Chapter

Canine Hepatic Carcinoma: Diagnoses and Treatments Via Global State-of-the-Art Approach and Traditional Chinese Veterinary Medicine

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Abstract

This chapter discusses effective diagnostics and treatment of canine hepatic carcinoma (CHC), where state-of-the-art global technologies are complemented by traditional Chinese veterinary medicine (TCVM). The biokinetic Ga-67 model of CHC is proposed to clarify the Ga-67 metabolic mechanism among various organs. It is aimed at identifying the best routine for detecting the metastatic or primary CHC and substantiating the optimal further treatment. The routine examination of CHC can be performed via Ga-67 nuclear examination or MRI, biological index, X-ray, and abdominal ultrasound. The available methods of animal cancer treatment imply separate or combined application of surgery, radiation therapy, and chemotherapy targeted at the particular cancer cells. However, there is also a general concern on the quality of life of pets/canine patients. This leaves enough space to the TCVM (including acupuncture and famous herbal drugs) with a long application history in Asia and growing usage as alternative treatment in other regions. However, its current applications to domestic animals/pets suffering from carcinomas are based on individual expert opinions, while there are no outlined veterinary treatment strategies and guidelines for clinical practice in this field. A comprehensive combination of state-of-the-art global technologies and TCVM is considered instrumental in curing canine hepatic carcinoma.

Keywords: canine hepatic carcinoma, nuclear examination, Ga-67 biokinetic model, traditional Chinese veterinary medicine, acupuncture

1. Introduction

1.1 Motivation and purpose

Dog owners are aware of the sad fact that their pets are vulnerable to various tumors that may occur at any age/location and cause severe complications. In particular, canine hepatic tumors correspond to 0.6 to 1.3% of canine neoplasms, while

about 7–36% of dogs are metastasized from other organs [1–9]. The canine patients, which usually suffer from systemic metabolic stress and cachexia, require a surgery or chemotherapy based on the veterinarians' recommendations and life expectations. Noteworthy is that different tumor types of primary carcinoma can arise from different cell types listed in **Table 1** [2]. The major types of primary liver cancer are hepatocellular carcinoma (HCC), bile duct carcinoma, neuroendocrine (carcinoid) tumor, and mesenchymal tumor (sarcoma). Hepatocellular carcinoma (HCC) is generally found in dogs, especially elder ones. Compared with the modular or diffuse forms, the majority of HCC has a lower rate of metastasis. A single massive HCC tumor can usually be removed by surgical treatment. However, the most difficult clinical treatment is the diffuse HCC involving in the entire liver. Dogs with multiple liver lobes' HCC are not recommended to undergo surgical resection, have a poor prognosis and very limited treatment options [2–4, 10–13]. Bile duct carcinomas are the second common malignant liver tumor in dogs. Neuroendocrine tumors are quite rare and mostly nodular or diffuse, while primary liver sarcomas, including hemangiosarcoma, fibrosarcoma, and hepatocellular carcinoma, are unusual clinically. Dogs with liver tumors can be either asymptomatic or exhibit nausea, vomiting, weight loss, loss of appetite, diarrhea, lethargy, or PU/PD. Occasionally, yellowing of the skin and eyes like jaundice, or neurological signs (hepatic encephalopathy), such as seizures, disorientation, and weakness, are observed. Liver carcinoma grows slowly and manifests itself too late [2–6, 14–16]. This study attempts to set up the Ga-67 nuclear examination protocol for liver carcinoma canine patients, which would guide the veterinary expert and dog owner on the further optimal treatment: intensive surgery/chemotherapy or/and traditional Chinese veterinary medicine.

1.2 Definition of critical terminology

In this study, the global state-of-the-art approach to the above problem implies the conventional medicine based on modern science and advanced evaluation methods of canine physical and biochemical conditions. The respective treatment methods include chemotherapy, drugs, radiology, and surgery. Local tumor ablation and radiotherapy have been applied in veterinary medicine for decades. Chemotherapy is related to the use of several anti-cancer drugs administered intravenously, orally, or subcutaneously, which circulate in the patient's body and attack cancer cells. The most common chemotherapy drugs for treating liver cancer are listed in **Table 2**. Alkylating agents react with DNA strands and change the DNA structure. The commonly utilized

Classification	Types
1. Hepatocellular	a. Hepatic adenoma b. Hepatocellular carcinoma c. Hepatoblastoma
2. Biliary	a. Biliary adenoma (or cystadenoma) b. Biliary carcinoma
3. Neuroendocrine	a. Neuroendocrine carcinoma or carcinoid
4. Mesenchymal	a. Hemangiosarcoma b. Leiomyosarcoma c. Fibrosarcoma d. Osteosarcoma e. Malignant mesenchymoma f. Chondrosarcoma

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Table 1.
Primary hepatobiliary tumor types.

Drug	Indications	Toxicity	Dosage and Route of Administration
Alkylating Agents			
Cyclophosphamide	Lymphoma, Sarcoma, Carcinoma	Sterile hemorrhagic cystitis BM*, GI#	Typically 200–250 mg/m^2 IV or PO
Chlorambucil	Lymphoma (lymphocytic) CLL§, MCT※, to replace Cyclophosphamide if sterile hemorrhagic cystitis occurs	BM* (mild)	Variable PO
CCNU (Lomustine)	Lymphoma, MCT※	BM*, liver	Dogs: 60–90 mg/m^2 PO q3wk Cats: 50 to 60 mg/m^2 PO or 10 mg/cat PO q3 to 4wk
Melphalan	MMΨ, Plasma cell tumors	BM*	0.1 mg/kg/day PO x 10 days, then 0.05 mg/kg QOD; 0.2 pulse dose at 7 mg/m^2 daily for five days q3wk
Anthracyclines			
Doxorubicin	Lymphoma, Sarcoma, Carcinoma	BM*, GI#, hypersensitivity reaction, perivascular damage with extravasation, cumulative myocardial toxicity (dogs), nephrotoxicity (cats)	Dogs:≧15 kg: 30 mg/m^2 IV q2 to 3wk Dogs: < 15 kg: 1 mg/kg IV q2 to 3wk Cats: 1 mg/kg or 25 mg/m^2 q3wk
Mitoxantrone	Lymphoma Carcinoma	BM*, GI#, perivascular damage with extravasation	Dogs: 5 to 6 mg/m^2 IV q3wk Cats: 6 to 6.5 mg/m^2 IV q3wk
Platinum Drugs			
Carboplatin	Sarcoma, Carcinoma	BM*, GI#	Dogs: 300 mg/m^2 IV q3wk Cats: 240 to 260 mg/m^2 IV q3 to 4wk
Cisplatin	Sarcoma, Carcinoma	BM*, Nephrotoxicity, Fatal pulmonary edema (cats)	Dogs: 70 mg/m^2 IV q3wk (saline Do not use in cats emesis, diuresis)
Antimetabolites			
Methotrexate	Lymphoma	BM* (mild), GI#	0.8 mg/kg IV once weekly
Cytosine arabinoside	Lymphoma	BM* (mild), GI#	Variable; SQ, IM. IV.
Gemcitabine	Lymphoma, MMΨ, Carcinoma. feline SCC¶	BM*	Limited studies Dogs: 100 to 1000 mg/m^2 IV; 50 mg/m^2 twice/wk. with RTω Cats: 25 mg/m^2 twice/wk. with RTω

