

# **Positron-emission tomography-based staging is cost-effective in early-stage follicular lymphoma**

## **Short running title:**

Cost-effectiveness of staging PET in follicular lymphoma

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## **ABSTRACT**

**Rationale:** The objective was to assess the cost-effectiveness of staging positron emission tomography/computed tomography (PET/CT) in early-stage follicular lymphoma from the Canadian health care system perspective.

**Methods:** The study population was FL patients staged as early-stage using conventional CT imaging and planned for curative-intent radiation therapy (RT). A decision analytic model simulated the management after adding a staging PET/CT vs. using staging CT alone. In the no-PET/CT strategy, all patients proceeded to curative-intent RT as planned. In the PET/CT strategy, PET/CT information could result in an increased RT volume, switching to a non-curative approach, or no change in RT treatment as planned. Subsequent disease course was described using a state-transition cohort model over a 30-year time horizon. Diagnostic characteristics, probabilities, utilities and costs were derived from the literature. Baseline analysis was performed using quality-adjusted life years (QALYs), costs (2019 Canadian dollars, CAD\$) and the incremental cost-effectiveness ratio. Deterministic sensitivity analyses were conducted, evaluating net monetary benefit at a willingness-to-pay threshold of \$100,000/QALY. Probabilistic sensitivity analysis using 10,000 simulations was performed. Costs and QALYs were discounted at a rate of 1.5%.

**Results:** In the reference case scenario, staging PET/CT was the dominant strategy, resulting in an average lifetime cost saving of \$3,165 and a gain of 0.32 QALYs. In deterministic sensitivity analyses, the PET/CT strategy remained the preferred strategy for all scenarios supported by available data. In probabilistic sensitivity

analysis, the PET/CT strategy was strongly dominant in 77% of simulations (i.e., reduced cost and increased QALYs), and was cost-effective in 89% of simulations (i.e., either cost-saving or with an incremental cost-effectiveness ratio below \$100,000/QALY).

**Conclusion:** Our analysis shows that the use of PET/CT to stage early-stage FL patients reduces cost and improves QALYs. Patients with early-stage FL should undergo PET/CT prior to curative-intent RT.

## **INTRODUCTION**

For patients with early-stage follicular lymphoma (FL), definitive radiation therapy (RT) is a potentially curative treatment, with a 10-year event free survival of 40-50% (1-3). On the other hand, advanced-stage disease is considered incurable, but is still associated with a long median overall survival of 15-20 years (4), given its indolent nature and response to various treatments.

Since its introduction, computed tomography (CT) scan has been an integral part of lymphoma staging, allowing anatomic visualization of nodal and extranodal disease. In the current era, fluorodeoxyglucose (FDG)-positron emission tomography (PET) combined with CT in a single procedure (PET/CT) is considered state-of-the-art imaging in lymphoma (3,5,6). A recent retrospective cohort study of early-stage FL patients staged with PET/CT suggested a modest improvement in intermediate-term outcomes when compared to conventionally staged early-stage FL cohorts (7,8), and guidelines have been revised to recommend both staging CT

and staging PET/CT to confirm localized disease or in the case of suspected transformation (4,9). Nevertheless, not all centers have shifted to routinely utilizing PET/CT in the staging of FL patients (3,5,6,10). Furthermore, neither the prior studies nor the recent guidelines considered the potential downstream impact of PET/CT staging on patient outcomes or the cost-effectiveness of adding functional imaging to CT alone.

A complete assessment of the impact of staging PET/CT requires the altered outcomes of the patients who are upstaged to be accounted for. Furthermore, evaluation of quality-adjusted life expectancy and cost-effectiveness facilitates comparison of staging PET/CT with other medical interventions for which these outcomes have been described. Thus, we sought to determine the impact of staging PET/CT on quality-adjusted life years (QALYs) and cost to the Canadian health care system in patients with early-stage FL planned for curative-intent RT.

## **METHODS**

The population examined was patients with low-grade (grade 1-3A) FL staged as early-stage (stage I-II) using conventional CT imaging and planned for curative-intent radiation therapy (RT); the age of the base case patient was 60 years old. A decision analytic model was developed to simulate the management of patients after adding a staging PET/CT to the staging approach vs. using staging CT alone (see Figure 1). In the no-PET/CT strategy, all patients proceeded to curative-intent RT as planned. In the PET/CT strategy, PET/CT information could result in an

increased RT volume, switching to a non-curative approach, or no change in treatment.

Patients' subsequent disease course was described using a state-transition cohort model over a 30-year lifetime horizon. A simplified version of the model is displayed in Figure 2. Patients upstaged to advanced-stage on PET/CT were managed with rituximab monotherapy, watchful waiting, palliative RT (4Gy in 2 fractions), or bendamustine-rituximab. Patients staged as early-stage received curative-intent RT (24Gy in 2 fractions). On relapse/progression, patients were treated with either bendamustine-rituximab plus rituximab maintenance if they hadn't previously received it, and salvage chemotherapy if they had. After bendamustine-rituximab, patients could receive up to 3 further lines of chemotherapy after which they transitioned into a palliative state and eventually death. Patients were assumed to still have indolent disease on relapse/progression rather than transformation to high-grade disease.

Direct medical costs from the Canadian health care system perspective were estimated from published literature and adjusted to 2019 CAD\$. Incremental cost-effectiveness ratios (ICER) were calculated, and a willingness-to-pay (WTP) threshold of \$100,000 per QALY was adopted (11). QALYs and costs were discounted at an annual rate of 1.5% (12).

