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復發多中心型淋巴瘤犬隻之飼主化療經驗調查

Survey on Owners' Perspective with Chemotherapy for Relapsed Canine Multicentric Lymphoma

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復發多中心型淋巴瘤犬隻之飼主化療經驗調查
Survey on owners' perspective with chemotherapy for relapsed canine multicentric lymphoma

本論文係安芝萱君（R11643009）在國立臺灣大學獸醫學系、所完成之碩士學位論文，於民國一一四年一月十日承下列考試委員審查通過及口試及格，特此證明

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誌謝

自從大學以來，我就開始對小動物腫瘤學產生濃厚的興趣，雖然學校沒有相關課程，但我仍積極找資源自學，從自修教科書、舉辦讀書會、甚至請教其他學校的老師們，最後有緣來到台大進修。謝謝我的指導教授王尚麟老師，讓我進到夢想的地方學習臨床與研究。除此之外，老師的做人處事，也教導了我很多人生經驗，一路走來面對了很多困難的狀況，但也一路面對、檢討、改進。

研究所的一路上受到非常多人的幫助。包含讓我參與基礎研究的廖泰慶老師；實習醫師時期的郁荃學姊、儀楓學姊，給我非常多寶貴的實作機會以及知識。最重要的是實驗室夥伴們，相互鼓勵、支持與交流，讓我們成為一個最堅強的團隊：英碩、熊、甄姊、佳慧、之昀、佑邦、肇偉、家惠，有人已經畢業，有人剛進入實驗室還在努力，即使大家的起跑點都不一樣，但我們在這個時刻交會了。謝謝逸茹，陪我經歷一切大小的事情，給我建議與陪伴，讓我有機會成為更好的人，希望我也能帶給妳一樣的感受。也感謝我的家人，支持我念研究所，考上的當下你們比我還要開心。希望你們健康快樂，也希望我可以讓你們感到驕傲。最後，我的狗強強，我在 2021 年的聖誕節親手送你當小天使。你當初得了淋巴瘤，我不知道該怎麼辦，但我現在知道了。你是我對腫瘤有興趣的初衷，我時常想念你，你是最棒的小狗，我會永遠記得你！

期許自己能永遠善良、同理、充滿感恩，並且追求持續進步，照顧好飼主與寵物的珍貴情感，也照顧好自己跟身邊的人。

01.17.2025 安芝萱

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中文摘要

犬多中心性淋巴瘤通常對化療有良好的反應，適當治療往往能達到中位生存時間約 12 個月。然而，即使達到完全緩解，大多數患者最終仍會復發，且後續治療的效果與持續時間通常不如初次治療。在癌症復發的情況下，飼主可能更重視生活品質而非延長壽命。為了更好地理解這些優先事項，我們設計了一份問卷，針對接受多藥化療的復發犬隻飼主進行調查。

共有 125 隻犬在復發後接受治療，分發 140 份問卷，最終回收 50 份問卷。治療後，犬隻的生活品質顯著下降，其中 52%的飼主報告生活品質下降，30%表示無變化，僅有 18%認為有所改善（$p = 0.012$）。在與初次化療比較副作用時，42%的飼主認為副作用更為嚴重，42%認為相同，16%認為較輕（$p = 0.034$）。整體而言，58%的飼主認為治療結果不如預期，28%認為符合預期，14%認為超出預期（$p < 0.001$）。儘管面臨這些挑戰，52%的飼主並不後悔選擇治療，16%表示不確定，32%表示後悔。在復發後化療期間，當副作用較第一次治療更嚴重時，飼主更可能表達後悔（標準化殘差 = 2.8），而復發間隔時間或治療效果與後悔程度無顯著相關。在復發時，飼主主要關注的問題包括疾病快速進展（28%）、化療副作用（19%）和預後不良（14%），其他因素如高齡、治療成本和頻繁就診的影響比例均低於 10%。

本研究強調，在復發後選擇繼續化療是一個複雜且充滿挑戰的決策過程。儘管治療結果通常不如初次治療，但仍有三分之二的飼主不後悔接受治療。後悔與副作用相較於初次化療的嚴重程度經驗有關，因此建議復發後化療應盡可能控制副作用的發生。

關鍵詞：犬隻、化療、犬多中心性淋巴瘤、復發

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Abstract

Canine multicentric lymphoma generally responds well to chemotherapy, with appropriate treatment often resulting in a median survival time of 12 months. However, even after achieving complete remission, most patients eventually experience relapse, and the effectiveness and duration of subsequent treatments are often less favorable compared to initial treatment. In cases of cancer relapse, owners may prioritize quality of life over extending survival time. To better understand these priorities, we designed a questionnaire for owners whose dogs received multi-drug chemotherapy following relapse.

A total of 125 dogs received treatment after relapse, and 140 questionnaires were distributed, resulting in 50 responses. The quality of life for dogs treated after relapse significantly declined, with 52% of owners reporting a decline, 30% indicating no change, and only 18% perceiving improvement (p = 0.012). When comparing side effects to the initial round of chemotherapy, 42% of owners believed the side effects were more severe, 42% believed they were the same, and 16% believed they were milder (p = 0.034). Overall, 58% of owners felt the treatment outcomes were worse than expected, 28% thought they matched expectations, and 14% believed they exceeded expectations ($p < 0.001$). Despite these challenges, 52% of owners did not regret their decision to continue treatment, 16% were unsure, and 32% expressed regret. Owners were more likely to regret their decision if side effects during the post-relapse period were more severe than previous treatment (standardized residual = 2.8), while no significant differences were found regarding the relapse interval or treatment effectiveness. At the time of relapse, the primary concerns for owners included the rapid progression of the disease (28%), chemotherapy side effects (19%), and poor prognosis

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(14%), with other factors such as advanced age, treatment costs, and frequent visits accounting for less than 10%.

This study highlights the complex and challenging nature of deciding to continue chemotherapy after relapse. While the outcomes are often less favorable than those of the initial treatment, two-thirds of the owners expressed no regret in pursuing treatment. Regret was associated with the perceived severity of side effects compared to the initial chemotherapy experience; therefore, minimizing side effects as much as possible is recommended.

Keywords: canine, chemotherapy, multicentric lymphoma, relapse

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List of abbreviations

ABBREVIATIONS	
CHOP protocol	C, cyclophosphamide; H, doxorubicin; O, vincristine; P, prednisolone
HRQoL	Health-related quality of life
LHOP protocol	L, L-asparaginase; H, doxorubicin; O, vincristine; P, prednisone
PARR	PCR for antigen receptor rearrangement
POQoLS	Pediatric Oncology Quality of Life Scale
QoL	Quality of life
VCOG-CTCAE	Veterinary Cooperative Oncology Group—Common Terminology Criteria for Adverse Events

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Chapter 1 Introduction

Lymphoma is the most common hematopoietic tumor in dogs, an estimated incidence rate of 20–100 cases per 100,000 dogs [1, 2]. It is defined as a proliferative disorder of malignant lymphoid cells, multicentric lymphoma is the most common type, and are mostly of B-cell origin. which primarily affects peripheral lymph nodes initially and progresses to systemic disease involving visceral organs and bone marrow.