Drug	Indications	Toxicity	Dosage and Route of Administration
5FU	Sarcoma, carcinoma	BM*, GI#, Neurotoxicity, Fatal neurotoxicity in cats	Dogs: 150 mg/m^2 once/wk. IV, topically Do not use in cats
Antimicrotubule Agents			
Vincristine	Lymphoproliferative cancer, Sarcoma	BM*, GI#, Constipation (ileus), Peripheral neuropathy, Perivascular tissue reaction	0.5 to 0.75 mg/m^2 IV weekly or every other week
Vinblastine	Lymphoma, MCT※	BM*, GI#, Perivascular tissue reaction	2 to 2.2 mg/m^2 IV weekly
Miscellaneous			
L-Asparaginase	Lymphoma	Hypersensitivity reaction	400 lU/kg or 10.000 IU/m^2 SQ or IM (10,000 IU maximum) weekly
Procarbazine	Lymphoma	BM*, GI#	Variable; dogs: 50 mg/m^2/day

**: BM; bone marrow, #: GI; gastrointestinal, §: CLL; chronic lymphocytic leukemia, ※: MCT; mast cell tumor, Ψ: MM; multiple myeloma, ω: RT: radiation therapy, ¶: SCC; squamous cell carcinoma.*
Source: https://veteriankey.com/chemotherapy/, chapter 44: Chemotherapy.
Alkylating agents react with DNA strands and changing the DNA structure. Anthracycline antibiotics exert their cytotoxic effect through different mechanisms, including free radical formation, DNA intercalation, and protein synthesis inhibition. Platinum drugs act at the N7 position of guanine and adenine residues, suggesting DNA as the primary target of the drug. Antimetabolites are drugs that interfere with enzymes or affect DNA synthesis. Antimicrotubule Agents interfere with the mitotic spindle, which inhibits cellular division and proliferation.

Table 2.
Classification of chemotherapy drugs for treatment.

alkylating agents in veterinary oncology are chlorambucil, cyclophosphamide, melphalan, and lomustine. The common toxicity of cyclophosphamide is related to sterile hemorrhagic cystitis. Anthracycline antibiotics exert their cytotoxic effect through different mechanisms, including free radical formation, DNA intercalation, and protein synthesis inhibition. An example of such medicine is Mitoxantrone, which is metabolized in the liver and eliminated via feces and urine. Platinum drugs act at the N7 position of guanine and adenine residues, having DNA as their primary target and being eliminated via kidneys [6]. Antimetabolites are drugs that interfere with enzymes or affect DNA synthesis. Their chemo group, methotrexate, is primarily eliminated via renal excretion. Finally, there are antimicrotubule agents, which interfere with the mitotic division process, inhibiting cell division and proliferation.

Quite a recent treatment introduced to veterinary oncology is radiology or radiation therapy. It rapidly became one of the most common procedures of cancer treatment, insofar as it could be clinically performed when surgical resection of the tumor remaining after chemotherapy would be problematic or too dangerous. Radiotherapy can make cells unable to replicate and eliminate the cell division and proliferation. However, radiation therapy can damage normal cells, rather than only malignant ones. A well-designed radiotherapy program is intended and designed to maximize tumor effect and minimize normal

tissue effect. The benefit of radiotherapy is a cure for tumors and a split course treatment before surgery or chemotherapy [17].

The alternative approach to the above "targeted instrumental and drug invasion into the injured body part" is the overall improvement of the whole body and emotional well-being of a patient. In case of canine patients, this approach is reduced to the Traditional Chinese Veterinary Medicine (TCVM), which has been introduced several thousand years ago as a system of health care and is being implemented globally nowadays as alternative medicine [12]. Briefly, the TCVM has accumulated a vast list of robust diagnoses of canine diseases based on basic symptoms and appearances (tongue color, skin conditions, iris, pulse, etc.). A veterinarian analyzes these symptoms and the related overall system problems. The proposed cure is TCVM-based herbal medicine aimed to fine-tune the immune system and prevent a reoccurrence of an illness or future problem as illustrated in **Figure 1** [18, 19].

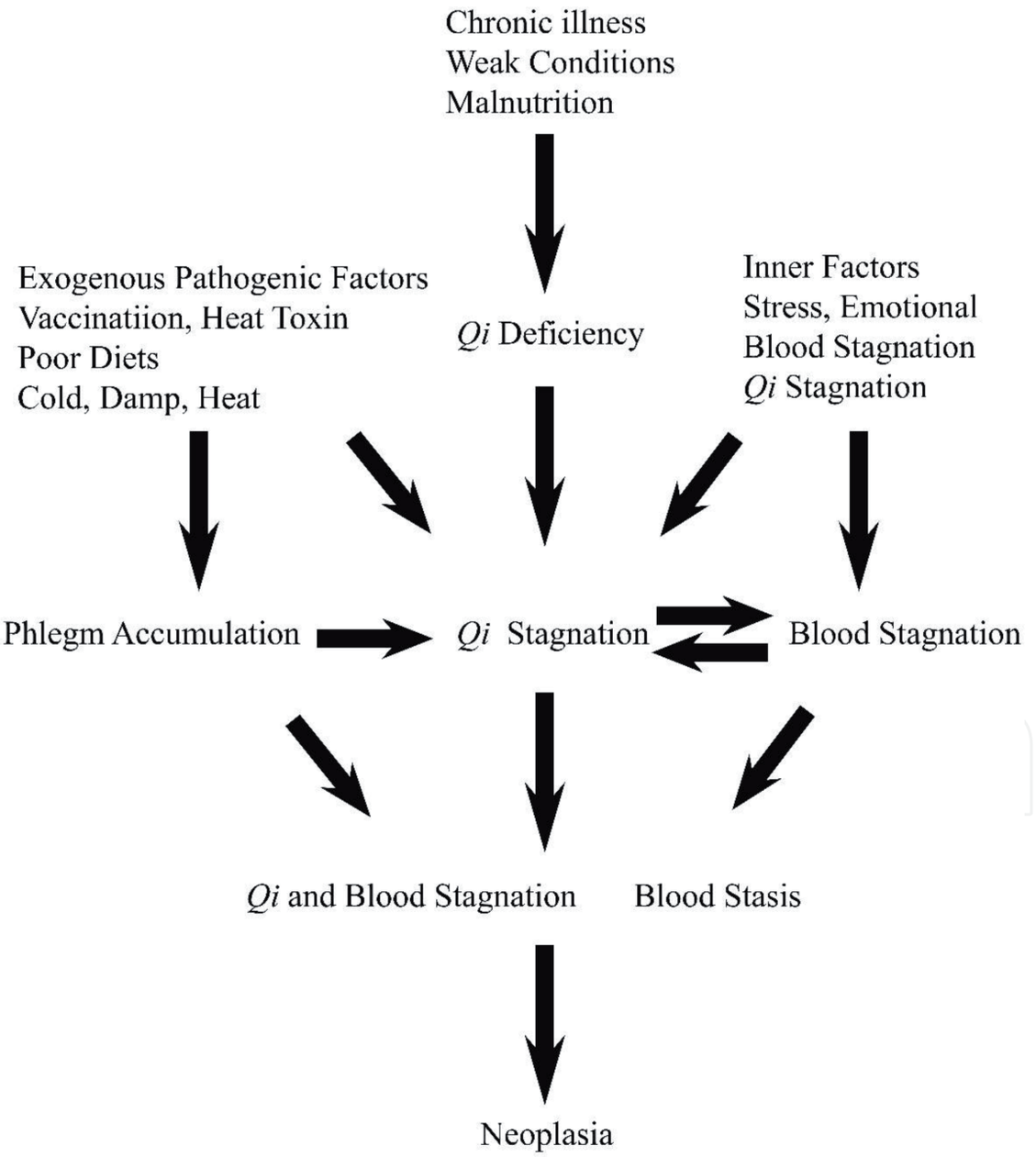


Figure 1.
Etiology of neoplasia in TCVM. The factors contributing to form phlegm, qi and blood stagnation, blood stasis, and eventually, neoplasia, are summarized. It is shown that qi deficiency is the root of cancer and phlegm, qi/blood stagnation, and blood stasis are one part of the branches. (cited from Huisheng Xie, Vanessa Preast, TCVM fundamental principles, 2nd edition).