Various sensitivity analyses were performed to address model uncertainties and to establish the thresholds whereby each treatment strategy would be preferred. The baseline values and probability distributions are listed in Supplemental Tables 1 and 2. Deterministic one-way sensitivity analysis was

performed to evaluate each variable's influence on the net monetary benefit at a WTP of \$100,000/QALY. Probabilistic sensitivity analysis was performed using 10,000 simulations, each using a parameter set drawn from the distributions described in Supplemental Tables 1 and 2. TreeAge Pro 2019 (TreeAge Software, Williamstown, MA, USA) was used to construct the model and perform the analyses.

### **Transition Probabilities**

The probabilities used in the model are shown in Supplemental Table 1(3,13-22). The diagnostic probabilities of PET/CT were derived from a study by Wirth et al. assessing the impact of PET/CT on early-stage FL (13). Based on Wirth's data (as described in the supplement), a uniform distribution ranging between 62% (8/13) and 92% (12/13) was used in sensitivity analysis to conservatively estimate the uncertainty of the probability of a new PET/CT finding of advanced-stage disease. Similarly, a uniform distribution ranging between 0% (0/6) and 100% (6/6) was selected for the probability of early-stage disease truly outside the planned RT field for those in whom this was diagnosed on PET/CT.

Probabilities reflecting disease course were derived from randomized controlled trials (RCTs) if available and cohort studies if no relevant RCTs had been published. Further details are found in the supplement (14,15,19,20,23,24). The probability of death from other causes was the age-related mortality per 6-month cycle according to Statistics Canada life tables (22).

## **Utilities and Costs**

A utility value representing health-related quality of life was assigned to each health state based on published values (Supplemental Table 1(25-29)).

Costs were considered from the perspective of the Canadian health care system and were adjusted to 2019 Canadian dollars with the Consumer Price Index

(<http://www.bankofcanada.ca>). Based on Wirth et al. (13), we accounted for the additional cost of a biopsy in approximately 16% of patients who have new findings on PET/CT. The costs of PET/CT and core biopsy were based on the 2019 Ontario Schedule of Benefits for Physician Services. The cost of a 12-fraction course (27) of intensity-modulated radiation therapy was derived from a Canadian costing model (30). Further medical costs and their derivations are detailed in Supplemental Table 2 (19,23,30-40).

## **RESULTS**

### **Cost-Utility Analysis**

In the base-case scenario, PET/CT was the dominant strategy. The no-PET/CT strategy resulted in 14.09 QALYs and a cost of \$98,657. The PET/CT strategy resulted in 14.40 QALYs at a cost of \$95,491, representing a gain of 0.32 QALYs and an average lifetime cost saving of \$3,165.

## Sensitivity Analyses

One-way sensitivity analyses were conducted for each variable, evaluating net monetary benefit at a willingness-to-pay threshold of \$100,000/QALY; a range of 0-100% was used for testing probabilities, 0-1 for utilities, and 0-\$500,000 for costs. As shown in supplemental figure 1, the no-PET/CT strategy became the preferred strategy only in scenarios that are not supported by available data, including when the probability of progression after rituximab monotherapy in advanced-stage disease was >8.3% per 6 months, probability of progression after watchful waiting in advanced-stage disease was <4% per 6 months, and utility of first remission was <0.66. The no-PET/CT strategy also became preferred when the proportion of advanced-stage patients requiring bendamustine-rituximab was >48.0%, receiving watchful waiting was >89.3%, and receiving palliative-intent RT was >75.4%. The model was robust to a very wide range of costs in one-way sensitivity analyses. The no-PET/CT strategy was only preferred when costs were unrealistically high: >\$36,040 for a PET/CT, >\$340,653 for bendamustine-rituximab after rituximab monotherapy, and >\$60,815 for a follow-up appointment. The model was not sensitive to the costs of RT, biopsy, salvage chemotherapy, rituximab maintenance, biopsy, bendamustine-rituximab after RT or watchful waiting, medical oncology consultation, or palliation.

The net monetary benefit of the PET/CT strategy increased with increasing probabilities of PET/CT detecting advanced-stage disease (pAS) and PET/CT detecting early-stage disease outside planned RT field (pORT). PET/CT also remained the optimal strategy across the range of relevant values for both

parameters in one-way sensitivity analyses. In two-way sensitivity analysis, the PET/CT strategy remained preferred unless  $p_{AS} < 1\%$  and  $p_{ORT} < 5\%$  (see supplemental figure 3).

One-way sensitivity analyses were also performed on the probability of new findings on the PET/CT being correct. When advanced-stage disease is detected on PET/CT, the probability of a true positive only needs to be  $>20.3\%$  for the PET/CT strategy to be preferred. PET/CT remained the optimal strategy across the full range of probabilities of a true positive in the setting of PET/CT detecting early-stage disease beyond the planned RT volume.

### **Probabilistic Sensitivity Analyses**

A probabilistic sensitivity analysis using 10,000 simulations was performed with the distributions described in Supplemental Tables 1 and 2. In 89.1% of simulations, the PET/CT strategy was cost-effective (i.e., either cost-saving and QALY-improving, or with an ICER below \$100,000/QALY) (see supplemental figure 2). In 77.1% of simulations, the PET/CT strategy was strongly dominant (i.e., reduced costs and increased QALYs).