Without therapy, dogs with lymphoma may die within 4-6 weeks [3, 4]. With treatment, although survival times and complication rates varied between studies, most dogs maintained a good quality of life (QOL) and achieved complete remission, which lasted a median of 7–10 months. The median overall survival time was 10–14 months [5]. The mainstay of treatment is multi-drug chemotherapy. CHOP protocol (C: cyclophosphamide; H: doxorubicin; O: vincristine; P: prednisolone) is the most frequently used in the veterinary field as an induction therapy. Various CHOP-based protocols have also been developed, with reported remission rates exceeding 80% and median survival times (MST) ranging from 10 to 12 months, and about 20% of dogs surviving beyond 2 years [6].

Chemotherapy drugs indiscriminately target rapidly dividing tumor cells and normal cells. As a result, the most common side effects of chemotherapy include bone marrow suppression, gastrointestinal symptoms, and hair loss. In dogs, the most frequently reported adverse reactions to chemotherapy are neutropenia (22%), vomiting (21%), diarrhea (20%), and loss of appetite (20%). According to the current chemotherapy adverse reaction grading system, 83% of patients experience VCOG grade I side effects. Furthermore, 77% of owners believe their dogs tolerate the

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treatment well, while only about 10% of patients experience severe side effects that significantly impact their QoL, leading to chemotherapy delays or discontinuation, hospitalization, or death [7, 8].

However, most dogs experience relapse either during or after the termination of the protocol. A small residual population of malignant tumor cells persistently exists, contributing to relapse and leading to the recurrence of clinical signs or measurable disease [9]. Re-induction or rescue protocols are warranted when progression occurs, but drug resistance is a major limiting factor. After the first relapse, the likelihood of achieving a second remission is about 50%, with a median progression-free period of 1.5 to 2 months [4, 10]. Though the response are not durable, but reinduction is still recommended at the first recurrence.

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Chapter 2 Literature review

2.1 Quality of life assessment in cancer patients

Most owners are concerned about the QoL of their animals and the negative side effects of treatment [11]. There is no universally accepted definition of QoL, but it is generally regarded as a multidimensional concept involving the subjective evaluation of factors contributing to overall well-being. There is growing acceptance that a treatment can be considered valuable if it improves a patient's subjective well-being, even without significantly impacting outcomes such as survival prolongation or halting disease progression. Such improvements can still be regarded as a success in cancer treatment. However, measuring an individual's perspective remains a challenge.

Health-related quality of life (HRQoL) assessment is particularly important in palliative therapy, where the goal is to improve QoL when a cure is not possible [12]. HRQoL is defined as encompassing concepts related to physical, psychological, cognitive, emotional, and social functioning, with an emphasis on the impact of health status on overall QoL. With the rise of animal welfare and ethical awareness, research in this area has grown significantly. The assessment of HRQoL in animals began with the Glasgow University Health-related Dog Behavior Questionnaire (GUVQuest), which was developed to evaluate chronic pain in dogs based on its impact on HRQoL [13]. Following this development, most subsequent QoL questionnaires have been specifically tailored to individual diseases.

The Pediatric Oncology Quality of Life Scale (POQOLS) is a 21-item questionnaire designed to assess the QoL of children undergoing cancer treatment. It is completed by parents or caregivers and focuses on three key domains to evaluate different aspects of the child's well-being: physical function and role restriction,

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emotional distress, and reactions to medical treatment [14]. The POQOLS has been widely used in pediatric medicine, demonstrating good reliability and reproducibility.

In addition to the POQOLS, several standardized measurement tools, such as the Pediatric Quality of Life Inventory and the Health Utilities Index Mark, have demonstrated similar efficacy in large meta-analyses. Overall, pediatric patients with hematologic malignancies tend to have poorer physical and mental health compared to those with other diseases [15].

The situation of veterinary patients is similar to that of pediatric patients, as both are unable to fully express their feelings and rely on caregivers or parents to observe and describe their conditions. Main family caregivers are generally considered the preferred choice of proxy, as they tend to have a higher correlation with the patient's condition than physicians, presumably due to their more frequent contact. [16-18]

Self-reporting plays a critical role in human medicine. Studies have shown that proxy reports tend to rate QoL lower than self-reports, a phenomenon known as the "disability paradox." [19-21]. A similar situation is observed in pediatric oncology, where 30% - 50% of children experience symptoms such as fatigue, nausea, pain, and loss of appetite during treatment. Unobservable symptoms, such as nausea and psychological states, often require self-reporting to fully capture the patient's experience [22]. These studies highlight inherent limitations in the accuracy of assessments for veterinary patients as well.

For cancer patients, one study developed a questionnaire to assess HRQoL in cancer-bearing dogs and cats, dividing it into domains such as happiness, mental status, pain, appetite, hygiene, water intake (hydration), mobility, and general health [12]. However, this approach does not differ significantly from general QoL assessments or those targeting other diseases, raising concerns about its ability to accurately reflect the QoL specific to the cancer population [23].

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Recent literature on the QoL in cancer-bearing dogs has assessed various domains, including vitality, companionship, pain, and mobility, using 17 questions to evaluate each aspect. The study found that owners tended to prioritize adherence to normal routines and interactions with their dogs over clinical symptoms when assessing QoL [24].

2.2 The impact of chemotherapy on dogs with lymphoma

Owners often weigh the benefits of extended survival against the potential side effects of treatment, which influences their willingness to continue chemotherapy [25]. When the goals of chemotherapy for dogs are categorized as cure, life prolongation, or quality of life improvement, veterinarians and owners often have differing attitudes. If the goal is either cure or life prolongation, 70% of veterinarians are willing to tolerate higher VCOG grade of side effects, compared to only 30–40% of owners. However, when the goal is to improve quality of life, both veterinarians and owners prefer lower levels of side effects, with only 20–25% of veterinarians willing to accept moderate to severe side effects.

Research from previous studies highlights that while treatment complications may occur during chemotherapy for lymphoma, many owners prioritize their pet's quality of life and report satisfaction with the outcomes. The likelihood of side effects during chemotherapy ranges from 52.0% to 65.0%, while 53.3% to 68.0% of patients experience stable or improved quality of life. Although 20% to 32% of patients may experience a slight decline in quality of life, 73.2% to 92.0% of owners are still willing to pursue chemotherapy again. These findings suggest that, despite the potential for side effects, most owners are satisfied with the treatment outcomes and believe their pets' QoL remains acceptable during chemotherapy [27]. Notably, even in elderly

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patients, the efficacy of treatment does not decrease, nor do the side effects become more severe [3].

