Journal of Oncology Research and Therapy
Diallo M, et al. Oncol Res Ther 10: 10264.
www.doi.org/10.29011/2574-710X.10264
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Research Article

Treatment of Hepatocellular Carcinoma (HCC) By Lipiodol Hepatic Chemoembolisation at the Senegal Army Training Hospital: About 41 Procedures

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Citation: Diallo M, Ndone A, Ndaw MDB, Diack A, Amar NI, et al. (2025) Treatment of Hepatocellular Carcinoma (Hcc) By Lipiodol Hepatic Chemoembolisation At the Senegal Army Training Hospital: About 41 Procedures. J Oncol Res Ther 10: 10264. DOI: 10.29011/2574-710X.10264.

Received Date: 20 January, 2025; **Accepted:** 28 January, 2025; **Published Date:** 31 January, 2025.

Abstract

Introduction: The diagnosis of HCC is often late in West Africa. Thus, only palliative treatment is available in the majority of cases. Hepatic chemoembolization (CHE) is a treatment of choice whose goal is to extend the survival of patients. The objective of this work is to assess the first activity of CHE in West Africa and to give its results. **Material And Methods:** This is about a descriptive retrospective study of 23 patients with intermediate stage (B) HCC according to the BCLC algorithm. A total of 41 HCC procedures were performed in 3 years. Some patients had multiple sessions. The vascular approach was Seldinger femoral arterial under local anesthesia, followed by catheterization and sometimes microcatheterization of the target arteries. An emulsion of Lipiodol and Doxorubicin-based chemotherapy was injected and then temporary embolization was performed with resorbable gelatin. Tumor response was assessed 1 month after HCC according to the LIRADS 2018 criteria and with a multiphasic CT scan. **Results:** The mean age of our cohort was 49 years. Uni- or multinodular forms were found in 21 patients with a predominant diameter of 2 to 5 cm. The infiltrating form was noted in 3 patients. Eight anatomical variants of hepatic artery arrangement were noted. No major complications were observed per or post procedure. 2 cases of post-CHE syndrome and one hematemesis were encountered post procedure. The tumor response was considered viable in 9 patients or 45%, and non-viable in 7 patients or 35%. The correlation between tumor response and lesion appearance highlights a rate of 100% viable responses for infiltrating lesions and a rate of 71.4% non-viable responses for nodular lesions. The survival rate over the 3 years of activity is 63%.. **Conclusion:** Hepatic CHE is a palliative treatment of choice in Senegal and throughout West Africa because the diagnosis of liver tumors, especially HCC, is often late. It is an available treatment with a controlled practice.

Keywords: Chemoembolization; HCC; SENEGAL; Army training hospital;

Introduction

Chemoembolization (CHE) is an interventional radiology technique that was developed in the 1970s mainly in Japan thanks to the Japanese surgeon Konno [1]. It consists in the intra-arterial hepatic injection of an anti-cancer agent via a vector and completed by arterial occlusion.

The anti-cancer agent is chosen according to the tumor treated and the vectors used are of two types: lipiodol and embolization microspheres [2].

Lipiodolated or conventional chemoembolization (CEL) is completed by the administration of resorbable embolization agents such as gelatin.

Lipiodol is a lipophilic iodinated contrast agent that has the property of remaining in contact with tumor and peritumoral tissue for several weeks. Its radio-opaque nature allows to control the injection of the emulsion and its fixation on HCC nodules. Finally, its ability to conform to the size of the vessels enables it to reach the portal venules through the arterio-portal anastomoses [2].

CHE with embolization microspheres loaded with an anti-cancer agent has the advantage of combining arterial occlusion and a controlled and progressive release of the agent, with minimal systemic passage [3].

CHE is mainly indicated in the palliative treatment of liver tumors, especially hepatocellular carcinoma [4].

According to the GLOBOCAN 2018 study, HCC is the second leading cause of cancer in our country in men, and the third leading cause in women [5]. This is due to the high prevalence of hepatitis B virus infection. HCC is very often diagnosed at an advanced stage due to still limited access to care and delays in consultations.