1.3 Background review and rationale study with reference

Liver carcinoma can be diagnosed or detected by using multiple methods. Histological findings are considered the most robust for canine patients. The TNM staging system for canine hepatocellular carcinoma (HCC) is summarized in **Table 3** [20]. Veterinary surgeons may perform additional blood examinations to look for signs of liver dysfunction. Surgery is one of the treatments for all liver tumors. However, right-sided tumors are more challenging to resect because the resection lesion is related to the vena cava [2]. For massive hepatic carcinoma, surgical resection via lobectomy is the treatment when complete resection is accepted [10, 11]. The mass ligation for complete lobectomy is not recommended for large dogs, or central or right divisional liver tumors, because this method will increase the risk of complications, such as bleeding or bile leakage. Surgical stapling devices are recommended to perform liver lobectomy; in these devices, overlapping rows of staples are quickly placed to attenuate vascular and biliary structures within the liver lobe's hilus. If stages T3, N1, or M1 in **Table 3** are confirmed by clinical-stage evaluations, no surgical resection is recommended [20] because it would not remove some malignant liver tumors. Therefore, chemotherapy becomes an alternative treatment. Unfortunately, according to many clinical practices and references, chemotherapy is not very effective liver carcinoma treatment. Thus, HCC treatment with intravenous gemcitabine or carboplatin is no longer performed. Instead, in the last decade, the Metronomic chemotherapy and Sorafenib treatment (5 mg/kg, twice daily) became widely used due to lower-dose usage and administration ease [6, 7].

Alternatively, radiotherapy is sometimes used to make the liver tumor smaller or incapsulate it. However, it is not applicable to most liver tumor cases because of its side-effects. The major complication is a radiation heat-induced damage to the adjacent unaffected liver tissue. A 3D-CRT (three-dimensional conformal radiation therapy) is introduced as a new viable treatment option for canine patients with an inoperable massive liver carcinoma. From 6 to 10 Gy per fraction are prescribed on the planning target volume, and the total dose is 18–42 Gy with 1 to 2 fractions per week [17].

1.4 The innovative features of this study

This study is the first attempt to apply the biokinetic Ga-67 model to canine liver carcinoma. The aim is to identify the best routine for detecting the metastatic or primary hepatic carcinoma and substantiating the optimal further treatment.

Classification	Stage
Primary tumor (T)	T0: no evidence of primary tumor Tl: solitary tumor of any size involving one lobe T2: multiple tumors of any size involving multiple lobes T3: tumor(s) with direct invasion of adjacent organs regional lymph nodes
Regional lymph nodes (N)	N0: no regional lymph nodes metastasis Nl: regional lymph node metastasis N2: lymph node metastasis Distant metastasis
Distant metastasis (M)	M0: no distant metastasis Ml: distant metastasis

Source: doi:10.3390/cancers12051272

Table 3.
The TNM staging system for canine hepatocellular carcinoma.

1.5 The specific rationale study with a solid description

The biokinetic model of Ga-67 evolution was elaborated in this study for the case–control group of canine liver carcinoma via in-vivo gamma camera/8-slice CT technique. The circulation of time-dependent concentrations of Ga-67 among organs was monitored and simulated. The obtained quantitative data for organs and branching ratios among organs were incorporated into the biokinetic model of Ga-67 radionuclide administered during the hepatic survey.

2. Diagnosis of canine hepatic carcinoma

Due to the absence of nerves in the liver, the early liver neoplasia is painless. Therefore, when canine patients are clinically examined, their liver disease if any is diagnosed as moderate or severe.

The clinical symptoms include depression, lack of appetite, vomiting, weight loss, diarrhea, PU/PD, abdominal distention, lethargy, icterus, and ascites. The neurological disorder is mainly caused by hypoglycemia, hepatic encephalopathy, or metastasis of the central nervous system as shown in **Figure 2** [9, 21–24].

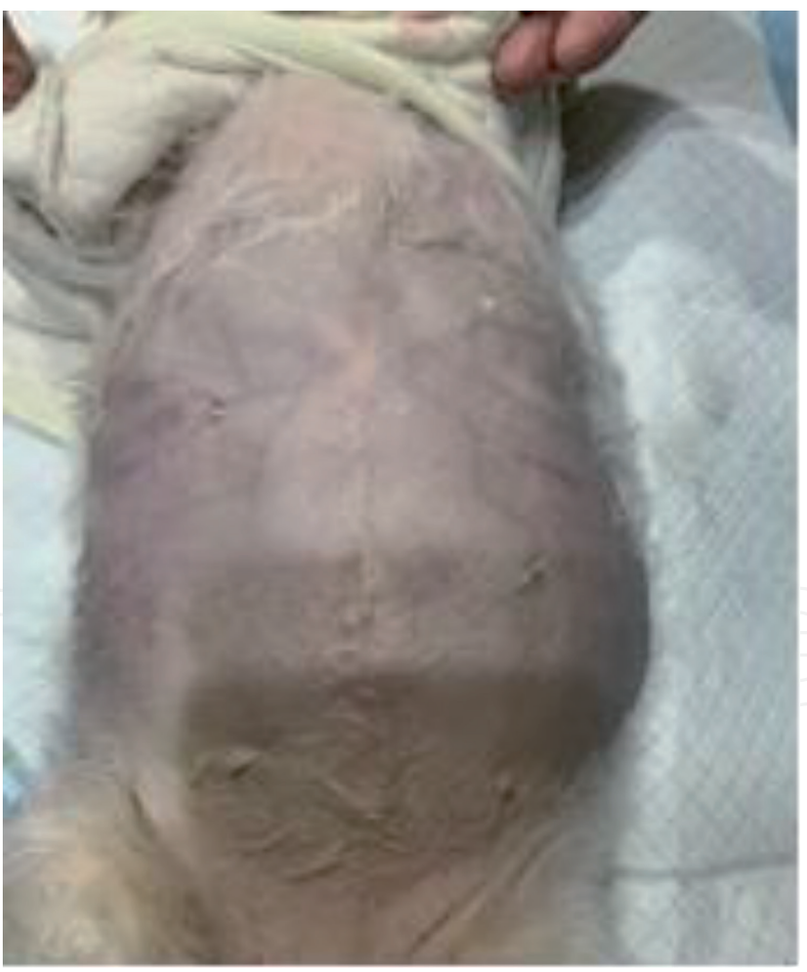


Figure 2.
A 12-year-old female Maltese had distention of the abdomen, was diagnosed with a liver tumor via ultrasound.

2.1 Biological index

Hematologic features, including mild non-regenerative anemia, inflamed leukocytosis, and thrombocytosis, are common in canine liver tumors [1, 15, 16].

Thrombocytosis is observed in approximately half of canine patients with massive HCC [1]. The prolonged blood coagulation (prothrombin time, thrombin time, and activated partial thromboplastin time) is rare unless the liver disfunction occurs, being observed in only 20% of HCC cases [1, 16].

Serum biochemistry indexes of dogs with hepatic neoplasia are commonly increased. Thus, elevated enzyme alanine transaminase (ALT), alkaline phosphatase (ALP), and aspartate aminotransferase (AST) are observed in liver tumors. Moreover, AST to ALT ratios below one are consistent with HCC or bile duct carcinoma [1].