2.3 Medical decision-making anxiety of proxies

In pediatric oncology, initial treatment decisions are typically made by parents under conditions of high emotional and time pressure, often without a comprehensive understanding of the disease or prognosis. Approximately 1 in 6 parents experience heightened regret within the first 3 months after treatment begins. However, this feeling is dynamic and can change based on the child's response to treatment, either increasing or decreasing. Over the entire process, 27% of parents experience at least one instance of strong regret, with a minority continuing to exhibit persistent strong regret. A key factor contributing to parental regret is whether they received adequate information during the decision-making process [28].

Shared decision-making (SDM) is an important concept referring to the process in which clinicians and patients jointly participate in making treatment decisions after discussing options, benefits, and risks, while considering the patient's values, preferences, and circumstances. This process can influence the success of medical interventions, as well as owner satisfaction and compliance. However, even in human medicine, discrepancies in consensus between physicians and patients may still occur [29].

In the face of incurable diseases, pet owners may have different perspectives on the necessity and expectations of treatment compared to veterinarians [25]. Effective veterinary-owner communication and proper owner education about chemotherapy treatment protocols are crucial for successful treatment outcomes [30].

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Over-treatment can also contribute to caregiver burden, particularly in cases of chronic or palliative care for companion animals, where owners may experience heightened anxiety, depression, and a decline in social functioning [31].

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Chapter 3 Objectives

Currently, for canine lymphoma patients, chemotherapy is generally recommended following a relapse. However, there is limited research on owners' perspectives regarding pursuing chemotherapy in such circumstances. The primary aim of this study was to evaluate owners' views on the acceptability of their dogs' QoL after reinduction therapy at the first recurrence. The secondary objective was to identify the factors influencing owners' decisions to pursue reinduction chemotherapy following a relapse.

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Chapter 4 Material and methods

4.1 Patient selection

A retrospective study was conducted on canine patients diagnosed with multicentric lymphoma at National Taiwan University Veterinary Hospital from 2001 to 2024. Each patient was diagnosed through fine-needle aspiration, with ambiguous cases further evaluated using flow cytometry, PCR for antigen receptor rearrangement (PARR), or excisional biopsy. Following diagnosis, chemotherapy was administered using either a 25-, 19-, or 15-week CHOP protocol (C: cyclophosphamide; H: doxorubicin; O: vincristine; P: prednisolone) or a 19- or 15-week LHOP protocol (L: L-asparaginase; H: doxorubicin; O: vincristine; P: prednisone). Patients who experienced disease progression or death during induction were initially excluded, as were those who received no further treatment after relapse. However, regardless of the response to reinduction therapy or treatment completion, all cases were included once post-relapse treatment had commenced.

4.2 Method of questionnaire distribution

The owners of the included cases were contacted via text message with a link to an anonymous online survey. The text messages were sent through the Newsleopard platform (Newsleopard™, 2024). Contact information was obtained from the hospital's electronic medical record system. If a patient had multiple owners, the survey was sent to all of them simultaneously.

The online questionnaire consisted of nine questions: seven single-choice questions and one multiple-choice question, and one open-ended question. The choice questions were measured on either a scale from 0 to 2 or a Likert scale from 0 to 5.

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Likert scales were also integrated within the questionnaire to allow participants to rank the importance of key themes surveyed. Multiple-choice questions require at least one answer to be selected. Owners had the option to decide whether to respond to the open-ended question. Completing the entire questionnaire required approximately 3 minutes.

4.3 Questionnaire design and the Questionnaire

Three key themes were adapted from previous research and were embedded within the questionnaire: owner perception of the benefits and side effects of chemotherapy, willingness to repeat chemotherapy. The questionnaire was adapted from several studies with primary references including the Canine Lymphoma Quality of Life Questionnaire, the Small Animal Cancer Quality of Life Questionnaire, and the Owner-Dog Bond Questionnaire [12, 23]. Covering various aspects of QoL, treatment response, and chemotherapy side effects is challenging, particularly when attempting to quantify these factors. Since caregivers' subjective perceptions are central to assessing satisfaction, this study focuses on subjective outcomes and side effects of treatment following relapse, comparing them to previous chemotherapy experiences and expectations. This approach aims to improve response efficiency and minimize potential misinterpretations. Furthermore, understanding factors that cause hesitation in resuming chemotherapy, such as treatment costs, prognosis, and frequent follow-up visits, can provide insights into the challenges owners face when making decisions.

Including open-ended questions allows owners to freely share their personal perspectives, providing additional insights that complement and expand upon the ideas generated by multiple-choice questions or the survey design [32]. The owners were asked the following questions in sequence:

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1. How long did it take from the end of the first treatment to the relapse? (options: 3 months, 6 months, 9 months, over a year)
2. How has the quality of life changed after receiving chemotherapy following tumor relapse? (options: got worse, remained the same, got better)
3. Did the second round of chemotherapy alleviate your dog's symptoms? (options: got worse, remained the same, got better)
4. The side effects during chemotherapy following relapse were severe. (options: totally disagree, partially disagree, neutral, partially agree, totally agree)
5. How do you perceive the side effects of chemotherapy after relapse compared to the first round of chemotherapy? (options: more severe, the same, less severe)
6. What was the treatment outcome after receiving chemotherapy following tumor relapse? (options: worse than expected, as expected, better than expected)
7. Upon discovering your dog's lymphoma relapse, what were the reasons that made you hesitate to receive chemotherapy? (multiple selections allowed)

- The disease progressed faster than expected.
- The prognosis of the disease was poor.
- The side effects of chemotherapy were significant.
- The method of administration: such as frequent injections.
- The patient was too old.
- The cost was too high.
- Frequent follow-up visits were required.
- Others: ___(Fill-in-the-blank item)

8. If you could do it all over again, would you choose to let your dog receive treatment after a relapse? (0 = no, 1 = unsure, 2 = yes)
9. Additional suggestions and thoughts. (open-ended question)

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Original Chinese version of the questionnaire content listed in **Table 1**. The data was initially compiled using Google's built-in form analysis tool for basic statistical summarization.

4.4 Statistical analysis

Most of the questions in the questionnaire consisted of categorical variables with ordinal options. Chi-square test was employed to analyze the relationship between relapse time and various questionnaire items, and conducted a post-hoc analysis to obtain standardized residuals for identifying specific trends. Logistic regression was applied to examine the associations between the decision to pursue treatment again and individual survey questions. A *p*-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics (version 29).

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Chapter 5 Results

5.1 Study population

A total of 172 eligible canine multicentric lymphoma patients were initially included in the study. After excluding those who experienced disease progression during chemotherapy induction, did not relapse, or did not continue further treatment after relapse, 125 patients were ultimately included. Of these, 88 patients treated with the CHOP protocol received 93 text messages, 19 patients on the 19-week LHOP protocol received 22 text messages, and 18 patients on the 15-week LHOP protocol received 25 text messages. In total, 140 questionnaires were distributed, with 50 responses received, resulting in a response rate of 26%, as shown in **Figure 1**.