In the management of HCC, European and American learned societies recommend the use of the Barcelona Clinic Liver Cancer (BCLC) algorithm [6]. Chemoembolization is recommended at intermediate stage B in patients with an unresectable tumor, with preserved liver function, without portal or extrahepatic invasion.

The non-invasive nature, the possibility of repeating the procedure a large number of times, as well as the local delivery of chemotherapy, make it a palliative treatment of choice.

The establishment of angiography facilities in Dakar thanks to the concomitant development of interventional cardiology, has allowed, in particular at the main hospital of Dakar, the performance of a certain number of hepatic chemoembolization procedures. This has driven us to assess this activity with the general objective of providing its first results. The specific objectives being to analyze the epidemiological and CT aspects of the HCCs in our cohort, to describe our technique of lipiodolated HCC and to analyze patient survival.

Materials and Methods

This is about was a retrospective, descriptive and analytical study of 41 chemoembolization (CHE) procedures performed in 23 patients between October 2019 and August 2022.

We included any patient with HCC who had received one or more courses of lipiodolated CHE. (CEL) Patients whose records presented incomplete epidemiological, clinical, paraclinical or evolutionary information were excluded.

The data collection was done using a standardized survey form from patient records, the CHE protocol register and scanner reports.

Data entry and processing were carried out using EXCEL and Sphinx plus software.

Data are expressed in absolute value, percentage, mean, median and were used to draw up graphs and tables.

The CELs were performed in hospital and in a multipurpose angiography room equipped with a General Electric brand device and the OPTIMA IG 5 330 model. Under strict aseptic conditions and local anesthesia, right femoral vascular access was performed followed by the placement of a 5 French caliber Desilet valve introducer. This was followed by catheterization or microcatheterization of the hepatic arteries using Cobra or Simmons probes with a diameter of 4 F or 5 F mounted on hydrophilic guides or microcatheterization mounted in microguides. Prior angiographies allowed for global vascular mapping in order to identify the arteries feeding the tumors (Figure 1 shows the equipment required for such a procedure). This was followed by an injection of the CHE product obtained by emulsion of a mixture of 10 ml of Lipiodol Ultra Fluide from Guerbet laboratories and an anti-cancer agent (50 mg of Doxorubicin). The complete emulsion was achieved through the technique known as the “pumping method”, using two 20 cc syringes and a 3-way tap, allowing the successive passage of the contents from one syringe to the other (Figure 2).

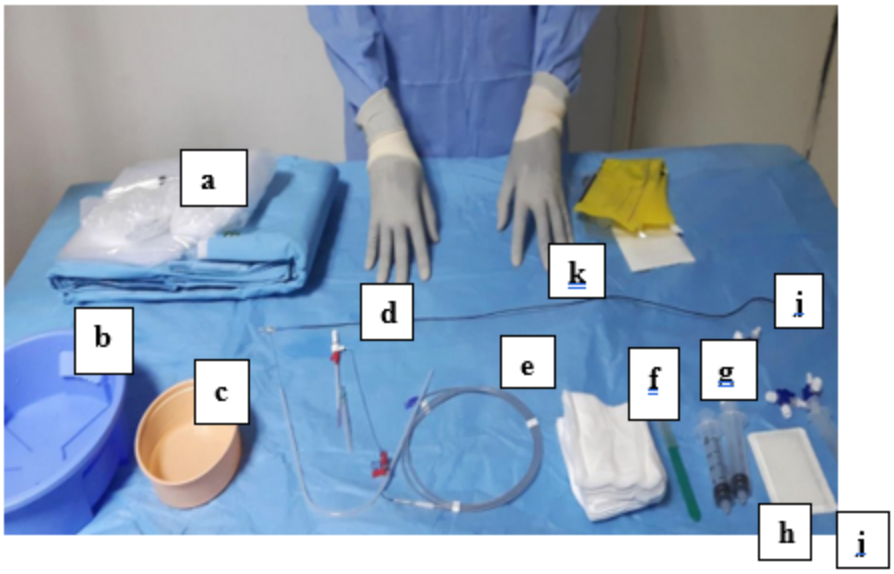

Figure 1: Equipment required for performing a CHE.

a: Sterile field; b: Water tank; c: Cupule; d: Desilet; e: Hydrophilic guide; f: Compresses; g: Scalpel blades,

h: Syringe; i: Resorbable gelatin tablet; j: Three-way stopcock; k: Cobra 4 probe French.