## **DISCUSSION**

Our analysis shows that adding PET/CT to the staging of early-stage FL patients reduces cost and improves QALYs. The existing literature on PET/CT in low-grade FL has focused on its diagnostic accuracy and impact on clinical

management (13,41-44). Although such analyses are important, they do not demonstrate the effect of PET/CT on clinical outcomes. Moreover, while outcomes of PET/CT staged early-stage FL have been reported (7,8), the comparison with outcomes for conventionally staged early-stage FL does not reflect the true effect of staging PET/CT, given the exclusion of some patients after upstaging on PET/CT. Our decision analysis allows a more comprehensive evaluation of highly relevant endpoints, QALYs and cost-effectiveness. To our knowledge, this is the first cost-effectiveness analysis (CEA) assessing the impact of PET/CT in early-stage FL.

While several studies demonstrate that PET/CT changed Ann Arbor staging in a significant proportion of patients with follicular lymphoma (41,42,45), the vast majority of additional lesions detected by PET/CT have not been accompanied by subsequent biopsy and confirmation of lymphoma. A systematic review showed that only 3 of the 349 patients included across 7 studies had histological confirmation. While the false negative rate for PET/CT in early-stage FL is low (42,43,46,47), the false-positive rate is uncertain and limited by a lack of systematic biopsies of relevant sites; thus, the implications of upstaging solely on the basis of PET/CT are unclear (10,48). There were two parameters in our model that were related to the false vs. true positive rate of PET/CT, which were both tested in one-way sensitivity analyses: 1) the probability that a new PET/CT finding of advanced-stage disease is a true positive, and 2) the probability that a new PET/CT finding of early-stage disease outside the planned RT field is a true positive. When advanced-stage disease is detected on PET/CT, the PET/CT strategy is advantageous as long as the probability of a true positive is >20%; in other words, only if there is a high

proportion (>80%) of “false-positives” (i.e., patients whose PET/CT show advanced-stage disease but truly have early-stage disease) leading to inappropriate treatment will the PET/CT strategy be detrimental. In the context of a new PET/CT finding of early-stage disease outside the planned RT field, the model is not sensitive to the true positivity rate; this is because inadvertently enlarging the RT field does not lead to a significant reduction in QALYs, given the low toxicity of RT (27). The uncertainty of PET/CT diagnostic accuracy was incorporated conservatively into the probabilistic sensitivity analysis using wide uniform distributions. Our model remained robust in deterministic and probabilistic sensitivity analyses, suggesting the PET/CT strategy is very likely to increase QALYs and reduce cost regardless of the exact value of the true positive rate.

The upstaging of FL by PET/CT has been investigated in a few studies, but to our knowledge, Wirth et al. is the only group that also reported the proportion of patients whose RT field was enlarged due to PET/CT findings (13). Thus, Wirth et al.’s study had the most complete data from which we derived our PET/CT-related transitional probabilities. However, given such scarce data on the probability of RT field enlargement, and the wide variation in the probability of upstaging across studies (13,49-52), we tested these parameters in sensitivity analyses. As expected, the benefit of PET/CT decreased with decreasing proportion of new findings identified; however, the no-PET/CT strategy only became preferred if the probability of PET/CT detecting advanced-stage disease was <0.09% *and* the probability of PET/CT detecting early-stage disease outside the planned RT was <4%, a scenario which is extremely unlikely.

Of the patients upstaged to advanced-stage, a small proportion would have indications for chemoimmunotherapy, receiving bendamustine-rituximab according to our model, while the other patients are treated with rituximab monotherapy or watchful waiting. A large randomized controlled trial by Ardeschna et al. investigating upfront rituximab monotherapy vs. watchful waiting for asymptomatic stage II-IVA FL demonstrated significant improvements in progression-free survival and the time to initiation of the next treatment, with no overall survival benefit at a median follow-up of 4 years (18). Furthermore, a CEA comparing the two approaches showed that rituximab monotherapy increased life expectancy and QALYs over watchful waiting while being cost-saving (23), and the UK NICE guidelines recommend that rituximab monotherapy is offered to patients with asymptomatic advanced-stage FL (53). Despite the benefits of rituximab monotherapy, it is not universally used in asymptomatic advanced-stage FL; its utilization over watchful waiting and palliative-intent RT depends on factors such as physician practice and patient preference. Although the net monetary benefit of the PET/CT strategy decreases with increasing probability of watchful waiting (pWW) or palliative-intent RT (pPRT), the PET/CT strategy was preferred as long as  $pWW < 89\%$  and  $pPRT < 75\%$ . As our baseline pWW of 17.7% and pPRT of 5.6% were derived from a cohort predating randomized evidence on the benefit of rituximab monotherapy (14,19), it is unlikely that pWW would approach 89% and pPRT would approach 75% in a given population. However, our model does suggest that the benefit of staging PET/CT over CT alone is smaller in a clinical practice where asymptomatic FL patients routinely undergo watchful waiting or palliative-intent RT; this is

because a large driver of the benefit of staging PET/CT is the diversion of advanced-stage patients to rituximab monotherapy, rather than RT (with no potential cure) followed by observation.

While our study population was defined as conventionally staged early-stage FL patients planned for curative-intent RT alone, it is worthwhile to consider the cost-effectiveness of staging PET/CT if alternative practices were employed for early-stage FL, such as RT plus adjuvant systemic therapy, systemic therapy alone, or watchful waiting. The main advantage of PET/CT is revealing disease that is not detected by CT alone, resulting in enlargement of the RT field, or a switch to systemic therapy or watchful waiting if the patient has advanced-stage disease; in a practice where all early-stage FL is treated with RT *plus* adjuvant systemic therapy, PET-CT would likely still be cost-effective, as the aforementioned benefits would still apply. In our current model, the main disadvantage of the “no PET/CT for staging” strategy is that some patients are treated inappropriately with curative-intent RT when in fact there is no curative potential; this disadvantage is likely exacerbated when an additional inappropriate treatment (i.e., R-CVP) is added, thereby, increasing the net benefit of the staging PET/CT strategy. In a practice where early-stage FL patients are treated with systemic therapy or watchful waiting, the upstaging from a PET/CT would likely result in more patients treated with systemic therapy than watchful waiting; given the superior PFS and cost-effectiveness associated with rituximab induction over watchful waiting (18,23), we suspect that staging PET/CT would remain cost-effective in this setting. On the other hand, in a practice where all early-stage FL patients are treated with systemic

therapy or all are treated with watchful waiting, a staging PET/CT would not change management, and would be therefore unlikely to be cost-effective.