5.2 Relapse status and the decision to repeat treatment

Using logistic regression, the analysis examined the choice made if given the chance to decide again. Among the factors analyzed, the perception of chemotherapy side effects relative to the first round showed a strong and statistically significant positive association with the decision to opt for further treatment (OR = 13.824, p = 0.045) as showed in **Table 2**. Other factors, including the time interval from the end of the first treatment to relapse (OR = 0.344, p = 0.581), changes in QoL (OR = 3.369, p = 0.295), symptom alleviation (OR = 1.893, p = 0.444), and overall treatment outcome (OR = 0.511, p = 0.579), did not demonstrate significant associations with the decision to pursue repeated chemotherapy.

Post-hoc analysis revealed that owners who perceived side effects as "more severe" were significantly more likely to refuse treatment again (standardized residual = 2.8), while those who perceived side effects as "the same" were significantly more

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likely to remain uncertain (standardized residual = 2.0). Other categories, including willingness to treat ("Yes") and perceptions of "Less severe" side effects, showed no significant differences (standardized residuals < 1.96) as presented in **Table 3**.

5.3 Analysis of individual questions

Among the 50 respondents, 44% reported that relapse occurred within 3 months of completing the first treatment, while 28% indicated that relapse occurred after more than a year, demonstrating a significant difference in relapse timing ($p = 0.025$), which showed in **Figure 2**.

Descriptive analysis and Chi-square analysis were summarized in **Table 4**. Regarding QOL after receiving chemotherapy, 52% of owners reported a decline, 30% observed no change, and 18% noted improvements ($p = 0.012$). For symptom alleviation after the second round of chemotherapy, 44% of owners felt symptoms worsened, while 40% reported improvements ($p = 0.032$). When evaluating the severity of chemotherapy side effects, 28% of respondents strongly agreed that the side effects were severe, with an additional 10% partially agreeing. In contrast, 34% either partially or totally disagreed with the perceived severity of side effects, but the result did not indicate statistical significance ($p = 0.116$). Comparing the side effects to those of the initial chemotherapy, 42% of respondents perceived them as more severe, 42% observed no change, and only 16% reported milder side effects. The Chi-square test revealed a significant difference in perceived severity ($p = 0.034$). Regarding overall treatment outcomes, 58% of owners found the results to be worse than expected, 28% found them as expected, and only 14% noted better outcomes ($p < 0.001$). Overall, 52% of owners indicated they would opt for chemotherapy again if faced with a similar decision, while 32% would decline further treatment, and 16% remained uncertain ($p = 0.008$).

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5.4 Relapse interval and chemotherapy experience

A Chi-square test of independence was conducted to explore the relationships between the time from the end of the first treatment to relapse and various factors related to the dogs' subsequent chemotherapy experiences. The significant impact of relapse timing on QOL after receiving chemotherapy were identified at the 6-month (p = 0.035) and 9-month (p = 0.003) intervals. Although not statistically significant, the 3-month interval approached significance (p = 0.057). Owners' perception of side effects compared to the first round of chemotherapy also demonstrated significant differences at the 6-month (p = 0.037) and over-a-year (p = 0.037) intervals. No significant differences were observed for factors such as symptom alleviation, general side effects, or treatment outcomes, with p-values > 0.05 across all intervals as presented in **Table 5**.

Post-hoc Chi-square analysis with standardized residuals was performed to identify significant deviations from expected counts for perceived chemotherapy side effects and QoL changes across relapse intervals. A significant result was observed for "QoL – Better" in the "Over a year" interval, with a standardized residual of 2.2, indicating a significantly higher-than-expected perception of better QoL changes in this group. No significant differences were found for other categories, as all standardized residuals remained below | 1.96 |, suggesting that most deviations from expected values were not statistically meaningful as presented in **Table 6.**

5.5 Factors influencing the decision to repeat treatment at the time of relapse

A total of 113 responses were collected for the multiple-choice question regarding the decision to continue treatment upon discovering a relapse. Statistical analysis of the

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factors influencing the decision to pursue further chemotherapy revealed that the most common concern was the faster-than-expected progression of the disease (28%), followed by significant side effects of chemotherapy (19%), a poor prognosis (14%), advanced patient age (11%), administration methods and high treatment costs (both 10%), and frequent follow-up visits (8%), as shown in **Figure 3**.

Based on the frequency distribution, for dogs that relapsed within 3 months, 70% (N=14/20) of owners cited "The disease progressed faster than expected" as their primary concern, followed by 50% (N=10/20) reporting "The side effects of chemotherapy were significant." In the 6-month group, the most reported concern was "The prognosis of the disease was poor" at 82% (N=9/11), followed by both "The side effects of chemotherapy were significant" and "Frequent follow-up visits were required," each at 36% (N=4/11). In the 9-month group, which had a very small sample size (N=5), "The patient was too old" was the leading factor at 60% (N=3/5), while no participants cited "The cost was too high" or "Frequent follow-up visits were required." In the "Over a year" group, "The prognosis of the disease was poor" was most significant at 57% (N=8/14), whereas "Frequent follow-up visits were required" was the least reported concern at 7% (N=1/14) as presented in **Table 7**.

5.6 The responds of open-ended questions

A total of 23 participants responded to the open-ended questions. Among them, 5 reported that the effects of chemotherapy were unsatisfactory or did not last long, while the majority expressed positive satisfaction with the treatment. None of the participants provided feedback on the questionnaire design or raised concerns about the completion process, nor did anyone leave additional comments on the multiple-choice questions.

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Chapter 6 Discussion

The primary goals for most owners in choosing treatment for pets with cancer are to improve QoL and extend lifespan. Canine multicentric lymphoma is a type of tumor that responds well to chemotherapy, and owners are generally very satisfied with the initial effects of treatment. A study interviewed 25 owners whose dogs with lymphoma underwent chemotherapy, approximately half of the owners reported varying degrees of chemotherapy side effects. However, up to 90% did not regret their choice of treatment. Recent studies have revealed similar results [26]. The HRQoL scale was incorporated to evaluate the chemotherapy experiences of dogs with multicentric lymphoma. Owners were asked to complete a questionnaire at the beginning, middle, and end of the chemotherapy period. The scale assessed factors such as happiness, mental status, appetite, hygiene, coat condition, water intake, and activity level. A total of 15 dogs were included in the study. The results indicated considerable owner satisfaction and significant improvements in the dogs' appetite, overall health, and QoL [30].

