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Medico-economic study of the management of hepatocellular carcinoma by chemo-embolization

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KEYWORDS
Medico-economic analysis; Cost minimization; Chemo-embolization; Hepatocellular carcinoma

Abstract
Purpose: This study has two aims. The first is to compare conventional lipiodol chemo-embolization (Trans Arterial Chemo-Embolization — TACE) to one using pre-loaded particles (Trans Arterial Chemo-Embolisation-Drug Eluted Bead — TACE-DEB) using a cost minimization study. The second is to define the fundable nature of TACE-DEB and the conditions under which it is cost-effective.

Materials and methods: Retrospective study of patients treated by chemo-embolization (n = 31: TACE; n = 32: TACE-DEB) during the year 2010. The cost minimization study was conducted from the hospital perspective. Direct medical costs were calculated and compared using the readjusted ENCC (National Studies of Costs by Common Methodology) method. The affordability of the two techniques and definition of a cost-effective hypothesis (break-even point) were also established.

Results: All DRGs combined, lengths of stay (TACE: 4.90 ± 3.36; TACE-DEB: 5.03 ± 3.36) does not change significantly. An average upper mean cost for TACE-DEB is described (TACE: 2869.05 €; TACE-DEB: 3960.10 €). The affordability calculations in the study show that, overall, TACE-DEB can be funded regardless of DRG. A ratio of 1.3 procedures using the conventional (TACE) method would enable TACE-DEB procedures to be funded.

Conclusion: This medico-economic analysis demonstrates that the TACE-DEB procedure is fundable.

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Liver cancer, or hepatocellular carcinoma (HCC), is the third leading cause of cancer deaths throughout the world [1]. It is the fifth most common cancer in the world and has an estimated incidence of approximately 700,000 new cases annually [2]. Because it is paucisymptomatic resulting in late diagnosis, only a third of patients suffering from HCC are eligible for curative treatment. Clinicians offer palliative care with embolization of the feeder vessels for two-thirds of inoperable, non-metastatic HCC (Child A-B, intermediary stage by the BCLC [Barcelona Clinic Liver Cancer] classification [1,2]. Two embolization approaches are currently available using interventional radiology techniques. The first is based on the principle of injecting a chemotherapy emulsified in lipiodol followed by vascular embolization with resorbable particles. This is the conventional technique or TACE (Trans Arterial Chemo-Embolization). The second more recent technique uses non-resorbable microspheres loaded with cytotoxic agents, usually doxorubicin. These are carried out in a single interventional stage and are commonly called TACE-DEB (TACE-Drug Eluting Beads).

Both techniques have been shown to offer similar efficacy in terms of patient’s length of survival [3]. TACE-DEB has significant technical advances as it does not require extemporaneous preparation; light anesthesia can be given and liver function is protected by targeted chemo-embolization. Access to this latest technique in healthcare establishments is currently still limited, particularly because of a lack of specific reimbursement by the health insurance system. The economic and organizational landscape of the healthcare system in France changed greatly in 2004 with the hospital funding reforms and introduction of activity based tariffs (TAA) (law no. 2003-1199 of 18 December 2003). As such, healthcare establishments are funded by their activity (type and volume of procedures) by amounts linked to the hospital stays (SRG: Stay Reference Group). In parallel, and in order to allow access to expensive new medicinal products and devices (MD), a list of reimbursable products in addition to the SRG was introduced. This system is limited in terms of the time delay to approve new procedures and devices, particularly new technological and therapeutic developments such as the TACE-DEB technique. The cost of this new technique is therefore only partially covered by the stay tariff.

As TACE-DEB and TACE are similarly effective, and in view of the technical advantages of TACE-DEB and its lack of reimbursement we set out to conduct a medico-economic study to support healthcare establishments in making decisions.

We have carried out a retrospective medico-economic cost minimization analysis to establish the least expensive chemo-embolization technique from the hospital’s perspective [4]. The cost minimization analysis is the main aim of this study. In parallel, a secondary objective was to establish whether or not chemo-embolization was fundable for the establishment, based on a affordability analysis and measurement of the break-even point.