Several limitations to our model need to be considered. Autologous and allogeneic hematopoietic cell transplantation (HCT) were not included as salvage therapy. HCT is controversial (54,55) and uncommonly used in FL, especially in a low-burden population like this one (56,57), thus HCT would be unlikely to have a large impact on results. If HCT were to be included, it would lead to more conservative estimates, as HCT should preferentially increase expenditures in the no-PET/CT strategy because more people in this strategy would require salvage therapy due to fewer of them receiving potentially curative RT and fewer receiving rituximab monotherapy. Furthermore, salvage therapy options are rapidly evolving with varying practice patterns across centers which could affect costs; however, the model was extremely robust to costs for salvage therapy. As in many prior CEAs in FL (56,58-62), we did not account for the possibility of transformation to high-grade disease, which occurs at a cumulative incidence of approximately 1-2% per year (3,63,64). As this transformation risk applies to patients in both strategies, it is unlikely that incorporating it would significantly change the impact of staging PET/CT.

In conclusion, our study indicates that the addition of PET/CT for staging of early-stage FL patients planned for curative-intent RT reduces lifetime costs and improves patient QALYs. Patients with early-stage FL should therefore undergo PET/CT prior to curative-intent RT. While the costs of drugs and imaging studies are typically higher in the United States than in Canada, our model was not sensitive to

any such cost until it far exceeded its true cost in either country. Therefore, while our analysis focuses on Canada, the results are relevant to international health care settings such as the United States, where clinical pathways are similar.

## **DISCLOSURE STATEMENT**

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("Studie Voorschot Middelen"), and the Gordon and Betty Moore Foundation. No other potential conflicts of interest relevant to this article exist.

## **KEY POINTS**

Question: Is the addition of staging positron tomography/computed tomography (PET/CT) cost-effective in early-stage follicular lymphoma?

Pertinent Findings: A decision analytic and state-transition cohort model simulated patients' management and disease course after adding staging PET/CT vs. using conventional CT staging alone. Staging PET/CT was found to be the dominant strategy, resulting in both lifetime cost saving and gain in quality-adjusted life years.

Implications for patient care: Patients with early-stage FL should undergo PET/CT prior to curative-intent radiation therapy.

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Figure 1. Decision tree depicting management after staging PET/CT vs. no staging PET/CT (M – State-transition cohort model; PET/CT – positron emission tomography/computed tomography; RT – radiation therapy)