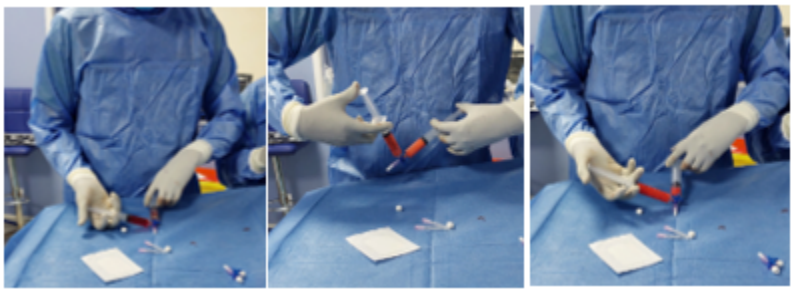

Figure 2: Preparation of the emulsion of the anti-cancer agent and the vector (lipiodol) by the "pumping method."

The injection of this mixture was performed in free flow in the right and/or left hepatic arterial branches, or directly in the artery supplying the tumor in the case of supra-selective catheterization. Temporary embolization of the arteries feeding the lesion by a resorbable gelatin slurry completed the procedure. The technical success was demonstrated by a lipoidal capture at the tumor region (Figure 3).

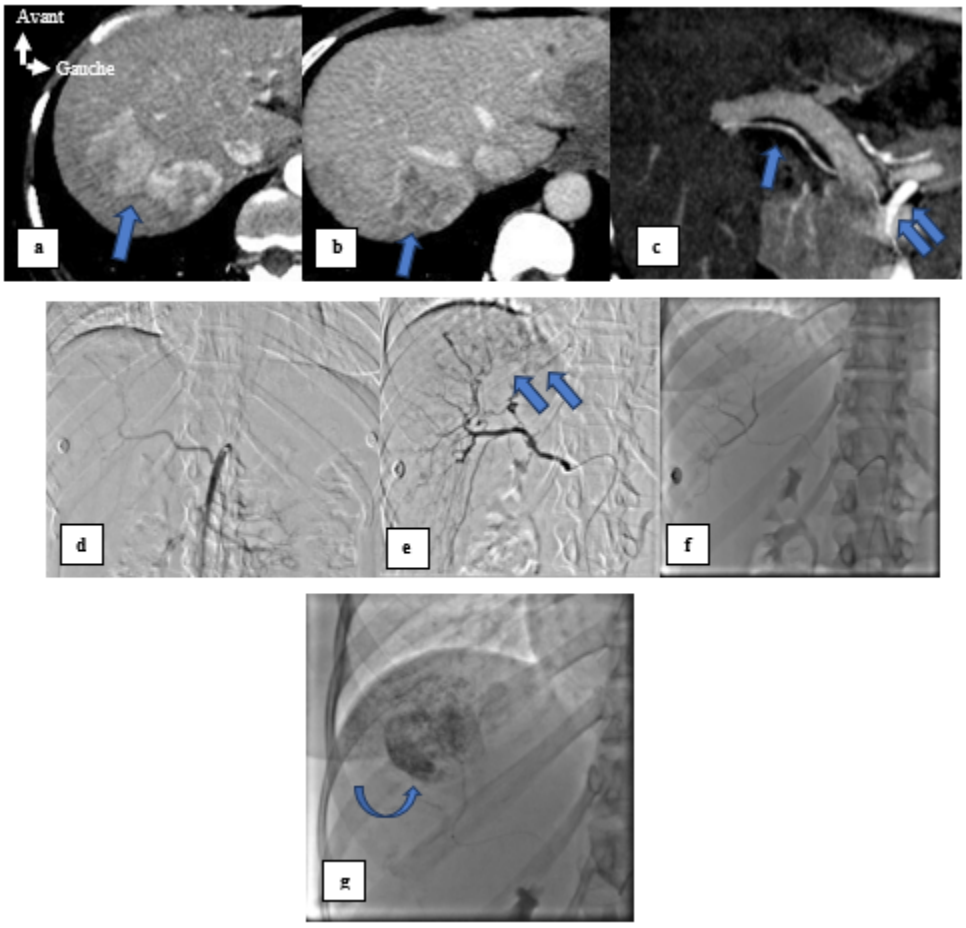

Figure 3: 40-year-old female patient, chronic hepatitis B virus infection. Bi-nodular HCC of segment VII with wash-in and wash-out on CT scan (arrow in a and b) and right hepatic artery (single arrow in c) arising from the superior mesenteric artery (double arrow in c). Treatment by CEL with subtracted angiography after catheterization of the superior mesenteric artery (d) with a cobra probe then of the right hepatic artery with a Simmons type probe (e). Tumor blush at the level of the hepatic dome (double arrow in e). Microcatheterization of the main feeding artery then injection of the Doxorubicin and Lipiodol emulsion followed temporary embolization with resorbable gelatin. Lipiodol uptake at the end of the procedure at the level of the region of interest (curved arrow in g).

At the end of the procedure, the desilet was removed and manual compression for at least 10 minutes was applied to the puncture site to prevent any bleeding, then a compressive dressing was applied for 24 hours.

A post-procedure monitoring was required in the hospitalization room with strict bed rest in the supine position without bending the leg on the punctured side, monitoring of vital signs (temperature, blood pressure, pulse) and checking of the compressive dressing, with removal of the latter the next day. Symptomatic treatment was prescribed if fever, abdominal pain or any other symptoms appeared.