The increased content of α-Fetoprotein is used as a robust indicator of HCC in human patients [23, 24]. This indicator is less suitable for dogs with hepatic neoplasia, being intrinsic to other types of canine liver tumors. However, about 75% of dogs with HCC had increased serum α-Fetoprotein, as reported in [25, 26]. Hypoalbuminemia, hypoglycemia, hyperglobulinemia, and elevated bile acid concentration are also observed in canine liver tumors.

2.2 X-ray examination

Regular abdominal radiography images of canine patients obtained via a diagnostic X-ray device are used for diagnosing, staging liver tumors, and planning the surgery operation if any. Abdominal radiography may identify a cranial abdominal mass with caudal and lateral recumbency shift of the stomach. Ascites may interfere with visualizing a mass as depicted in **Figure 3**. Assessment of thoracic radiographs is considered critical to exclude metastatic disease.

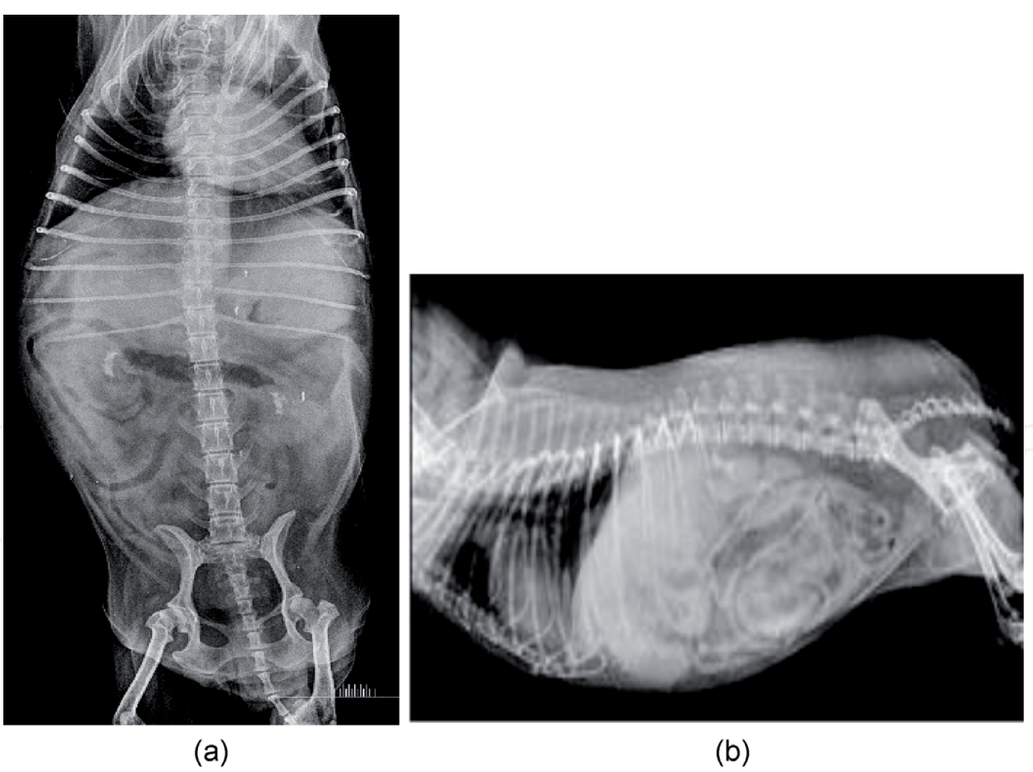
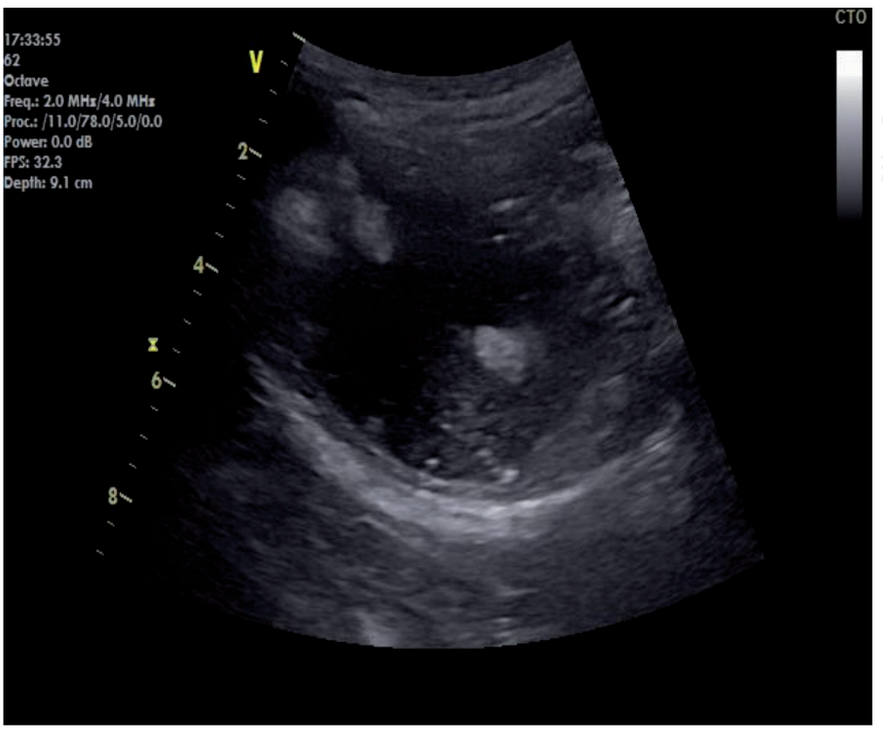


Figure 3.
(a) Right lateral recumbency of abdominal radiography. (b) Dorsal ventral recumbency of abdominal radiography. Two X-ray images were obtained from a Maltese with icterus and abdominal swelling. The liver board line is not obvious, rough, and hepatomegaly.

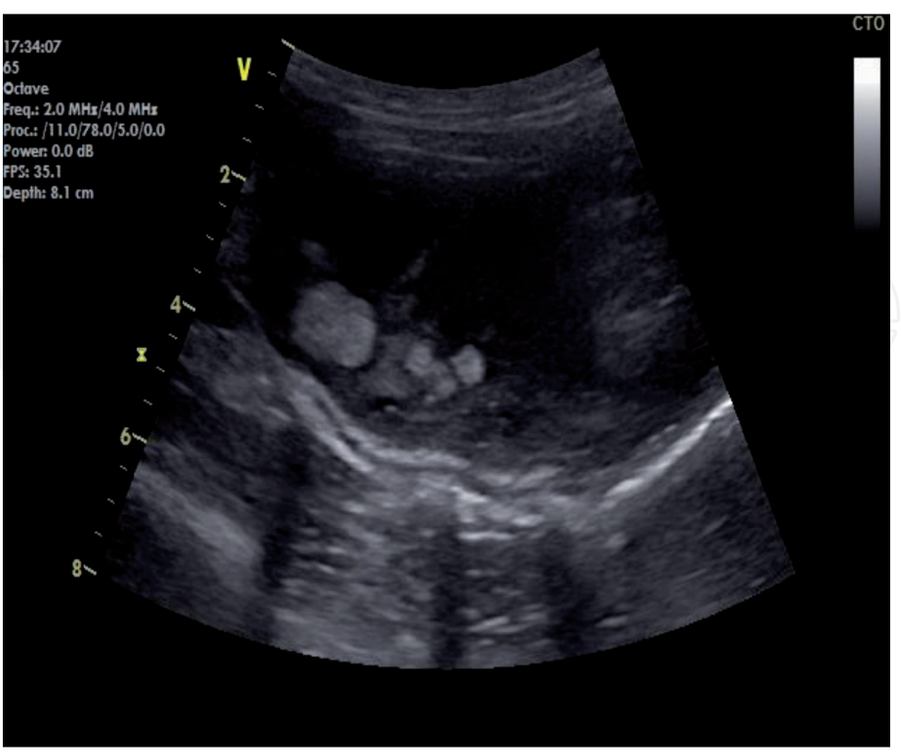
2.3 Abdominal ultrasound examination and MRI