Most past studies have primarily focused on patients undergoing initial chemotherapy, making the high satisfaction levels unsurprising. In contrast, this study targets patients receiving treatment after relapse, where only 52% of owners indicated they would choose the same treatment again, and 32% expressed regret about their choice. Side effects experienced during treatment compared to the first round of chemotherapy play a critical role in whether owners feel regret about their decision. This was evident in both the comparison between regret and no regret (OR = 13.8, p = 0.045) and between uncertainty and no regret (OR = 22.7, p = 0.032). Patients experiencing worsened side effects were more likely to regret the decision (Standardized residual = 2.8); however, some patients with worsened side effects were

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still willing to undergo chemotherapy again (n = 7). This indicates that changes in side effects are important, but they are not the sole determining factor. Among the participants, 38% agreed to varying degrees with the statement, "The side effects during chemotherapy following relapse were severe," while 34% disagreed ($p = 0.116$). This suggests that the side effects of chemotherapy following relapse were not necessarily perceived as very severe. The severity of side effects during chemotherapy may be attributed to multiple factors, including the specific drugs used, the aging process, and the progression of concurrent chronic diseases, which can lead to more unpredictable reactions. Tolerance for side effects may vary depending on the treatment goals and can differ between veterinarians and owners. When the goal is to cure cancer or extend life, veterinarians are generally more willing to accept higher levels of side effects. Conversely, if the goal of chemotherapy is to improve QoL, tolerance for side effects decreases significantly [25]. It is reasonable to suggest that during initial chemotherapy, extending life is likely the primary consideration. However, for patients undergoing treatment after relapse, the owner's tolerance for side effects may decline further.

Owners' decisions regarding chemotherapy for their pets are often directly influenced by prior chemotherapy experiences. When deciding on chemotherapy for their pets, owners are likely influenced by the treatment experiences of their family members or friends who have undergone chemotherapy [33]. It is reasonable to assume that the population willing to undergo chemotherapy again in this study was generally satisfied with their overall experience during the initial treatment, and their past experiences likely shaped their expectations.

In general, the expected response rate and duration of remission after relapse are only 40–50% of those achieved during initial chemotherapy. The median duration is approximately 2 months, with only a small proportion of patients experiencing longer responses [5, 10]. In this study, 58% of owners believed the results were below

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expectations, consistent with findings from previous studies. This did not influence their feelings of regret regarding post-relapse chemotherapy (p = 0.579). A similar observation has been made in humans. When parents face the situation of their child being diagnosed with incurable cancer, 38% choose to pursue treatment for their child. Among these, 61% believed that the treatment caused suffering for their child, and 57% felt that the treatment was ineffective. Parents whose children experienced severe side effects were less likely to recommend such treatments to others [34].

This suggests that side effects might be more likely make the owners symbolize the "harm" with "medical decisions" from the owner's perspective.

Regret is a complex emotional response, and similar challenges are faced in both pediatric hematology-oncology and veterinary fields. Caregivers or parents often feel overwhelmed upon receiving a cancer diagnosis, while patients are unable to fully express themselves. In many cases, parents make treatment decisions without fully understanding potential adverse effects. This highlights that, even in human medicine, cancer treatment decisions are frequently made under highly emotional and insufficiently informed circumstances. A study revealed one-sixth of parents reported experiencing intense regret at least once within 3 months of starting treatment for their children, and 45% reported feeling mild regret [35]. Regret may also change over time. In one study, parents were surveyed at the time of diagnosis, as well as four and twelve months after starting treatment. The results revealed that some parents (9%) no longer felt regret, while 7% who initially felt satisfied with their decisions began to experience regret. Throughout the study, only a small number (3%) of parents consistently felt regret, but 27% experienced intense regret at least once during the study period. This suggests that feelings of regret can fluctuate with disease progression and changes in the patient's condition. Regret was found to be unrelated to prognosis or relapse status but was closely associated with receiving high-quality information and parents

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maintaining a calm mindset [28]. In this study, the questionnaire was distributed after the patients had passed away, ensuring that fluctuations in feelings about treatment decisions were no longer influenced by the patient's condition.

For patients experiencing relapse, the initial approach often involves reinduction using the same protocol [4]. However, as drug resistance develops, the treatment strategy would be gradually adjusted. The use of rescue chemotherapy is generally associated with lower response rates, typically lasting only 2-3 months, and may exhibit greater toxicity compared to first-line chemotherapy [5]. The chemotherapy regimens administered to dogs after relapse may vary, leading to differences in the risks and severity of side effects, which also results in limitations in this study. Currently, no studies have specifically investigated whether patients undergoing chemotherapy after relapse experience more severe side effects. Such research may be limited by the effects of the drugs used, as well as the clinical signs that manifest as the disease progresses, which could pose significant challenges to this type of investigation.

When additional cancer treatment is likely to cause more harm than benefit, palliative care becomes the primary care for advanced-stage cancer patients. In human medicine, palliative care includes primary care, which focuses on basic physical and psychological support, as well as advanced specialist care, which involves complex symptom management and discussions about care goals. For patients with relapsed or refractory lymphoma in human medicine, the high uncertainty of prognosis often leads to rapid deterioration within a short period [36]. The average length of stay for hospice care is only 9 days, indicating a very short period between the cessation of active treatment and death [37]. A study revealed that although 55% of respondents who opted for chemotherapy for their pets were aware of the potential side effects, they found it challenging to accept the impact of vomiting, diarrhea, or inappetence on the patient's QoL. Nevertheless, most respondents considered QoL more important than life

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extension; however, owners generally overestimated the life-prolonging benefits of chemotherapy [33]. In canine cancer patients, achieving a cure through chemotherapy is often challenging, especially for relapsed lymphoma, where chemotherapy can also be considered part of palliative care. The ethical debate over whether chemotherapy aligns with the best interests of animal welfare has recently gained attention [38]. For dogs with relapsed lymphoma, chemotherapy is commonly recommended, but determining the appropriate timing for palliative care remains challenging. This difficulty may also explain the relatively lower satisfaction observed in this study.

In this study, 66% of patients experienced relapse within six months after completing the first treatment, while 28% faced their first relapse more than a year later. We hypothesized that shorter relapse intervals, due to faster development of drug resistance and increased likelihood of initiating rescue therapy, would result in poorer treatment outcomes and more severe side effects. However, the statistical results of this study do not support this hypothesis. The analysis revealed that while relapse intervals initially appeared to influence perceptions of QoL and side effects, the post-hoc analysis identified significance only in the "Over a year" group for better QoL impacts (p = 0.037, residual = 2.2). Notably, the "Over a year" group was not significant in the original QoL analysis (p= 0.116), further supporting the conclusion that relapse intervals may not consistently impact QoL, perceived side effects, or treatment outcomes.

The most frequently cited concern upon relapse was the rapid progression of the disease (28%), followed by chemotherapy side effects (19%) and the poor prognosis (14%). Among patients with a relapse interval of six months, 82% perceived the prognosis as poor, compared to 57% of those with a relapse interval of over one year. Current research on prognostic factors lacks standardized criteria. Although there are numerous studies on prognostic factors, their findings vary significantly due to

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differences in patient populations, tumor types, staging, immunophenotypes, medications, and even terminology definitions. Immunophenotype and initial treatment response (i.e., whether complete remission is achieved) may be more reliable prognostic indicators [6]. However, this study is limited by its design and cannot confirm these factors.