Hospitalization was usually scheduled for 24 to 48 hours, but could be extended depending on the symptoms.

A control scan was performed 1 month after the CHE with a multiphasic protocol.

The cost of a CHE session is estimated at seven hundred thousand CFA francs (700,000) including days of hospitalization.

We studied the epidemiological parameters (age and sex of patients), clinico-biological parameters using the WHO clinical score and the Child-Pugh clinico-biological score [7], tumor parameters (size, shape and number of lesions), technical aspects

of CEL, response to treatment using the Liver Reporting And Data System (LIRADS) [8-9] which allows in a standardized way to classify the residual tissue into viable, non-viable or equivocal viability as summarized in Table III and finally the evolution and survival of patients.

Results

The average age of the population under study was 49 years with extremes ranging from 23 to 72 years. The age group 40-49 years was predominant. There was a male predominance with a sex ratio of 6.6, meaning 20 men against 3 women.

Clinical data could be exploited in 21 of our patients, and 20 patients had a WHO clinical score of 0, and only one had a WHO clinical score of 2, before the CHE was performed.

The assessment of the impact of the lesions on liver function could be done in 21 of our patients. Two patients had Child-Pugh scores B7 and B8 and the remaining 19 were classified as Score A before the procedure. The patient who had a WHO score of 2 also had a Child-Pugh score of B7. Of the 23 patients included, the diagnosis of HCC was made by CT scan. The most common radiological presentation of the tumors was the multinodular form representing 46% of the lesions with a predominant size in the 2 to 5 cm range, followed by the simple nodular form. Three patients presented an infiltrating form. Figure 4 summarizes the distribution of the different aspects found.

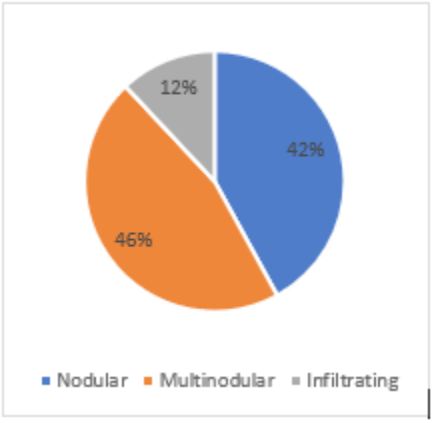

Figure 4: Lesional aspects of CHCs on CT before lipiodol-assisted CHE.