Materials and methods

Patients

This retrospective study was carried out on patients suffering from inoperable, non-metastatic HCC. The patients received a course of hepatic chemo-embolization between 1st January 2010 and 31st December 2010 at the Nantes University Hospitals, either TACE (26 patients) or TACE-DEB (24 patients). Each course received by the patient was deemed to be a new procedure. No age or sex criteria were included. The different stages of the liver disease were defined according to the Barcelona classification. Post-hospital admission consequences were not included. The doxorubicin-loaded particles used were DC-Beads™ (Terumo, Louvain, Belgium) and the (lipiodol) embolization particles used for the TACE were either resorbable (Gelatins: GelitaLason or GelitaPutty™, Gelita Medical, Estissac, France) or non-resorbable (Embogold™ calibrated particles, Merit Medical, Voisins le Bretonneux, France).

Treatments

The indication for TACE or TACE-DEB was decided in a weekly multidisciplinary meeting attended by a radiologist, a surgeon, a gastroenterologist, an oncologist and a radiotherapist. The decisions were consistent with the guidelines from the Barcelona conference [5] and the TACE and TACE-DEB procedures were carried out using standard protocols in the Departments of Radiology. In both treatment types, the angiographic techniques used involved catheterization of the hepatic artery from a femoral approach and then selective catheterization of the arterial pedicles feeding the tumors. In the case of TACE, this was followed by infusion of an emulsion containing 10 mL of Lipiodol™ (Guerbet, France) and doxorubicin (50–75 mg/m²) followed by embolization with hemostatic gelatin fragments or microspheres, depending on angiographic findings and the operator’s usual practice until flow stagnated in the 2nd and 3rd order branches of the hepatic artery. In the case of TACE-DEB, treatment involved an injection of a mixture of 4 mL of DC-Bead™ loaded with 150 mg of doxorubicin and non-ionic iodinated contrast medium.

Cost minimization study

Perspective

The perspective used was that of the hospital, counting expenditure related to the length of stay for each procedure and DRG (Diagnostic Reference Group) costs according to the ENCC (French National Scale for Common Methodology Costs) [6], readjusted for the actual length of stay in the establishment.

Measurement of costs

As the cost minimization study was retrospective, we considered the direct medical costs which were analyzed using the readjusted ENCC method [6]. Briefly, DRGs are used to estimate the costs from PMSI data (Programme to Medicalise Information Systems) and from ENCC. Average national costs are reprocessed in order to apply to the establishment in which the study is being carried out. Allocation to different expenditure lines is used to obtain two types of costs: fixed and variable. The fixed costs are clinical expenditure, logistics, and general administration and are applied on a daily basis to obtain a fixed daily cost. Variable costs do not
depend on length of stay and are the medical and technical expenditure and costs directly related to the patient \cite{7}.

The DRG categories examined in this study were °malignant hepatobiliary or pancreatic system disorders” from level 1 (no significant severity) to level 4 (major severity) representing the severity levels from each of the patients. These severity levels take account of case severity by incorporating associated complications or morbidities. Each DRG has a tariff, which is shown in Table \ref{table:1}.

Calculation of consumable costs
All of the IMD and other consumables required for the procedure were recorded and their costs were calculated from the hospitals’ agreed tender prices. A microcosting analysis was carried out to prepare the loaded particles in the UPCO (Clinical and Oncology Pharmacy Unit). This method was used to precisely establish the resources used by each patient in a procedure: surgical time, equipment used, laboratory investigations and imaging, etc. Calculation of resources the resources consumed was used to establish the actual costs attributable to the different strategies (Table \ref{table:2}).

Calculation of establishment hospitalization costs
The DRG representing the different stays chosen were provided by the Nantes University Hospital Medical Information Department (DIM). The related lengths of stay were recovered from the Nantes University Hospitals with Clinicom™ software (Intersystems France, Paris, France). The fixed and variable costs were weighted by DRG and length of stay.