In contrast, factors such as the patient's age, administration method, cost, and frequent follow-up visits were selected by less than 10% of respondents. This may be because patients with relapse had already undergone initial chemotherapy and were less likely to reject these aspects, making them less significant considerations [39]. Alternatively, patients with such concerns may be more inclined to opt against further aggressive chemotherapy.

Although not included in the multiple-choice options, studies on palliative care for pets with cancer suggest that the owner's circumstances—such as mental health, financial constraints, personal experiences of friends or family, work situation, and emotional attachment to the pet—or the veterinarian's circumstances—such as experience with oncology or palliative care and clinic equipment limitations—may also be relevant factors [40]. This study included an open-ended field in the multiple-choice question design, but no respondents provided additional information. Previous studies have shown that only approximately 30% of dogs experiencing relapse after CHOP chemotherapy underwent further treatment [41, 42]. This study could not assess whether owners who chose not to treat their dogs' relapse experienced different levels of concern, highlighting the need for further research to explore these factors.

This study utilized an anonymous online questionnaire, which offers several advantages, including cost-effectiveness and increased response accuracy. Anonymous responses can enhance the response rate and reduce the likelihood of participants declining or providing false information due to concerns about data privacy. Compared

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to telephone interviews, online questionnaires also provide better confidentiality [43, 44].

This study is limited by recall bias regarding the perceived effectiveness or side effects of treatment. Additionally, the use of an anonymous online questionnaire makes it difficult to clearly define the respondent population, and biased respondents may be more likely to participate [45]. To enhance confidentiality and reduce response time, the questionnaire was designed without collecting detailed information about patients or owners. Future research on post-relapse chemotherapy could address these limitations by incorporating such data and including patients whose owners chose not to pursue treatment. This would allow for a more comprehensive understanding of decision-making experiences and their influencing factors.

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Chapter 7 Conclusions

This study suggests that, despite the discrepancy between expectations and experiences, the majority of owners did not express regret over their decision. Compared to the initial chemotherapy experience, the perception of side effects plays a crucial role in determining whether regret arises. Therefore, during chemotherapy for relapsed cases, more active preventive and symptomatic care should be considered to minimize the occurrence of side effects.