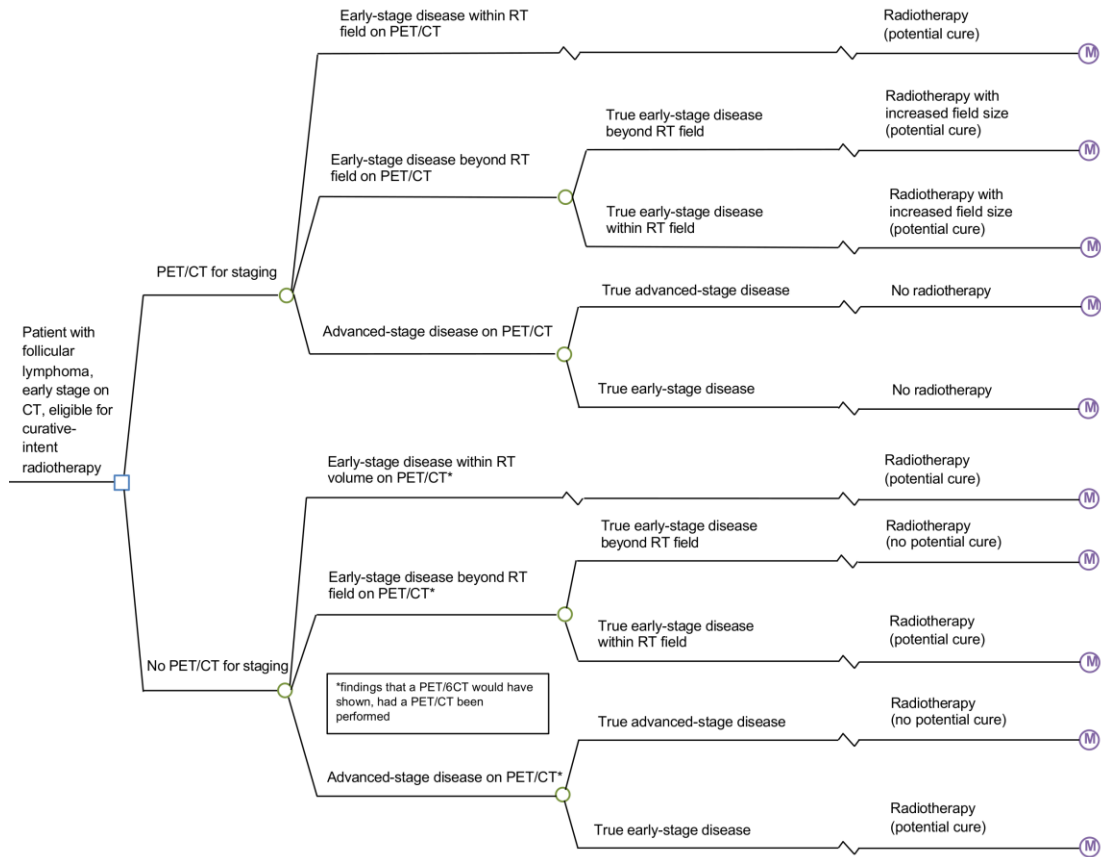
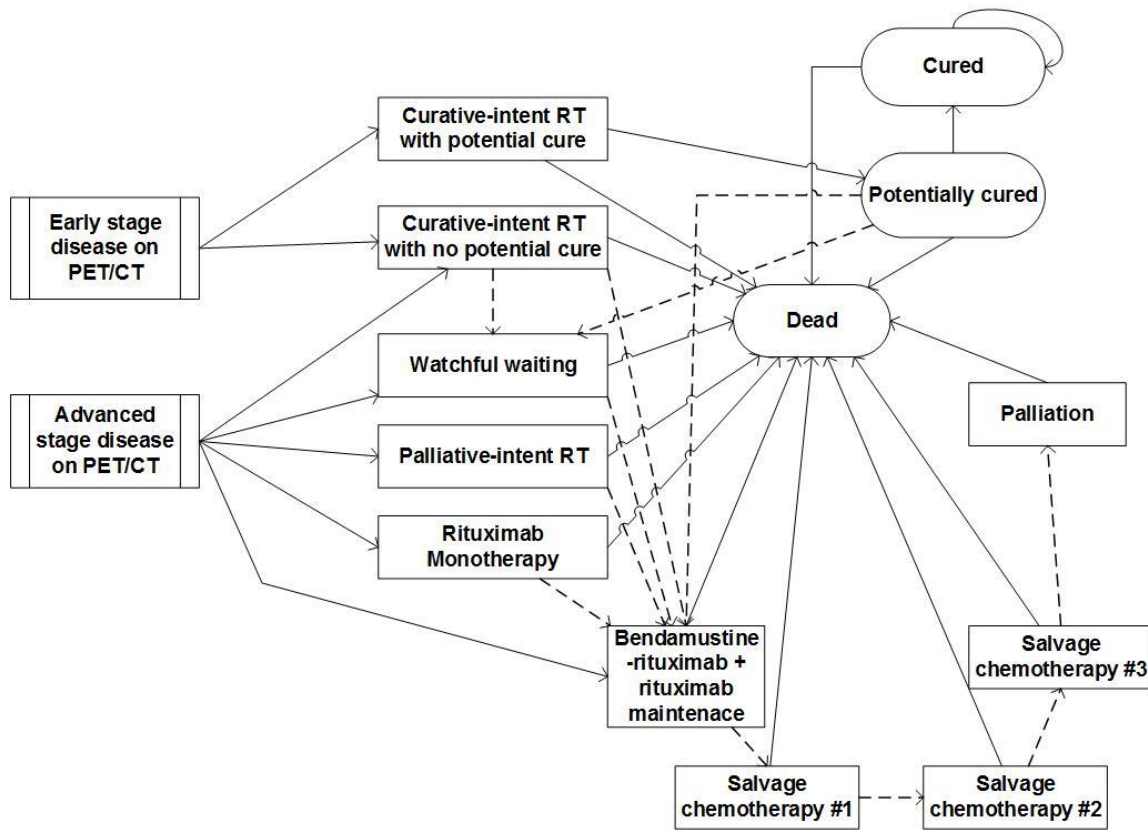
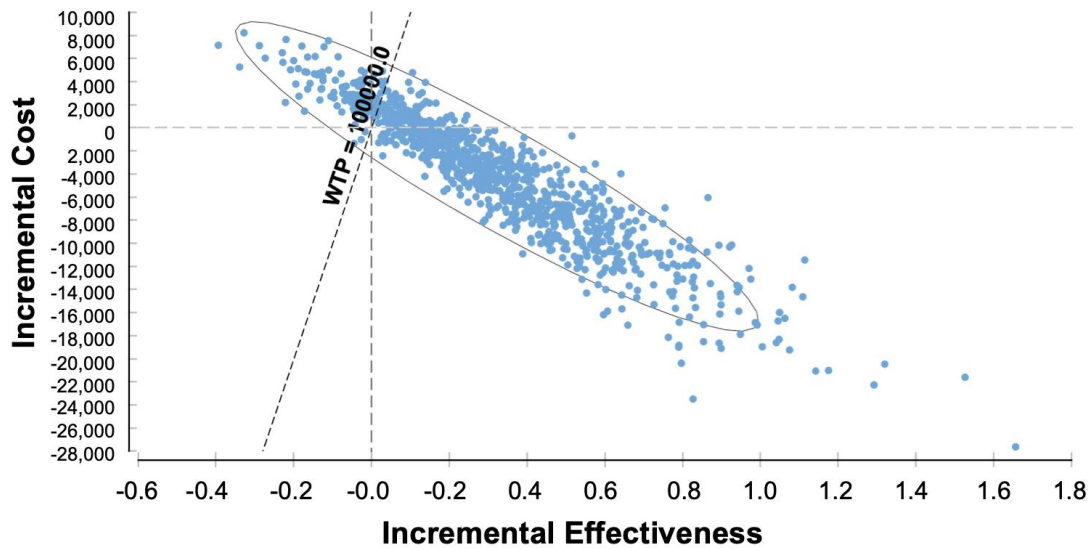