Over the 41 cures performed, no particular technical difficulties were encountered, even in cases of variant hepatic arteries. Indeed, 8 patients presented an anatomical variant with a right hepatic artery arising directly from the superior mesenteric artery in 6 patients and a common hepato-spleno-mesenteric trunk. All these variants were clearly highlighted on the scans before the procedures.

Two cases of post-chemoembolization syndrome were mentioned and one patient had presented a hematemesis post-procedure without clinical-biological severity.

Tumor responses were assessed one month after the CHE sessions and on a multiphasic abdominopelvic CT scan with contrast injection. They were assessed in 20 patients and we found a majority of viable lesions, i.e. 45%, 35% non-viable lesions. Figure 5 shows an example of a CT scan for assessing tumor response. The cross-tabulation between the lesion appearance and tumor response shows that the type of tumor response depends on the lesion appearance. In fact, single nodular lesions are correlated with a better response while infiltrating lesions are correlated with a poor tumor response. (Table 1)

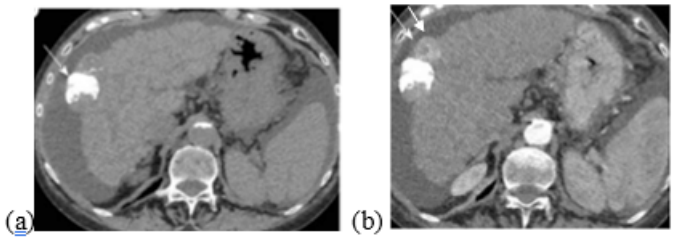

Figure 5: Axial post-TACE scan images with spontaneous contrast (a) and with contrast injection in the arterial phase (b): total lipiodol uptake of a nodule (single white arrow) of segment 5 not enhanced in the arterial phase (non-viable TR) associated with an adjacent nodule (double arrow) presenting partial lipiodol uptake and moderate enhancement in the arterial phase (equivocal TR).

LIRADS / **Lesion appearance**	LR-TR viable	LR-TR equivocal	TR non viable
Nodular	14,3 %	14,3 %	71, 4 %
Multinodular	58, 3 %	25%	16, 7 %
Infiltrating	100%	0,0 %	0,0 %

Table 1: Correlation between lesion appearance and tumor response.

Additional courses were performed for patients with viability on control scans. In total, 41 courses were performed in our 23 patients, an average of 1.7 courses. The maximum number of courses performed in a patient is 5.

Four patients underwent combined treatment with CEL. These included acetization, alcoholization, and surgical resection.

The evolution of our patients was marked by the occurrence of 7 deaths, 5 lost to follow-up or 5 patients who defaulted and 11 people still alive at the end of the study, i.e. a survival rate of

63% over 33 months. The infiltrating forms had a more pejorative prognosis with a survival that did not exceed 01 year.

Table 2 summarizes the correlation between patient survival and the forms of presentation of HCC.

Survival / Lesion appearance	< 1 year	1 year	2 years	3 years
Nodular	12,5%	62,5%	25%	0%
Multinodular	23,1%	46,2%	15,4%	15,4%
Infiltrating	33,3%	66,7%	0%	0%

Table 2: Correlation between lesion appearance and survival.

Discussion

Due to the diagnosis of HCC occurring most often at a late stage and especially in Africa, curative treatment can only be offered to 25% of patients [10]. Since 2015, CHE has been the palliative treatment of reference offered to patients not eligible for curative treatment according to the EASL recommendations [11-12]. Proof of the benefit of CHE in the overall survival of patients with unresectable HCC came late, and was supported by several meta-analyses, in particular that of Oliveri in 2011, which highlighted a benefit of approximately 20% [14-15]. Indeed, before the 2000s, the prospective studies of GETCH and Pelletier 1990-1998 had not reported any effect [16]. During the 2000s, three of the four published prospective studies highlighted a benefit of CHE on survival, notably those of Llovet and Lo [17-18].