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Figures

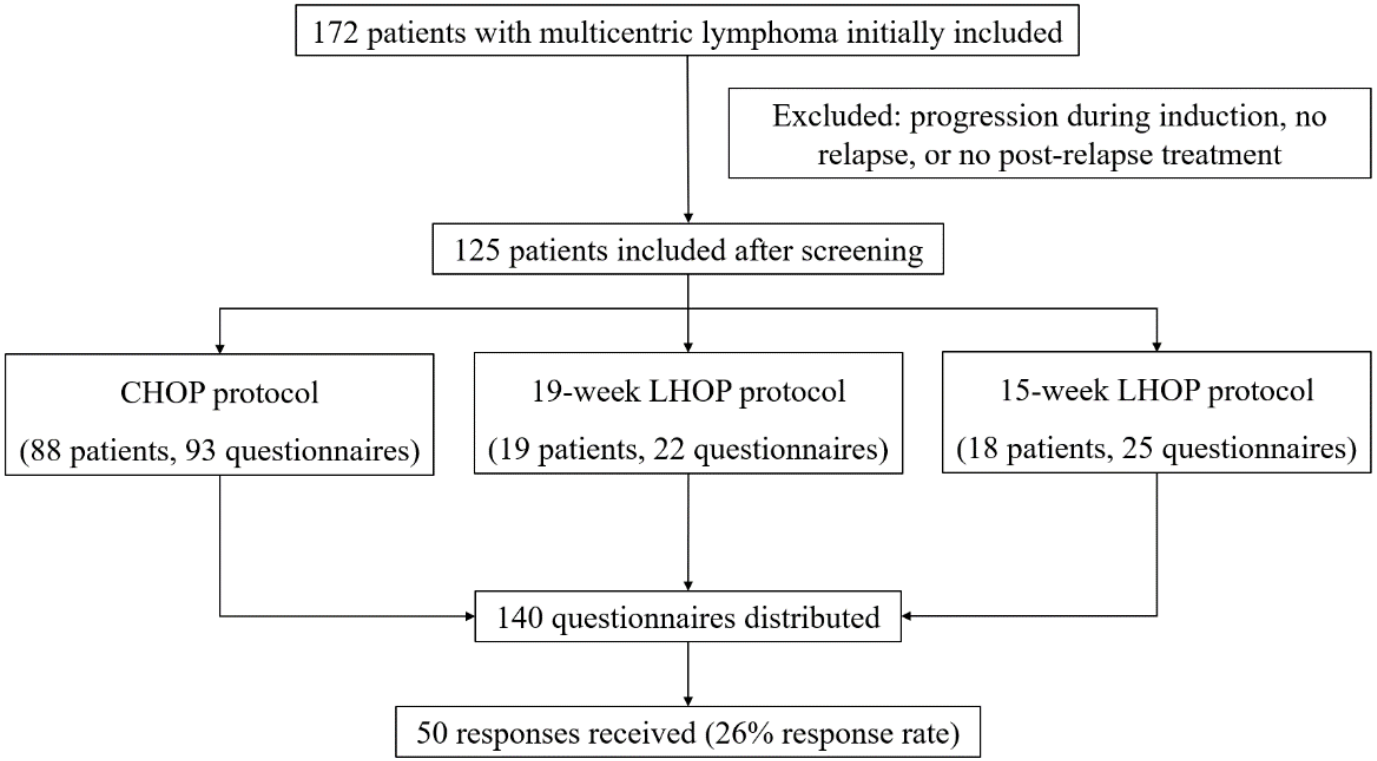

Figure 1. Case enrollment process and results

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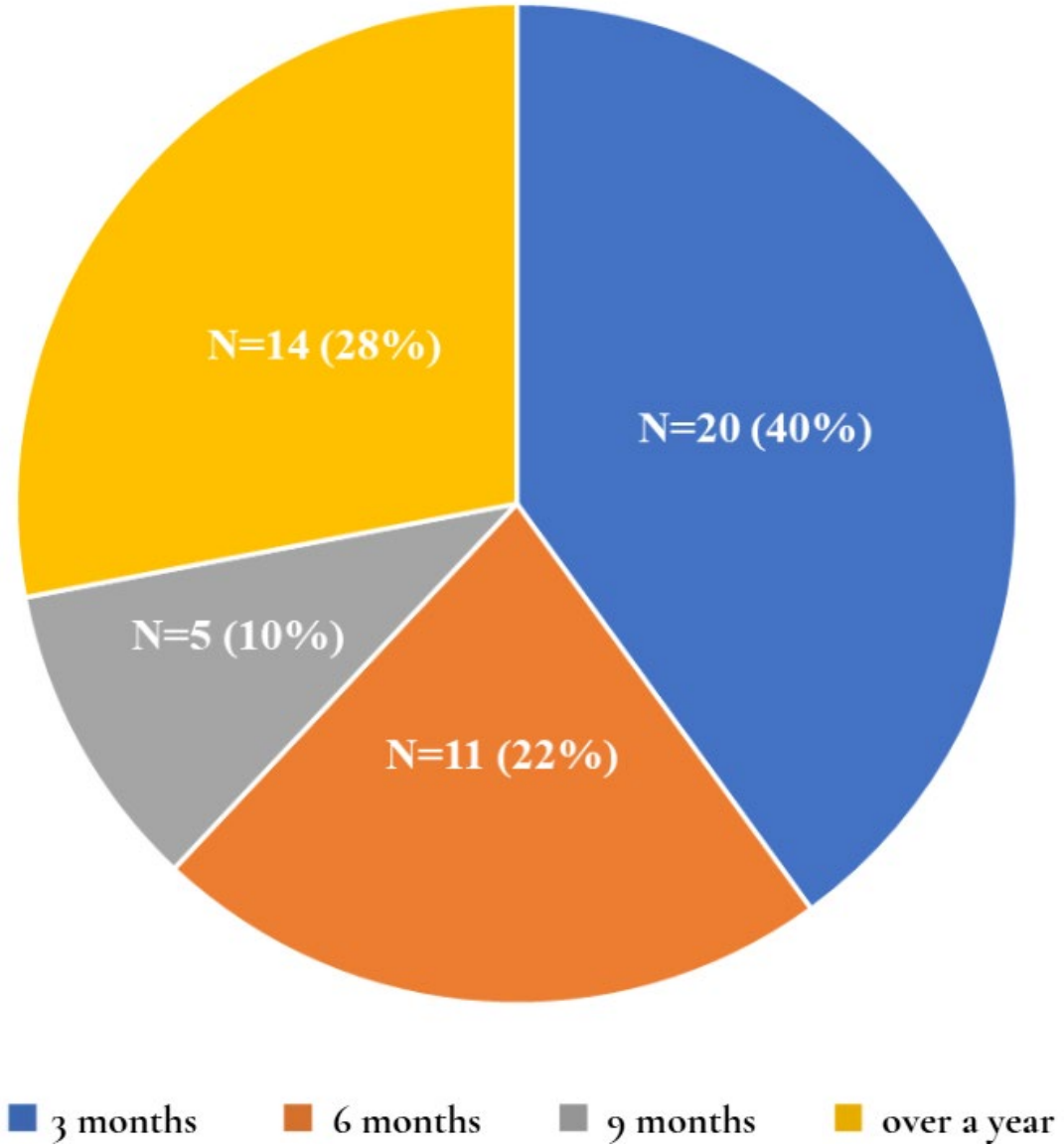

Figure 2. Study population categorized by relapse interval

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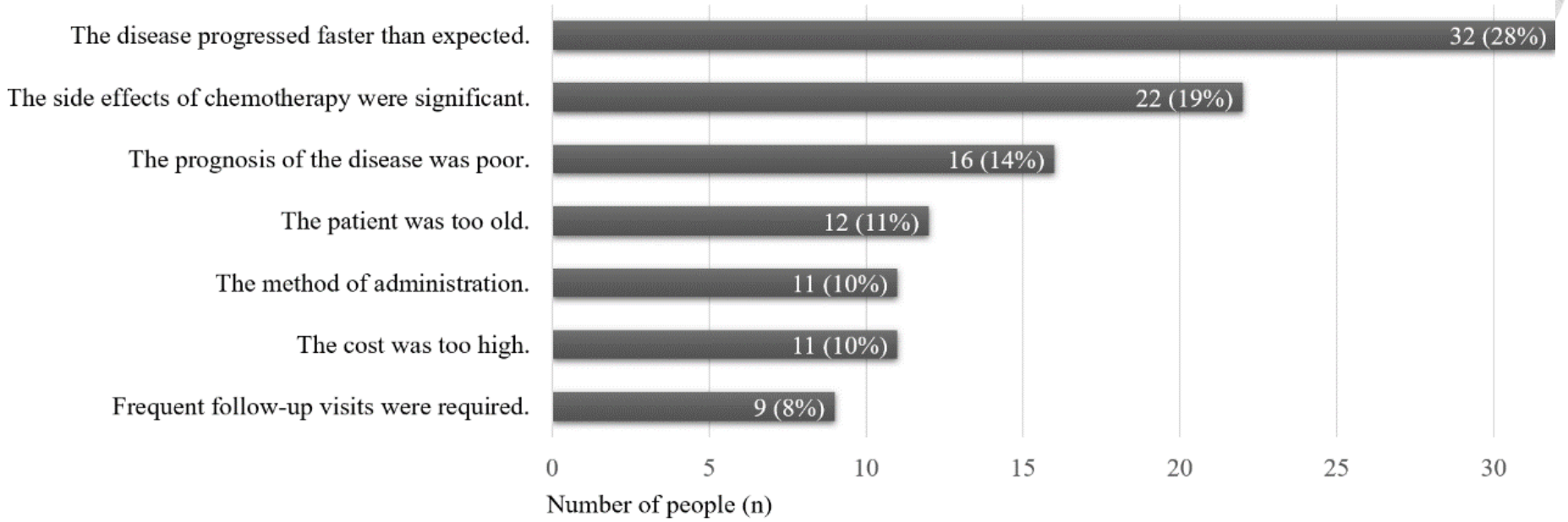

Figure 3. Distribution of factors influencing decision-making at relapse: multiple-choice question results

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Tables

Table 1. The original questionnaire in Chinese

問題	選項	選項特性
從第一次治療結束到復發，大約經過了多久時間？	3 個月 6 個月 9 個月 超過一年	單選題
你認為在復發後化療期間的生活品質如何？	0: 變糟 1: 持平 2: 變好	0-2 單選線性刻度
你認為復發後的化療有緩解狗狗的症狀嗎？	0: 變糟 1: 持平 2: 變好	0-2 單選線性刻度
復發後化療的副作用是嚴重的。	1: 完全不同意 5: 完全同意	1-5 單選線性刻度
你認為相較於第一次化療，復發後化療的副作用嚴重程度？	0: 比第一次化療嚴重 1: 差不多 2: 比第一次化療輕微	0-2 單選線性刻度
你認為復發後化療有達到預期的效果嗎？	0: 比預期效果差 1: 差不多 2: 比預期效果好	0-2 單選線性刻度
在發現狗狗腫瘤復發的當下，你認為有哪些原因讓你猶豫是否要再次接受化學治療？	疾病進展得比預期來得快 疾病預後不佳 化療副作用 給藥方式，例如：不想再讓狗狗頻繁打針 病患年紀太大 價格昂貴 需要頻繁回診 其他__	多選題
如果一切可以重來，你會選擇再次讓狗狗在復發後進行化療嗎？	0: 不會 1: 不確定 2: 會	0-2 單選線性刻度
其他的建議與想法		開放式問答