Figure 2. Simplified state-transition cohort model (dotted arrows represent transition to next state after relapse/progression; solid arrows represent transition to next state without relapse/progression; RT – radiation therapy; PET/CT – positron emission tomography/computed tomography)



**Incremental Cost-Effectiveness,  
PET/CT for staging vs. No PET/CT for staging**



## SUPPLEMENT

### Expanded Methods

#### *Transition probabilities*

The probabilities used in the model are shown in [Supplemental Table 1](#). The diagnostic probabilities of PET/CT were derived from a study by Wirth et al. assessing the impact of PET/CT on early-stage FL ([13](#)). In this study, 42 patients were found to have early-stage FL on conventional CT and subsequently had a staging PET/CT; based on this PET/CT, 13 (31%) patients were upstaged to advanced-stage disease, 6 (14%) remained classified as early-stage disease but required enlargement of the RT field to encompass findings that were not seen on the conventional CT, and 23 (55%) had no new findings. Of the 13 patients who were upstaged to advanced-stage, 8 (62%) were confirmed to be true positives either by biopsy (N=3), subsequent disease failure that was consistent with the PET abnormalities (N=3), or retrospective identification of missed abnormalities on CT (N=2); one (8%) had an apparent false positive with bilateral symmetrical uptake in hilar lymph nodes that was later found to be reactive rather than malignant; and the other 5 (36%) had no confirmation. Thus, to conservatively estimate the uncertainty of the probability of a new PET/CT finding of advanced-stage disease, a uniform distribution ranging between 62% (8/13) and 92% (12/13) was used in sensitivity analysis. Of the 6 patients whose RT fields required enlargement, none of them had a biopsy or other means to confirm whether these additional suspicious findings were true disease involvement ([13](#)). Similarly, a uniform distribution ranging between 0% (0/6) and 100% (6/6) was selected for the probability of early-stage disease truly outside the planned RT field for those in whom this was diagnosed on PET/CT.

Probabilities reflecting disease course were derived from randomized controlled trials (RCTs) if available and cohort studies if no relevant RCTs had been published. The overall response rate to bendamustine-rituximab was 93% according to a RCT by Rummel et al ([19](#)). A lower response rate to bendamustine-rituximab of 88% was modeled in individuals who received rituximab monotherapy ([23](#)). The probability of progression after bendamustine-rituximab according to Rummel et al.'s trial was 6.8% per 6-month cycle, but the trial was performed without rituximab maintenance; on the basis of the PRIMA trial, the progression probability of Rummel et al.'s study was adjusted by the hazard ratio for progression on rituximab maintenance versus watchful waiting (hazard ratio, 0.60). Since a progression-free survival benefit from maintenance therapy might not be similarly preserved after bendamustine-rituximab (which has not been tested in clinical trials), this possibility was explored in sensitivity analyses. The response rate after second-line therapy (i.e., salvage chemotherapy #1) was 85% based on a study by van Oers et al ([20](#)). A 20% penalty was applied to the response rate with each subsequent line of salvage chemotherapy, which was explored in sensitivity

analyses. The probability of progression after salvage chemotherapy #1, #2 and #3 were assumed to be constant (23).

The baseline estimates of advanced-stage patients managed with watchful waiting and radiotherapy were 17.7% and 5.6%, based on the National LymphoCare Study, a multicenter, longitudinal observational study of 2,728 patients with FL (14). Of advanced-stage patients receiving treatment, the baseline estimate of patients requiring bendamustine-rituximab was 3.0%, derived from the proportion of patients in a population-based CT-staged early-stage FL cohort (3) meeting criteria for first-line bendamustine-rituximab per Rummel et al.'s trial (19). The remaining advanced-stage patients were treated with rituximab monotherapy. The probabilities of advanced-stage patients being managed upfront with watchful waiting vs. bendamustine-rituximab vs. rituximab monotherapy were explored in sensitivity analyses.

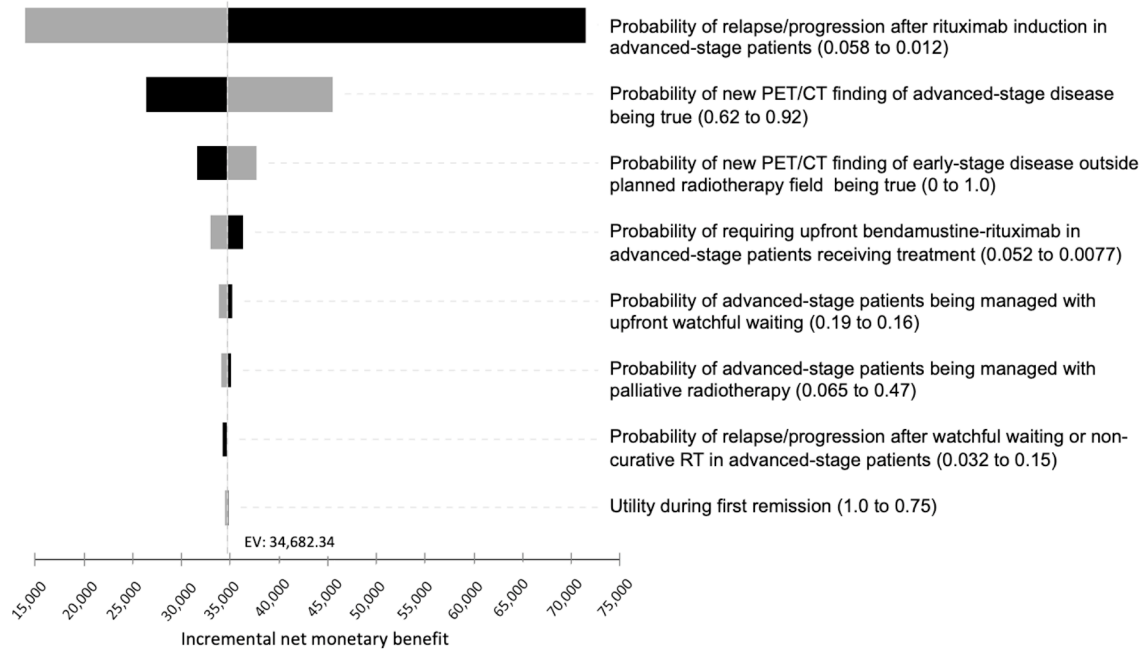
Of early-stage patients who relapse after potentially curative RT, the proportion of patients treated with bendamustine-rituximab was based on a multicenter retrospective study showing that 24% of patients in this setting had systemic therapy (15); this estimate was explored in sensitivity analysis. For early-stage patients who did not receive potentially curative RT, rate of relapse requiring bendamustine-rituximab was 2.9% per 6-month cycle, derived from a large population-based study by Barzenje et al (16).