SRG reimbursement
The Nantes University Hospital DIM searched for the theoretical and actual SRG reimbursement rates for each procedure carried out during the study period.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>List of DRG linked to the SRG 2010 tariffs and upper and lower limits.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRG</td>
<td>Wording</td>
</tr>
<tr>
<td>07M061</td>
<td>Malignant, hepatobiliary or pancreatic system disorders, level 1</td>
</tr>
<tr>
<td>07M062</td>
<td>Malignant, hepatobiliary or pancreatic system disorders, level 2</td>
</tr>
<tr>
<td>07M063</td>
<td>Malignant, hepatobiliary or pancreatic system disorders, level 3</td>
</tr>
<tr>
<td>07M064</td>
<td>Malignant, hepatobiliary or pancreatic system disorders, level 4</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Table 2</th>
<th>Description of medical devices used depending on the type of embolization.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of embolization</td>
<td>TACE conv.</td>
</tr>
<tr>
<td>Embolization agents</td>
<td>1 Geli-Putty® hemostatic gelatin unit</td>
</tr>
<tr>
<td>or IMD</td>
<td>Or</td>
</tr>
<tr>
<td>1 bottle of embolization microspheres Celonova</td>
<td>124.17</td>
</tr>
<tr>
<td>Other consumables</td>
<td>1 TERUMO Angled 0.032 guide</td>
</tr>
<tr>
<td></td>
<td>1 Cobra Small 5F catheter</td>
</tr>
<tr>
<td></td>
<td>1 TERUMO 5F short introducer</td>
</tr>
<tr>
<td></td>
<td>1 2-way HP tap</td>
</tr>
<tr>
<td></td>
<td>1 Progreat 2.7 TERUMO* micro-catheter</td>
</tr>
<tr>
<td>TOTAL</td>
<td>400.76 to 524.93</td>
</tr>
</tbody>
</table>

Unit price (U.P.). Excluding tax (ex. tax) extracted from the establishments tendering database. *Quasi-routine use.
Affordability study

Affordability calculation: cost effectiveness was calculated using the following equation:

\[ \text{Affordability} = \frac{\text{SRG payment}}{\text{Total cost of stay}} \]

The total cost of the stay was the sum of the fixed and variable costs.

Calculation theoretical affordability

Theoretical affordability was calculated from the theoretical SRG payments set by the Decree of 27 February 2010 for the year 2010 according to the following equation [6]:

\[ \text{Theoretical affordability} = \frac{\text{Theoretical SRG 2010 payment}}{\text{Total costs of stay}} \]

Calculation of actual affordability

Actual affordability was calculated from the actual payments obtained from the DIM.

\[ \text{Actual affordability} = \frac{\text{Actual payment}}{\text{Total cost of stay}} \]

Affordability break-even point

The hypothesis used was based on defining a number of TACE procedures which could be performed in order to compensate for the average deficit due to a less cost-effective TACE-DEB procedure.

Results

Population

Thirty-one conventional TACE and 32 TACE-DEB courses were recorded in 2010.

Forty-nine of the procedures included or carried out in men and 14 in women. The sex ratio was uneven with 3.5 times more men than women treated. This is consistent with national epidemiological findings. The average age was 65 years old.

Patient distribution by DRG

Four DRG were involved (07M061, 07M062, 07M063, 07M064). The distribution of patients who underwent TACE or TACE-DEB according to the different DRG is shown below:

- DRG 07M061: 20 TACE, 26 TACE-DEB;
- DRG 07M062: 6 TACE, 4 TACE-DEB;
- DRG 07M063: 5 TACE, 1 TACE-DEB;
- DRG 07M064: 1 TACE-DEB.

Length of hospitalization

The average lengths of hospitalization for each DRG are listed in Table 3. When all of the DRGs were combined, there were no significant differences between the lengths of stay regardless of the chemo-embolization technique used.

Cost minimization analysis

The average total stay costs were used to make a financial comparison of the two types of chemo-embolization (Table 3).

When all of the DRG combined, the average cost of a TACE-DEB chemo-embolization was 3960.10 € compared to 2869.05 € for a TACE. This therefore represents an additional cost of 1091.05 €.

The embolization agents were responsible for the major additional cost of the difference between the average stay costs. The Doxorubicin loaded embolization particles were responsible for an additional cost of 879.44 €. These particles alone therefore made up 25% of the total stay cost whereas the IMD for lipiodol chemo-embolization only represented 2% of the total stay cost.

The average cost of the other consumables for the TACE-DEB procedure was 77.20 € more than the cost of a TACE procedure.

Affordability study

The first comparison of theoretical affordability was carried out before considering actual affordability.

The sum of the theoretical affordability for each of the chemo-embolizations by DRG is shown in Fig. 1. Regardless of embolization type, the theoretical SRG tariff for DRG 07M061 does not cover the cost of chemo-embolization. When the stay is included in DRGs 07M062 and 07M063, however, the conventional chemo-embolization technique (TACE) becomes cost-effective whereas the TACE-DEB technique remains in deficit. The TACE-DEB technique is only cost-effective when DRG 07M064 is used.