Abdominal ultrasound examinations are applicable to 94% of patients and allowed determination of an obvious mass in 99% of these patients. The efficiency

of the ultrasound method in detecting hepatic mass has been reported previously [1, 16]. In this study, the region containing the pathogenic mass (left, central, or right lobes) was correctly identified. This indicates that ultrasound examination is very sensitive in the identification of a mass as demonstrated in **Figure 4**. Besides the ultrasound examination, the magnetic resonance imaging (MRI) allows one to identify the tumor origin region. A variety of surgical planning modalities benefit



(A)



(B)

Figure 4.
(A) Ultrasonography of right medial liver tumor. (B) Ultrasonography of right lateral liver tumor. Survey abdominal sonography 14.5y spayed female cocker spaniel dog before Ga67 examination, several hyperechoic nodules are seen within a large hypoechoic portion in the right medial and lateral hepatic lobe.

from MRI accuracy in the localization of liver tumors; advanced imaging may be needed for precise tumor localization.

2.4 Ga-67 nuclear examination

Canine liver carcinoma cases were analyzed in this study via the nuclear examination technology. We have proposed a preliminary/simplified biokinetic model according to the general-purpose biokinetic model as recommended by the ICRP-30 report, to interpret the empirical data from the clinical examination of a case–control group of hepatic carcinoma dogs [27, 28]. In doing so, every dog was surveyed by a gamma camera/8-slice CT to derive eight complete scanned images within 72 hours. The raw outputs were processed with a self-developed program run in MATLAB to compose a thorough scenario of time-dependent Ga-67 nuclides' intensity changes among multiple compartments (organs or tissues) for dogs that underwent a nuclear examination after being injected the Ga-67-citrate. Each canine patient was administered 22.2 MBq (0.6 mCi) Ga-67 citrate solution via the intravenous injection. The Ga-67 citrate solution was carrier-free with radionuclide and radiochemical purity values exceeding 99.9 and 95.0%, respectively. All radiopharmaceutical capsules were fabricated by the Syncor International Corporation (USA). The position-sensitive gamma ray emitted from the Ga-67 dose administration for each study object could be robustly assessed and plotted for further analysis. **Figure 5** depicts the eight-compartmental biokinetic model of Ga-67 in liver figuring in the ICRP-30 report, which contains: (1) body fluid, (2) liver, (3) gastrointestinal (GI) tract, (4) kidney, (5) heart, (6) remainder, (7) bladder, and (8) excretion.

Figure 6 illustrates the fragments of scans obtained for a canine patient with liver carcinoma via a gamma camera: (A) The gamma camera/8 slice CT (GE Discovery NM/CT 670) facility indicates that the anesthetized dog was placed between two NM plates for scanning; (B) Close-up view of the anesthetized dog; (C) Particular scans were quoted directly from the E-CAM and implied the raw data

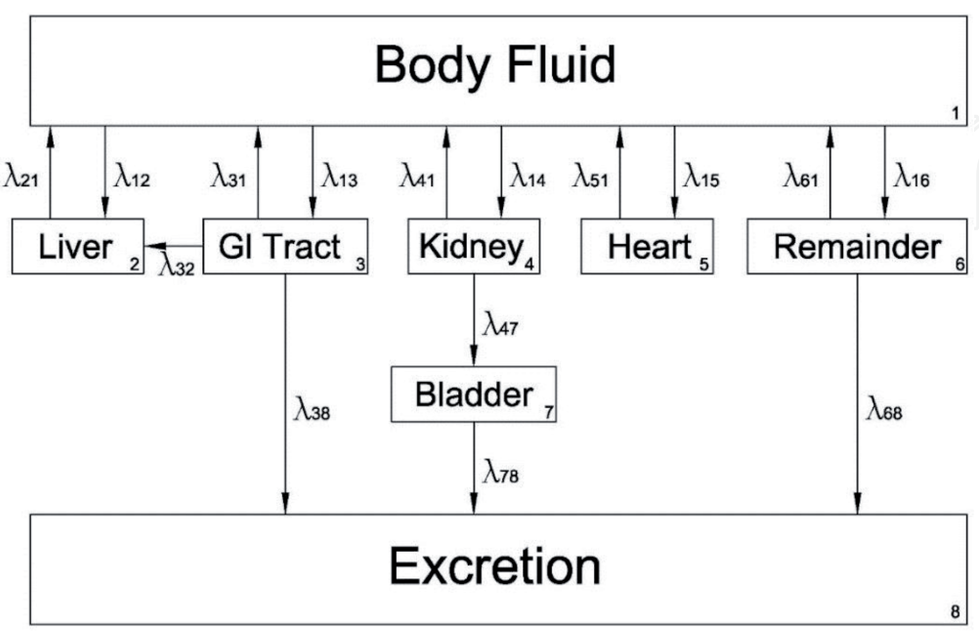


Figure 5.
A simplified biokinetic model of Ga-67 in the liver can be defined by eight major compartments: (1) body fluid, (2) liver, (3) gastrointestinal tract (GI tract), (4) kidney, (5) heart, (6) remainder, (7) bladder and (8) excretion according to ICRP-30 report.