#### *Utilities and Costs*

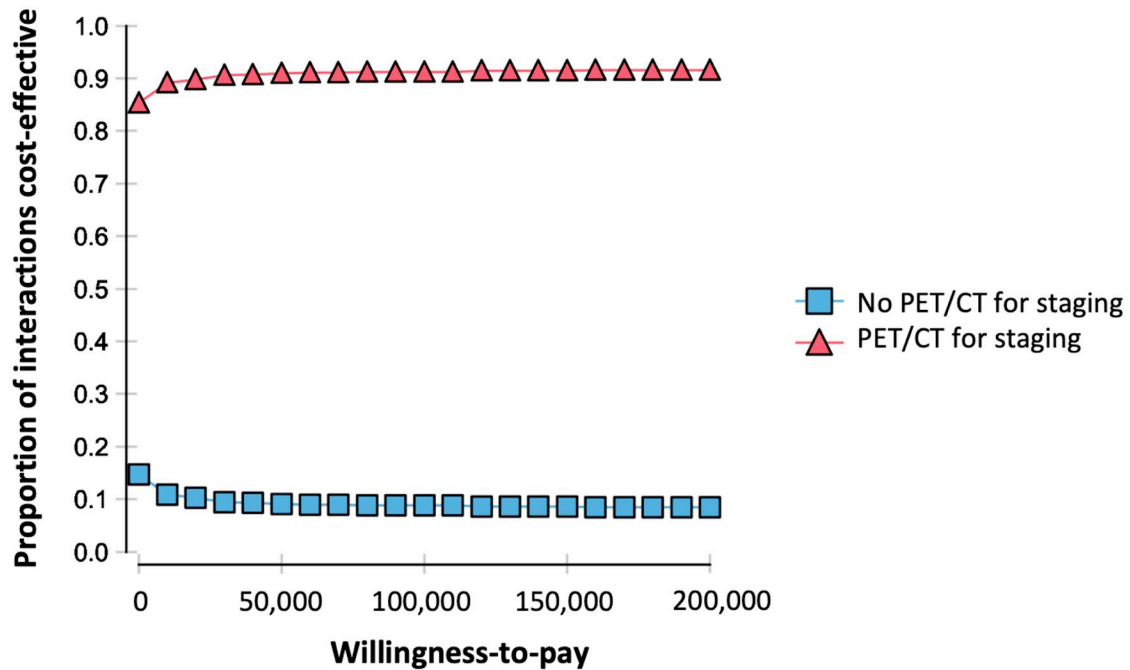
Drug acquisition costs for rituximab and bendamustine were determined from Canadian cost analyses (33,38). Supportive drug costs were obtained from hospital pharmacies. Pharmacy and nursing costs were obtained from hospital human resources departments. Resource utilization and overhead costs were extracted from published guidelines and statistics (33-35). Cost of medical visits, laboratory and imaging investigations were derived from the 2019 Ontario schedules of benefits for physician and laboratory services (32,36). The costs associated with adverse events were derived from the literature and incorporated into the total systemic therapy costs (37).

The cost of salvage chemotherapy was derived from a cost analysis by Herold et al (39). The cost of 6 cycles of rituximab was added only to the first course of salvage chemotherapy since patients would likely not receive rituximab with subsequent chemotherapy lines. The cost of palliation per 6 months was based on a Canadian costing study (40).