This evolution of the results has been explained by the improvement of techniques and by a more targeted selection of patients during studies carried out during the 2000s.

Retrospective studies, specifically those of Bronowicki and Huang, have suggested an extension of the overall survival of patients treated by CHE [19-20].

Among these respectful authors, those who evaluated the response to treatment all observed a good post-CHE tumor response.

In our study, the recruitment of patients who were candidates for CEL was done in consultation between hepato-gastroenterologists, visceral surgeons and interventional radiologists.

According to the BCLC, CHE is indicated at intermediate stage B, in patients with lesions that are too large or multifocal and cannot be treated curatively, but who remain asymptomatic, in excellent general condition with preserved liver function up to Child Pugh B 7.

HCC is considered a tumor with a strong male predominance, our study thus found a sex ratio of 6.6 M / 1 F. The average age of 49 years is comparable to another Dakar study by Niang FG with an average of 40 years [21] but lower than those in the literature, particularly by Lo [18], Roth and Addo [22-23] who have in their cohort respective average ages of 62 years, 62 years and 61 years. This younger average in our series could be explained by chronic HBV infection, more frequent in our regions and which favors the early occurrence of HCC without going through the stage of liver cirrhosis.

On the clinical-biological level, we followed the recommendations of European and American learned societies that recommend CHE at intermediate stage B of the BCLC classification. In our cohort, 22 patients presented a good general condition, i.e. 95%, and 1 patient was classified WHO 2 but the preservation of his liver function with a Child Pugh score B 7 allowed him to be included in the CHE activity. Roth also studied the clinical condition of his patients according to the WHO scale and objectified 85% of WHO score 0 and 15% of WHO score 1 [23]. Most studies only used the preservation of liver function as an inclusion criterion for their patients. In our study, patients had good liver function with a proportion of Child Pugh A score of 91% and 8% of Child Pugh B. Yet, one patient was classified as Child Pugh B 8 while his general condition was good with a WHO score of 1. These data are close to studies in the literature, in particular those of Llovet and Lo [17-18], pioneers of CHE for this type of patient with preserved liver function.

Radiologically, we have objectified a predominance of multi-nodular and nodular lesions representing 46% and 42% of patients respectively. In the majority of studies, the infiltrating form was not observed or constituted an exclusion criterion except in that of Llovet [17] where we also found a majority of multi-nodular form at 65% and 3% of infiltrating form against 13% in our cohort. Conversely, Yuen had included a majority of patients with nodular presentation with 47.5% [24].

Concerning the size of the lesions, we found, like Niang FG [21], a majority of lesions of 2 to 5 cm representing 53%, with extremes ranging from 2 to 14 cm. In the literature, the selected cohorts presented lesions of variable sizes from one study to another. The mean number of lesions treated is 2.3 lesions ranging from 1 to 6 nodules. In the multi-nodular presentation, patients with 2 to 3 nodules represented a majority of 69% as in Roth [23].

Tumor response assessment was performed in our study according to the LIRADS system version 2018. Tumor response is considered a strong indicator for predicting patient survival. In oncology, tumor response assessment was initially measured according to the WHO [25] and RECIST [26] criteria. These two criteria designated

for the assessment of chemotherapies addressed the reduction of lesion size but did not take into account tumor activity or viability. The EASL and AALD have thus adopted a modified version of the WHO criteria called EASL criteria in which the assessment of tumor response no longer took into account only tumor size but also the presence of intralesional necrosis [27]. Also, clinical studies of RECIST criteria have found that tumor response assessment based on size may be misleading when applied to other anticancer treatments, such as molecular targeted therapies or interventional therapies [26]. Indeed, they do not reflect tumor viability or tumor burden reduction [28].

Viable tumor formations therefore need to be detected using a multiphasic CT or MRI study. Viability is defined by the lesion contrast uptake.

A modified version of the RECIST criteria, called mRECIST, was thus adopted by a panel of experts, based on the fact that the target lesion with viable tissue must guide all measurements [29-30].