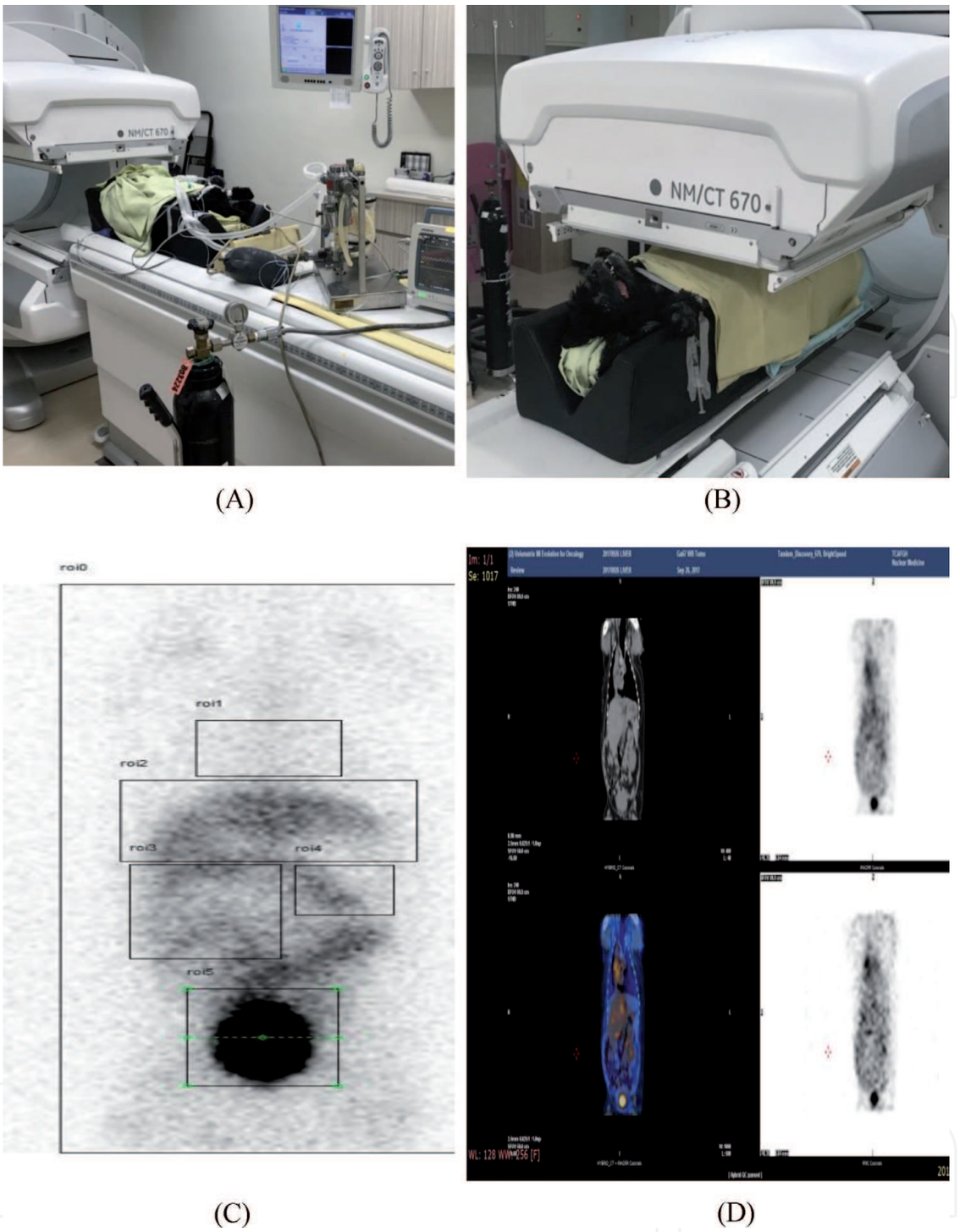


Figure 6.
(A) The gamma camera/8 slice CT (GE discovery NM/CT 670) facility indicates that the anesthetized dog was placed between two NM plates for scanning; (B) close up view of the anesthetized dog; (C) particular scans were quoted directly from the E-CAM and implied the raw data of fifteen-minutes' counting after 72 elapsed hours. Here, the full-size scanning of the dog contained regions of interest (ROI), indicated as follows: ROI0 (whole-body), ROI1 (heart), ROI2 (liver), and ROI3 (GI tract), ROI4 (kidney), and ROI5 (bladder); (D) the fusion plot from gamma camera and CT scanning.

of 15 min counting after 72 elapsed hours. Here, the full-size scanning of the dog contained regions of interest (ROI), indicated as follows: ROI0 (whole-body), ROI1 (heart), ROI2 (liver), and ROI3 (GI tract), ROI4 (kidney), and ROI5 (bladder); (D) The fusion plot from gamma camera and CT scanning. The CT was preset at 130 kV, 150 mA, 0.8 sec., spin width 0.625 mm, spiral speed 3.75 mm/s, and matrix size 512 × 512. The remainder was defined by subtracting all defined compartments (ROI1–5) from the whole body (ROI0).

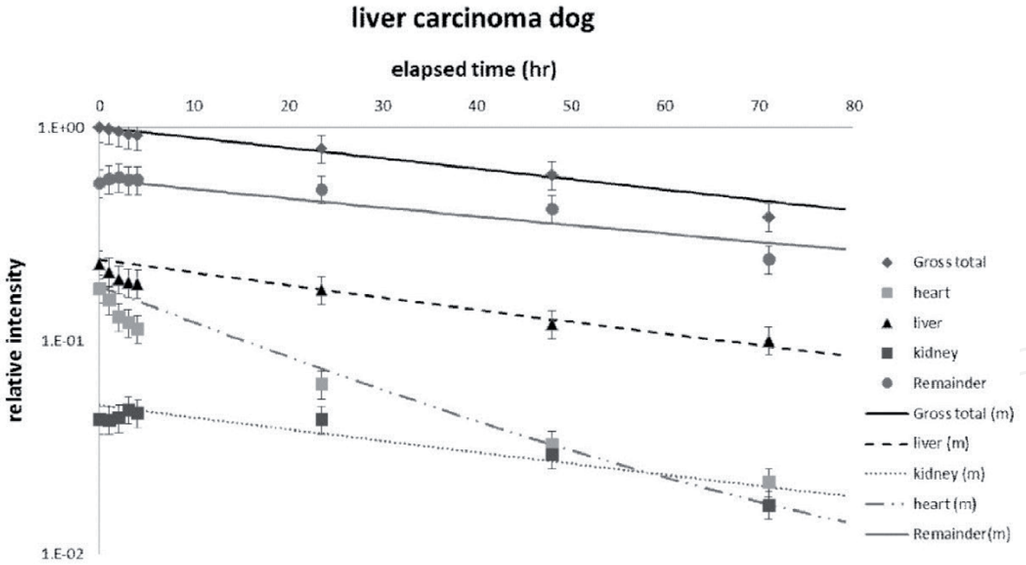


Figure 7.
The time-dependent curves of the Ga-67 concentration among various compartments for a liver carcinoma dog.

Figure 7 shows the time-dependent curves of the Ga-67 concentration among various compartments for the dog with liver carcinoma.

Liver and GI Tract: In contrast to the I-131 thyroid model or GI Tract model for human patients, the model of Ga-67 for liver carcinoma dog was elaborated by the simplification of the general-purpose biokinetic model, according to the ICRP-30 report. As seen in **Figure 5**, a complicated correlation among compartments allows one to use a MATLAB program to optimize the estimation via the empirical data [27]. The feedback path exists between compartments 2–6 and compartment 1. Each compartment has its biological half-life to transfer the Ga-67 radionuclides among compartments, which also confounds the theoretical estimation. Specifically, the liver provides a 22%-contribution of the body fluid (I_{12}, 0.22), which is the second-largest share, whereas the GI Tract has the largest share (I_{13}, 0.33 ~ 0.43) after the Ga-67 administration. However, 60% (I_{21}, 0.60) of the Ga-67 radionuclides returns as feedback to the body fluid with a biological half-life of 15 ~ 40 h. Meanwhile, the remaining nuclides of Ga-67 in GI Tract are transferred to the body fluid (I_{31}), liver (I_{32}), or directly to excretion (I_{38}) with a biological half-life of 20 ~ 600 h. Noteworthy is that the effective half-life is defined as the reciprocal of the sum of reciprocal radiological and biological half-lives ($1/T_{1/2(eff)} = 1/T_{1/2(R)} + 1/T_{1/2(bio)}$). Thus, in practice, either 600 or 20 h of biological half-life still perform as 69 or 16 h of the effective half-life from the continuous gamma camera scanning. Some of Ga-67 radionuclides were found to migrate from the GI Tract to the liver (I_{32}, 0.2 ~ 0.7). Since portal vein circulation provides the blood flow from gastrointestinal section to the liver, the excessive blood pressure will slow the liver's feedback path.

Kidney and bladder. Nearly 20% of Ga-67 nuclides were transferred to the kidney (I_{14}, 0.2), exhibiting nearly no feedback to body fluid (I_{41}, 0.07), in contrast to the bladder (I_{47}, 0.93), and then were fully transferred to excretion (I_{78}, 1.0).

Heart. Only 5–15% of Ga-67 nuclides were transferred to the heart (I_{15}, 0.05–0.15), whereas most of them exhibited an instant feedback to body fluid (I_{51}, 0.99) with a short biological half-time $T_{1/2}$ of 18–20 h. The derived biological half-life of the heart can be treated as a group of cardiac muscles, which provide the blood circulation loop in the whole body, with no apparent Ga-67 nuclides' repository effect.

A long biological half-life of liver for the liver carcinoma dog (40 h vs. 35 h or 15 h) reveals a potential risk of hepatic disorder, whereas the remaining data are

barely available to solidify the syndrome of liver carcinoma. The evolution of Ga-67 in the liver carcinoma survey model still plays an essential role in veterinary and human medical domains, since it quantifies the time-dependent concentration of Ga-67 nuclides among compartments of the case–control group and allows one to acquire robust raw data via in-vivo scanning.