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Table 2. Logistic regression analysis of relapse experience and its association with willingness to pursue treatment again

	Willingness to pursue treatment again Yes vs. No		
	Logit coefficient	Odds ratio	*p*-Value
Relapse interval	-1.068	0.344	0.581
Change of QoL	1.215	3.369	0.295
Symoptoms alleviation	0.638	1.893	0.444
Severity of side effects	-0.217	0.805	0.615
Side effects severity compared to induction	2.626	13.824	0.045*
Treatment outcome	-0.671	0.511	0.579

**p*-Value < 0.05 is considered significant.

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Table 3. Post-hoc crosstabulation for perceived side effects of chemotherapy after relapse and willingness to treat again

Willingness to treat again after relapse	Perception of side effects after relapse	Count	Expected count	Standardized residuals
No	More severe	14.0	6.7	2.8 *
	The same	2.0	6.7	-1.8
	Less severe	0	2.6	-1.6
Unsure	More severe	0	3.4	-1.8
	The same	7.0	3.4	2.0 *
	Less severe	1.0	1.3	-0.2
Yes	More severe	7.0	10.9	-1.2
	The same	12.0	10.9	0.3
	Less severe	7.0	4.2	1.4

*|Standardized residuals| > 1.96 indicates significance.

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Table 4. Chi-square analysis of responses to chemotherapy experience

	Options	Numbers	$\chi 2(df)$	p-Value	Standardized residuals
Relapse interval	3 months	20 (44%)	9.36 (3)	0.025*	2.12 *
	6 months	11 (22%)			-0.42
	9 months	5 (10%)			-2.12*
	over a year	14(28%)			0.42
Change of QoL	got worse	26 (52%)	8.92 (2)	0.012*	2.28 *
	remained the same	15 (30%)			-0.42
	got better	9 (18%)			-1.88
Symptoms alleviation	got worse	22 (44%)	6.88 (2)	0.032*	1.30
	remained the same	8 (16%)			-2.13 *
	got better	20 (40%)			0.81
Severe side effects	totally disagree	6 (12%)	7.4 (4)	0.116	-
	partially disagree	11 (22%)			
	neutral	14 (28%)			
	partially agree	5 (10%)			
	totally agree	14 (28%)			
Side effects compared to the first treatment	more severe	21 (42%)	6.76 (2)	0.034*	1.05
	the same	21 (42%)			1.05
	less severe	8 (16%)			-2.13 *
Treatment outcome	worse than expected	29 (58%)	15.16 (2)	<0.001*	3.01 *
	as expected	14 (28%)			-0.66
	better than expected	7 (14%)			-2.37 *
Willingness to repeat treatment	no	16 (32%)	9.76 (2)	0.008*	- 0.17
	unsure	8 (16%)			-2.13 *
	yes	26 (52%)			2.28 *

*p-Value < 0.05 and |Standardized residuals| > 1.96 are considered significant.

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Table 5. Chi-square analysis of relapse interval and chemotherapy experiences

	Relapse interval	$\chi 2(df)$	p-Value
Change of QoL	3 months	12.234 (6)	0.057
	6 months	13.569 (6)	0.035*
	9 months	9.009 (1)	0.003*
	over a year	7.400 (4)	0.116
Symoptoms alleviation	3 months	4.681 (6)	0.585
	6 months	4.963 (6)	0.549
	9 months	3.627 (1)	0.057
	over a year	3.273 (1)	0.070
Severity of side effects	3 months	9.278 (12)	0.679
	6 months	12.140 (12)	0.434
	9 months	1.851 (1)	0.174
	over a year	0.434 (12)	0.679
Side effects compared to the first treatment	3 months	11.985 (6)	0.062
	6 months	13.426 (6)	0.037*
	9 months	3.776 (1)	0.052
	over a year	0.037 (6)	0.037*
Willingness to repeat treatment	3 months	8.234 (6)	0.221
	6 months	9.556 (6)	0.145
	9 months	3.273 (1)	0.070
	over a year	3.273 (1)	0.070
Treatment outcome	3 months	3.515 (6)	0.742
	6 months	4.810 (6)	0.568
	9 months	0.332 (1)	0.565
	over a year	0.332 (1)	0.565

*p-Value < 0.05 is considered significant.

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Table 6. Post-hoc crosstabulation for perceived chemotherapy side effects and quality of life changes across relapse intervals

Relapse interval		Side effects compared to the first treatment			Change of QoL		
		More severe	The same	Less severe	Worser	The same	Better
3 months	Count	9.0	10	1	13	5.0	2.0
	Expected count	8.4	8.4	3.2	10.4	6.0	3.6
	Standardized residuals	0.2	0.6	-1.2	0.8	0.4	-0.8
6 months	Count	7.0	3.0	1.0	8.0	3.0	1.0
	Expected count	4.6	4.6	1.8	5.7	3.3	2.0
	Standardized residuals	1.1	-0.8	-0.6	1.0	-0.2	-1.4
9 months	Count	0	4.0	1.0	2.0	2.0	1.0
	Expected count	2.1	2.1	0.8	2.6	1.5	0.9
	Standardized residuals	-1.4	1.3	0.2	-0.4	0.4	0.1
Over a year	Count	5.0	4.0	5.0	3.0	5.0	6.0
	Expected count	5.9	5.9	2.2	7.3	4.2	2.5
	Standardized residuals	-0.4	-0.8	1.8	-1.6	0.4	2.2 *

*|Standardized residuals| > 1.96 indicates significance.

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Table 7. Frequency distribution of responses to multiple-choice questions by relapse interval

Relapse Interval	Rapid disease progression	Side effects of chemotherapy	Poor prognosis	Advanced age	The method of administration	High costs	Frequent follow-up visits
3 months	70% (N=14/20)	50% (N=10/20)	40% (N=8/20)	30% (N=6/20)	25% (N=5/20)	25% (N=5/20)	20% (N=4/20)
6 months	27% (N=3/11)	36% (N=4/11)	82% (N=9/11)	27% (N=3/11)	18% (N=2/11)	27% (N=3/11)	36% (N=4/11)
9 months	40% (N=2/5)	40% (N=2/5)	20% (N=1/5)	60% (N=3/5)	20% (N=1/5)	N=0	N=0
Over a year	21% (N=3/14)	43% (N=6/14)	57% (N=8/14)	14% (N=2/14)	14% (N=2/14)	21% (N=3/14)	7% (N=1/14)

*Each percentage indicates the proportion of participants within the specific relapse interval group who selected a particular option in the multiple-choice question. For example, “70% (N=14/20)" means that 14 out of 20 participants in the 3-month relapse group selected "The disease progressed faster than expected."

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