Kouame [31] and Varela [32] thus found a zero percentage of complete response according to the RECIST criteria against 26% for Varela and 40% of complete responses for Kouame according to the mRECIST criteria. This is explained by the fact that the RECIST criteria can classify treated lesions as stable or progressive while the necrosis can be total or even extensive to the adjacent parenchyma.

In 2017, LIRADS introduced a new algorithm for assessing tumor response by adding new concepts to characterize tumor viability: tumor washout and post-treatment enhancement identical to that before treatment [8-9].

In 2022, Dong's meta-analysis demonstrated that the LIRADS system has a better specificity than the mRECIST criteria but that their sensitivity is comparable for the detection of tumor viability [33].

In our study, according to the LIRADS system, we found 35% of non-viable lesions, 20% of equivocal lesions and 45% of viable lesions.

Unlike Kierans [34] who found a high percentage of 62.2% of non-viable lesions, and a low rate of equivocal and viable lesions representing 8.4% and 28.1% respectively.

Concerning the number of courses, there are no limits as long as they are well tolerated and there is a tumor response.

Several authors, including Delpoggio [35] and Malagri [36] have shown that the first session does not allow for a satisfactory tumor response. In our study, we performed a total of 41 courses with an average of 1.78 courses per patient. The performance of an additional course was motivated by the persistence of a zone of lesion viability on the control radiological examination.

Albrecht [37] whose work focused on 40 micrometer embolization microspheres had identical results with an average of 1.7 treatments per patient and a maximum of 5 treatments.

Delpoggio [35] suggests that loaded microspheres allow for an earlier objective response with an average of 1.28 versus 2.14 in the group that received lipiodol as a vector.

In our series, we objectified an anatomical variant in 8 patients, i.e. 35%, while Diop AN [38] and Niang FG [21] reported 19% and 24% of variants, respectively. The most common variant was the presence of a right hepatic artery found in 6 patients (75% of variants), associated with a common hepato-spleno-mesenteric trunk and an early bifurcation of the left branch of the proper hepatic artery.

Despite this high percentage of variants, only one technical issue was encountered during the performance of these 41 procedures.

CHE is associated with morbidity and mortality estimated at 15% and 6% respectively and complications are classified as minor and major [39].

The most common minor complication is post-CHE syndrome induced by tumor necrosis. Major complications are of several types and different etiologies.

We can cite tumor lysis syndrome linked to significant tumor necrosis responsible for multi-organ failure, vascular lesions induced by repeated treatments and the accumulation of anti-cancer agents, extra-hepatic embolization occurring by reflux of the embolization product.

In our study, we found only two cases of minor complications including one post-CHE syndrome and one case of hematemesis (4%) of patients without any case of major complications as in the cohort of Niang FG [21]. This corroborates the thesis of a minimal risk of major complications in Child Pugh A and B patients.

On the evolutionary aspect, a total of 7 patients were recorded as having died during the study period (30.4%) with 21.7% lost to follow-up, meaning patients who defaulted. Albrecht [37] found a similar mortality of 33.7%, however without any loss to follow-up or patients who defaulted recorded. Our results in terms of survival are below those in the literature with 43% survival at 1 year, 14% at 2 years and 7% at 3 years. Indeed, Niang FG [21] objectified 78.5% survival at 1 year, 50% at 2 years, and Diop AN [38] 100% at 1 year and 67% at 2 years, while that of Albrecht [37] on 40 micrometer microspheres observed a survival of 83.2% at 1 year and 61.6% at 2 years. Our results are explained by the fact that infiltrating lesions were included in our series and that these lesions are correlated with a poorer prognosis.

Conclusions

Primary liver tumors, HCC in particular, raise a public health issue in African countries, due to the endemic B viral infection. Diagnosis is often late and curative treatments can only be offered to a limited number of patients. Chemoembolization thus remains one of the main palliative treatments according to the EASL recommendations. It is a treatment that extends patient survival and is now available and accessible in our region and with a controlled practice.

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