3. Global state-of-the-art treatment

3.1 Hepatectomy

The liver surface is convex and it slightly touches the diaphragm. The liver is located on the left side of the caudoventral tract, contacting the stomach, duodenum, pancreas, and right kidney. There are six hepatic lobes: right medial and lateral, left medial and lateral, and quadrate and caudate lobes. The gallbladder is located between the right medial and quadrate lobes. The liver has two so-called afferent (ingoing) blood supplies: the portal system and the arterial system, while the efferent (outgoing) blood flow of the liver circulation is through the hepatic veins. The hepatic lobules, which are the basic functional units of the liver, are cross-sectioned in a hexagonal shape and the portal triads in the periphery. Portal triads consist of the hepatic artery, portal vein, and bile duct. From the anatomic and histologic views, the liver is complicated, and hepatic tissue is friable. Partial lobectomy is difficult and may injure blood vessels and bile ducts in canine patients with bleeding disorders. Many techniques for partial and complete liver lobe resection have been introduced, and numerous stapling instruments have been adopted for both lobectomies. The survey of Liptak et al. [1], which covered 48 dogs with large massive hepatocellular carcinomas during a decade, revealed that their median survival time exceeded 1,460 days after the hepatectomy procedure. However, numerous complications, including ongoing anemia, hepatopathy, ileus, and lack of appetite, are frequently after liver surgery. Therefore, a proper intensive care is recommended to mitigate these complications and minimize the related risks.

3.2 Chemotherapy

The most commonly chemotherapy is administered intravenously. According to clinical chemotherapeutic management of neoplastic cases, a significant advance in veterinary practice is observed. However, a large share of HCC canine patients cannot be cured by chemotherapy and require a further integration of conventional treatment modalities, such as surgery, radiation therapy, and innovative chemotherapy methods. Chemotherapeutic agents are generally administered at the maximum tolerated dose and at the highest dose intensity that is usually used in combination. Four advantages of combination chemotherapy include an increased log-kill, prevention of cancer drug resistance, targeting both dividing and resting cells, and allowing for lower doses with less toxicity [6]. Chemotherapeutic agents damage activated pathogenic cells but also affect normal tissues that divide rapidly and are sensitive to anti-mitotic drugs, such as cells in the bone marrow, digestive tract, and hair follicles. The most common side-effects of chemotherapy are myelosuppression, mucositis, and alopecia. In general, malignant tumors cannot be wholly removed surgically and imply a poor prognosis for canine patients. Palliative chemotherapy and other treatments may be gradually applied to delay the tumor progression. Any further health care should involve close monitoring and minimization of side effects.

3.3 Radiotherapy

As a general rule, surgical resection is considered the best treatment option if a primary tumor can be completely excised. If the region of extensive involvement, normal tissue, or volume of liver tumor make its complete removal problematic, then radiotherapy may be recommended by veterinarians as a palliative treatment of liver tumors. Its effectiveness against the canine liver tumor is limited by the fact that canine patients cannot tolerate cumulative doses exceeding 30 Gy [29]. A share of radiotherapy treatment in US veterinary facilities in 2001 study did not exceed 20% [30], while 92% of facilities in 2010 used the 3D computerized radiotherapy, and 20–100% (with median of 50%) of facilities implemented computer simulation treatment plans [31]. It should be noted the abdominal movement caused by breathing during radiotherapy of liver tumors strongly deteriorates the therapeutic effect, which issue can be resolved for human patients but is hard to control with canine ones.

4. TCVM treatment

4.1 Etiology and pathology

The available methods of animal cancer treatment imply separate or combined application of surgery, radiation therapy, and chemotherapy targeted at the particular cancer cells. However, there is also a general concern about the quality of life of pets/canine patients. This gives much space to the alternative medicine, in particular, the traditional Chinese veterinary medicine (TCVM), which not only focuses on the tumor but also accounts for the overall health condition by regulating the so-called *Yin* and *Yang* constituents. Through the balance of *Yin* and *Yang*, the patients suffering from the disease could also improve their physical health. Tumor, in the TCVM perspective, is the morphological tissue structure change, which imply functional changes of the specific organs or tissues. Those pathological changes of tissues are defined by TCVM as phlegm, toxin, dampness, blood, and stasis. Therefore, the tumor's mechanism can be briefly summarized from the TCVM standpoint as stagnation of blood or (heat-) toxin, accumulative dampness or phlegm, and Q*i (*energy*)* stagnation. The stagnation or lack of a free *Qi*/*Blood* movement results in the formation of pathological tumors in human and animal patients. Those with hepatic carcinomas often have the hormone/gastrointestinal symptoms [Liver (wood) Ke Spleen (Earth)] causing the Spleen *Qi* deficiency.

Spleen *Qi* is responsible for food intake and digestion; this process is called transformation and transportation. Both two functions of the spleen are critical for the production of *Zheng Qi*. *Zheng Qi* deficiency mainly focuses on the root of neoplastic formation. *Zheng Qi* is composed of Nutritive *Qi* and Defensive *Qi* (*Wei Qi*). As *Wei Qi* is a defensive deficiency, several external pathogenic factors (cold, wind, heat, summer heat, dryness, and dampness) cannot be easily detected and expelled from the body. These pathogenic factors will cause the blocking of *Qi* and impede the blood circulation. However, some other factors should be considered: emotional stress, unhealthy diet/lifestyle, and the environment. For example, negative emotional stress, inappropriate diet, and too humid environment are considered by TCVM as induction factors that trigger a liver tumor. Both internal and external factors may contribute to phlegm, *Qi,* and *Blood* stagnation, blood stasis, and ultimately lead to neoplasia [12, 19, 21, 22].

4.2 Pattern differentiation and treatment

The TCVM has been used as an alternative treatment for years in Asia. However, its current applications to domestic animals/pets suffering from carcinomas are based on individual expert opinions, while there are no outlined veterinary treatment strategies and guidelines for clinical practice in this field. The most lucrative concept accepted nowadays is a comprehensive combination of global/Western and TCVM components, the latter being aimed at adjunct therapy and recurrence prevention. Adjunct therapy should reduce the side-effects of chemotherapy, radiation therapy, and surgery. Based on the pattern differentiation, it is essential to treat the liver tumor using TCVM drugs and acupuncture techniques capable of regulating *Qi*, nourishing blood, strengthening the body and organs, and improving the resistance to pathogenic factors. The TCVM is likely to improve the canine patient's general conditions, remove the disease/pathogen, inhibit oncogenesis, alleviate side-effects, and improve the survival rate as shown in **Figure 8**.

