT to first-line FOLFOX chemotherapy for patients with liver-only and liver-dominant metastatic colorectal cancer did not improve overall survival compared with that for FOLFOX alone. Therefore, early use of SIRT in combination with chemotherapy in unselected patients with metastatic colorectal cancer cannot be recommended. To further define the role of SIRT in metastatic colorectal cancer, careful patient selection and studies investigating the role of SIRT as consolidation therapy after chemotherapy are needed.
2. **NICE 2013**, guidance on SIRT for primary intrahepatic cholangiocarcinoma
   1. Current evidence on the safety and efficacy of selective internal radiation therapy (SIRT) for primary intrahepatic cholangiocarcinoma is limited in both quantity and quality. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

Other guidelines

1. **NCCN 2015**, hepatocellular carcinoma
   1. Locoregional therapy should be considered in patients who are not candidates for surgical curative treatments, or as part of a strategy to bridge patients to other curative therapies.
   2. Radioembolization (RE) with yttrium-90 is listed as a locoregional therapy
   3. Listed as category 2B
   4. Sorefenib is recommended as first line, with locoregional therapy second line in the majority of these cases
   5. Evidence reviewed that yttrium-90 RE has been found to be safe and effective in the treatment of non-resectable cholangiocarcinoma
   6. For HCC, ablation therapy should be first line, and locoregional therapy, including yttrium RE, should only be considered when ablation is not feasible

HERC staff summary: New randomized controlled trial data of yttrium 90 compared to standard chemotherapy for either primary hepatocellular carcinoma or metastatic colorectal cancer in the liver find that this therapy is at best no better than standard chemotherapy. There is a concerning trend in the data that yttrium 90 actually reduces survival and increases serious complications, although this was not statistically significant. Yttrium 90 is a much higher cost therapy than traditional chemotherapy.

HERC staff recommendation:

1. Do not add yttrium-90 radioembolization (CPT 79445) as a treatment to Line 320 CANCER OF LIVER
2. Add a new entry to GN172/line 500 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS as shown below for yttrium-90 for treatment of primary hepatocellular carcinoma, or colorectal cancer metastatic to the liver
   1. Less cost-effective than conventional chemotherapy
   2. May be harmful

# GUIDELINE NOTE 172, INTERVENTIONS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS

Line 500

The following interventions are prioritized on Line 500 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS:

| Procedure Code | Intervention Description | Rationale | Last Review |
| --- | --- | --- | --- |
| 79445  C2616 | Radiopharmaceutical therapy, by intra-arterial particulate administration for use in treating primary hepatocellular carcinoma or colorectal cancer metastatic to the liver  Brachytherapy source, non-stranded, yttrium-90, per source, for use in treating primary liver cancer or metastatic cancer to the liver | Low cost-effectiveness compared to equally effective but less expensive standard chemotherapies; concern for possible harms compared to standard chemotherapy | January, 2018 |