Analysis of the distribution of procedures by theoretical affordability and (Fig. 2) shows firstly that the conventional TACE technique is generally cost-effective in 64% of cases, compared to 13% for TACE-DEB technique. On the other hand, affordability is particularly negative for TACE-DEB, 47% of procedures result in a loss of over 1000 € compared
Table 3  Comparison of lengths of stay and all mean costs between conventional TACE and TACE-DEB.

<table>
<thead>
<tr>
<th>DRG</th>
<th>TACE conv.</th>
<th>TACE-DEB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean length of stay DMS (d)</td>
<td>Mean cost of stay (€)</td>
</tr>
<tr>
<td>07M061</td>
<td>4.30</td>
<td>2801.24</td>
</tr>
<tr>
<td>07M062</td>
<td>4.33</td>
<td>2436.38</td>
</tr>
<tr>
<td>07M063</td>
<td>8.00</td>
<td>3659.52</td>
</tr>
<tr>
<td>07M064</td>
<td>5.00</td>
<td>3704.79</td>
</tr>
<tr>
<td>Mean of SRG and costs</td>
<td>4.90 ± 3.36</td>
<td>2869.05</td>
</tr>
</tbody>
</table>

Mean Length of Stay (DMS) and mean costs are expressed for each of the Diagnostic Reference Groups (DRG) included in this study. Lengths of stay were extracted from the healthcare software (Clinicom). The average cost of stay was assessed using the readjusted ENCC method. IMD and the consumable costs were determined by microcosting of reconstitution of the chemo-embolization particles. The mean of the DMS and the mean of the costs for all DRG by embolization technique were also calculated.
Overall, and calculated the Figure 4 of the TACE technique remains theoretically cost-effective in 64% of cases compared to 12% of the TACE-DEB technique.

to 9% of TACE procedures. Therefore eighty-seven per cent of TACE-DEB chemo-embolization produce a deficit.

The actual payments may differ from the theoretical SRG payments, particularly when expensive compounds (doxorubicin) or IMD which are additionally reimbursed are required (none in this situation). These payments can also be influenced by the patient reimbursement rates. Data on actual affordability are shown in Figs. 3 and 4.

Unlike the theoretical affordability assessment, actual affordability can show whether the conventional technique is fundable regardless of the DRG, including DRG07M061 (Fig. 3). Overall, the TACE-DEB technique is also fundable regardless of DRG (Fig. 3).

An analysis of the distribution of procedures by positive or negative affordability (Fig. 4) over the study period shows that almost all of the conventional procedures are fundable (97%). Only one stay was found to have negative affordability of 0 to −500 € which is explained by high use of concomitant MD as the patient underwent parallel radio-frequency ablation in parts of the tumor (Fig. 4).

In terms of the TACE-DEB procedures, we can consider that half of these are fundable. Actual affordability of over 0 € is seen for 50% of patients treated with TACE-DEB (Fig. 4).

**Affordability breakeven point**

In order to be cost-effective, an average of at least 1.3 times more conventional TACE procedures needs to be performed than TACE-DEB. In reality in 2010, 75 conventional TACE procedures and 33 TACE-DEB procedures were carried out, i.e. 2.3 times more conventional TACE than TACE-DEB procedures, which leads us to assume that the establishment profited from the chemo-embolizations carried out in 2010.

**Discussion**

The chemo-embolization techniques proposed recently to treat patients suffering from non-metastatic, inoperable HCC are new techniques whose financial impact on healthcare establishments is poorly understood. The only randomized phase II study (PRECISIONV study) which has been published to date comparing patients treated with conventional chemo-embolization (TACE) or chemo-embolization with loaded microspheres (TACE-DEB) showed no significant difference between the 2 procedures in terms of 6 month efficacy [3] The medico-economic analysis, and particularly a cost minimization analysis, therefore appeared to be a useful tool for healthcare establishments in deciding on their strategic choices [4]. From this, our study has shown that a ratio of 1.3 procedures using the conventional method (TACE) should allow TACE-DEB procedures to be funded.