The TCVM treatment is usually provided to canine patients undergoing a surgical treatment or after radiotherapy/chemotherapy. In most of these patients, tumors could not be eliminated entirely, and the adjunct treatment should improve their

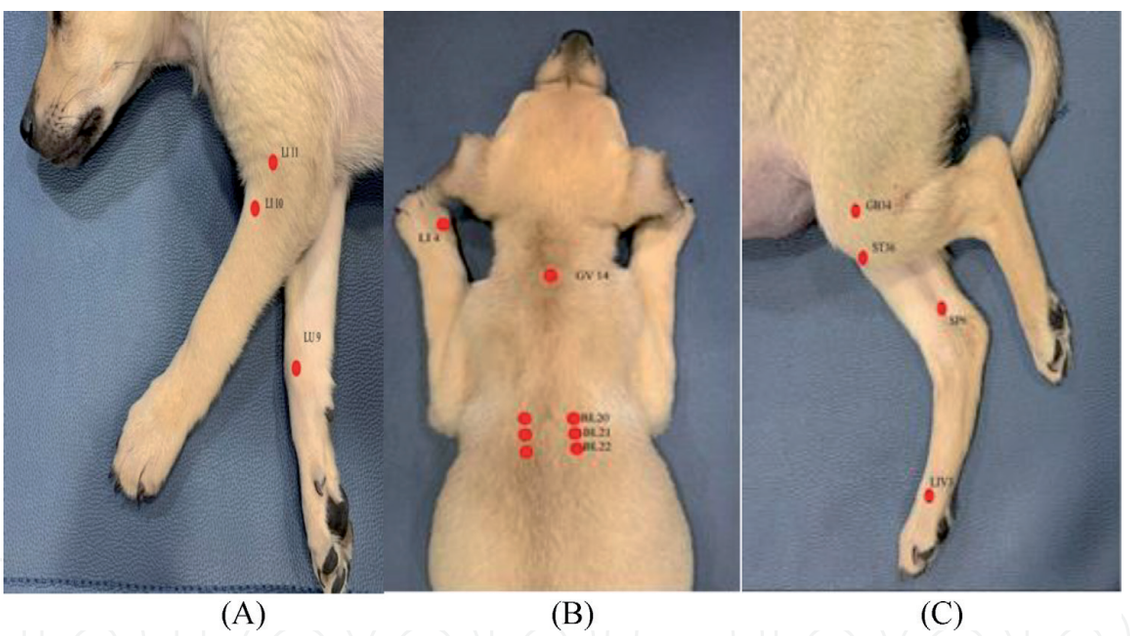


Figure 8.
Acupuncture points. (A) LU 9: In the depression distal palmar to the most medial prominence of the radial styloid process, overlying the radiocarpal joint, medial to the radial artery, and the tendon of the flexor carpi radialis muscle. LI 10: In the depression in the muscular groove between the extensor carpi radialis and the common digital extensor mm. Of the forelimb, two cun distal to the transverse cubital crease. This is most evident when the elbow is flexed.LI 11: In the depression in the transverse cubital crease, just cranial to the lateral epicondyle of the humerus, between the extensor carpi radialis and common digital extensor mm. This point is easily palpated when the elbow is flexed. (B) LI 4: In the depression between the 2nd and 3rd metacarpal bones, approximately in the middle of the 2nd metacarpal bone. GV 14: In the depression on the midline between the dorsal spinous processes of the 7th cervical and 1st thoracic vertebrae. BL 20: In the depression, 1.5 cun lateral to the caudal border of the spinous process of the 12th thoracic vertebra. BL21: In the depression, 1.5 cun lateral to the caudal border of the spinous process of the 13th thoracic vertebra. BL 20: In the depression, 1.5 cun lateral to the caudal border of the spinous process of the 12th thoracic vertebra. BL22: In the depression, 1.5 cun lateral to the caudal border of the spinous process of the 1st lumbar vertebra. (C) LIV 3: In the depression on the dorsum of the rear foot, between the 2nd and 3rd metatarsal bones, at the level of the junction of their heads and shaft, just proximal to their associated metatarsophalangeal joints. SP 6: In the depression 3 cun proximal to the tip of the tibia's medial malleolus, on the caudal border of the tibia. GB34: In the depression cranial and distal to the head of the fibula. ST36: In the depression, just lateral to the distal aspect of the cranial border of the tibial tuberosity (tibial crest), approximately in the middle of the cranial tibialis muscle.

quality of life, maintain their physical condition, and prolong survival time. TCVM has shown significant efficacy in the symptomatic treatment of canine patients suffering from the deficiency of vital *Qi*, leading to physical pain, fever, anorexia, nausea, gastrointestinal problems, fatigue, and constipation. Although liver heat and dampness are considered as the most probable causes for the formation of liver carcinoma and viral hepatitis in human patients, the animal/canine ones are less prone to viral pathogens. From the TCVM perspective, there are two patterns controlling liver carcinomas in small animals/dogs.

4.2.1 The first pattern: "blood stasis with Qi deficiency"

The *Qi deficiency* is more specifically related to "*Spleen Qi deficiency*", leading to "Blood Stasis". The main TCVM principles are to improve blood circulation, nourish the blood, resolve the stagnation or accumulation, tonify the spleen, and relieve pain. Refer to **Table 4**; acupuncture on specific points can improve and enhance the symptoms described earlier. *Xiao Yao San*, which is compounded by various herbs, is a transitional Chinese medicine described in the "Formulary of the Tai Ping Welfare Dispensary Bureau' Collections of Medicinal Formulations" compiled by Chen Shi-wen et al. in 1151. A modified herb formula of *Nei Xiao Wan*, called "Stasis Breaker", has been introduced by *Xie* et al. specifically for animals [19, 32] to reduce phlegms and stasis, clear toxin substances, and promote *Qi* and *Blood* circulation. The significant effect of "Stasis Breaker" breaks the blood stasis, softening the hard nodes and tumors. Furthermore, some studies prove that *Bai Hua She She Cao* and *Ban Zhi Lian* can inhibit cell mutation, tumor growth and clear the "heat-toxin" [19, 33, 34].

4.2.2 The second pattern of liver carcinoma: "blood stasis with Yin deficiency"

Heat and liver stagnation are supposed by TCVM to result in *Qi* and *Blood* stagnation. The consumption of fluid will injure the *Yin* in the *Middle Burn*. Once *Liver Yin* and *Kidney Yin* are injured, the tumor will be gradually formed. This treatment pattern focuses on nourishing *Yin* and *Blood*, resolving pain and stagnation, tonifying *Qi*, and resolving tumor. The recommended acupuncture points are shown in **Table 4**. [35]. *Yi Guan Jain*, a herbal medicine, described in the "Supplement to the Classified Case Records of Famous Physicians" by *Wei Zhi-Xiu* in 1770. It is intended to tonify the *Liver's* and *Kidney's Yin* and clear the "false heat". The combination of *Yi Guan Jain* and "Stasis breaker" effectively improves the immune system

Symptom	Acupuncture points
General *Qi* deficiency	LI -10, ST-36, CV-17, LU-9
Spleen deficiency/eliminate phlegm	BL-20, BL-21, ST-36, ST-40
Immunization	GV-14, LI-4, LI-10, LI-11
Smooth *Qi* and relieve pain	LIV-3, LIV-4, GB-34, GB-41
Anorexia	CV-12, Shan-gen
Vomiting	PC-6, GB-34, CV-12
Diarrhea	GV-1, SP-6
Ascites	SP-6, SP-9, BL-22,

Table 4.
TCVM acupuncture points for tumor.

performance, inhibiting tumor growth, mutation, and metastasis. This combination can also mitigate chemotherapy/radiotherapy side-effects and improve life quality [12, 19, 21, 22].

5. Conclusions

The global veterinary medicine is widely used to eliminate canine carcinogens by substantiated combinations of drug administration, surgery, chemotherapy, and radiotherapy treatments. However, their side-effects remain a challenging issue faced by clinical veterinarians and dog owners. In this respect, traditional Chinese veterinary medicine (TCVM), including acupuncture, herbs, food therapy, and massage, is considered a lucrative integrated treatment system. Using the pattern differentiation, as well as the proposed biokinetic Ga-67 model of canine liver carcinoma, the robust HCC diagnosis of canine patents can be obtained. A further application of global state-of-the-art and/or TCVM-based therapies can enhance the immune system, speed up the recovery, relieve pain syndrome, reduce chemotherapy toxicities, and improve quality of life of canine patients. Thus, the global integrative oncology comprehensively combines regulated clinical treatments with complementary and alternative medicine (TCVM in particular), yielding the synergistic curing effect.

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