Our analysis of economic data showed a significantly higher additional stay cost for TACE-DEB compared to a conventional TACE stay (average 1091.05 €). These
differences are explained by two main expenditure lines: firstly expenditure due to other consumables including non-
implantable MD used during the embolization technique
(catheter, guide, probe, micro-cathether). Micro-catheters
(335.00 € per unit excluding tax.) are used almost routinely
in TACE-DEB chemo-embolization whereas this is not the
case with the TACE procedure. The second cost plan explain-
ing the differences are the IMD made up of the embolization
agents.

A comparison of actual and theoretical affordability
shows that actual payments are on average 1.5 times greater
than theoretical payments, therefore reducing the addi-
tional cost and increasing affordability. These differences
can be explained by use of expensive molecules during the
stay, which require additional reimbursement (partic-
ularly doxorubicin). These costs are incorporated into the
actual payments by the Nantes University Hospitals conver-
gence rate and by patient reimbursement rates given by the
National Health Insurance Funds.

The theoretical payments were used in the subsequent
assessment of loaded particles in order to be able to remove
bias, particularly from differential patient reimbursement
rates.

The theoretical affordability studies showed that only
13% of TACE-DEB procedures are cost-effective compared
to 64% for conventional procedures. In order to examine
how loaded microspheres could be fundable, a break-even
affordability hypothesis was put forth. The two techniques
for the procedures become fundable when they are used
together in the ratio of 1.3 conventional TACE procedures
to each TACE-DEB procedure. This involves patient selec-
tion and selection of disease severity so that its activity can
be funded by the health care establishment.

This retrospective study has showed that the use of
loaded particles has a genuine financial impact although the
limitations of the study sample need to be considered.
The study population was not matched, which reduces the
power of the statistical tests, and in addition, low patient
recruitment in the DRG of patients with high co-morbidities
(DRG 07M063 and DRG 07M064) in the conventional TACE
group makes it difficult to interpret and compare the two
types of embolization. The cost minimization analysis which
was carried out, however, does show an additional cost of
chemo-embolization with loaded particles to treat HCC in
the establishment over the year 2010. These results are
consistent with those of another study which showed a sig-
nificantly higher annual cost for TACE-DEB [8]. Another study
has shown a lower overall cost for chemo-embolizations car-
rried out using HepaSphere™ loaded microspheres (Biosphere
Medical, South Jordan, USA) compared to conventional
chemo-embolization. [9]. This reduction in cost was mostly
due to the lower intrinsic cost of the HepaSphere™ com-
pared to the DC-Bead™ used in our study. This study also
only considered the first course of chemo-embolization and
not all of the courses received by the patients suffering
from HCC. In addition, patients recruited for chemo-
embolization with HepaSphere™ had uni- or paucifocal HCC
and multifocal or diffuse HCC was treated with conven-
tional chemo-embolization. These were therefore patients
suffering from less severe HCC who were selected to receive
chemo-embolization with HepaSphere™. Finally, this study
was based on two different versions of the DRG classifica-
tion (versions 10C and v11) which had fewer severity levels in the
10C version and resulted in a shift of patient classification,
towards severer co-morbidities which were therefore better
remunerated. Four levels of severity are listed in the current
version. The reimbursement of patients with co-morbidities is
financially lower (level 1 or 2) [10]. A study by the same

In addition to this cost analysis, this work shows that it is
possible to fund the DC-Bead™ for DRG 07M064. Along the
same lines as the studies discussed above [9,11], it would
probably be useful to continue investigations with particu-
lar emphasis on this DRG. As the Precision V study [3] showed
that DC-Bead™ laden particles offered a clinical benefit to
patients suffering from advanced HCC this new approach
would be particularly interesting. Future studies would also
need to take into account the anesthetic resources which are
more limited with the TACE-DEB technique, though this
is only rarely considered, and also take account of the fact
that patient tolerability is better for TACE-DEB than it is for
the TACE technique.

Conclusion
This study highlights the difference which may exist between
estimated hospital costs and the corresponding reimburse-
ment amount for the hospital stay. This shows sustainable
access to new surgical developments for each patient in
a context of hospital deficit reduction and the desire
for convergence between private and public healthcare
establishments. This study has demonstrated that TACE-
DEB procedures can be funded with a ratio of 1.3 to 1
(TACE/TACE-DEB).

Disclosure of interest
The authors declare that they have no conflicts of interest
concerning this article.

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