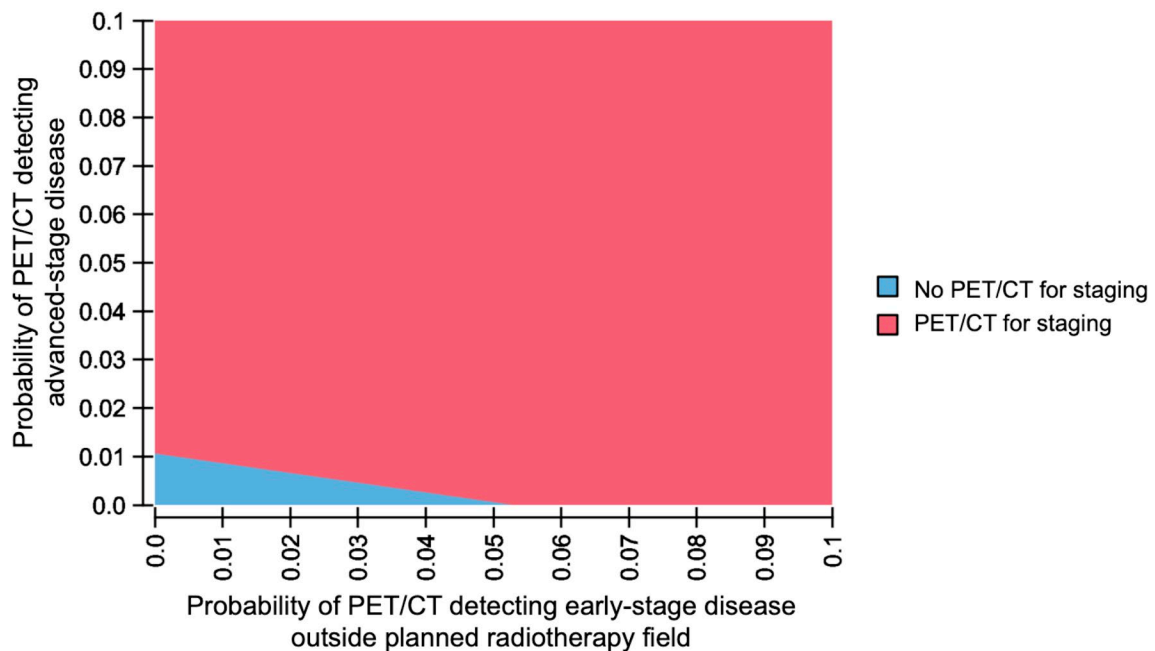
## Figures



Supplemental Figure 1. Tornado diagram of incremental net monetary benefit (NMB) for PET/CT relative to the no-PET/CT strategy with a willingness-to-pay of \$100,000/QALY. A positive incremental NMB means that PET/CT is the preferred strategy, while a negative value would mean no-PET/CT is preferred. For all parameters, we see that PET/CT is preferred across the full range of values. The gray shade depicts the higher end of stated range and the black shade depicts the lower end of the stated range.



Supplemental Figure 2. Cost-effectiveness acceptability curve, showing the proportion of simulations from the probabilistic sensitivity analysis in which each strategy was the cost-effective strategy, at different willingness-to-pay thresholds. This can be interpreted as the probability that each strategy is cost-effective



Supplemental Figure 3. Two-way sensitivity analysis on probabilities of PET/CT detecting new findings, evaluating net monetary benefit at a willingness-to-pay threshold of \$100,000/QALY

## Tables

Supplemental Table 1. Model parameters: probabilities and utilities normalized to a 6-month period

Parameter	Mean	Standard deviation	Distribution	References
<b>Diagnostic probabilities</b>				
Probability of PET/CT having no impact on planned RT	0.55	0.076	Beta	(13)
Probability of PET/CT detecting early-stage disease outside planned RT field	0.14	0.053	Beta	(13)
Probability of PET/CT detecting advanced-stage disease	0.31	0.070	Beta	(13)
Probability of new PET/CT finding of early-stage disease outside planned RT field being a true positive	Minimum: 0 Maximum: 1.0		Uniform	(13)
Probability of new PET/CT finding of advanced-stage disease being a true positive	Minimum: 0.62 Maximum: 0.92		Uniform	(13)
<b>Disease course probabilities</b>				
Probability of advanced-stage patients being managed with upfront watchful waiting	0.18	0.0073	Beta	(14)
Probability of advanced-stage patients being managed with palliative-intent RT	0.056	0.0045	Beta	(14)
Probability of requiring upfront bendamustine-rituximab in advanced-stage patients receiving treatment	0.030	0.011	Beta	(3)
Probability of relapse after potentially curative RT	0.037	0.015	Beta	(7)
Probability of relapse after potentially curative RT being treated with bendamustine-rituximab (vs. watchful waiting)	0.24	0.043	Beta	(15)
Probability of progression requiring bendamustine-rituximab after non-curative RT or rituximab induction in early-stage patients	0.029	0.015	Beta	(16)
Probability of progression after rituximab induction in advanced-stage patients	0.035	0.023	Beta	(18)

Probability of progression after watchful waiting or non-curative RT in advanced-stage patients	0.104	0.037	Beta	(17,18)
Probability of response to bendamustine-rituximab after no previous rituximab induction	0.93	0.016	Beta	(19)
Probability of response to bendamustine-rituximab after rituximab induction	0.88	0.020	Beta	(19)
Probability of progression after bendamustine-rituximab	0.041	0.018	Beta	(19)
Probability of response to salvage chemotherapy #1	0.85	0.023	Beta	(20)
Probability of response to salvage chemotherapy #2	0.65	0.031	Beta	(20)
Probability of response to salvage chemotherapy #3	0.45	0.032	Beta	(20)
Probability of progression after salvage chemotherapy	0.165	0.047	Beta	(20)
Probability of death from bendamustine-rituximab	0.0040	0.0039	Beta	(19)
Probability of death from rituximab maintenance	0.0020	0.0020	Beta	(19,21)
Probability of death from salvage chemotherapy	0.0040	0.0039	Beta	(20)
Probability of death in palliation	0.5 for a maximum of 2 cycles	-	Fixed	
Probability of death from other causes	Age-related mortality			(22)
<b>Utilities</b>				
Utility during watchful waiting	0.85	0.020	Beta	(25,26)
Utility during radiation therapy	0.85	0.020	Beta	(25-27)
Utility during rituximab induction	0.83	0.020	Beta	(25,26)
Utility during first remission after radiation therapy or rituximab induction	0.88	0.010	Beta	(25,26)
Utility during subsequent remissions or rituximab maintenance	0.79	0.030	Beta	(25,26)
Utility during bendamustine-rituximab	0.62	0.030	Beta	(28)
Utility during salvage	0.53	0.05	Beta	(29)

chemotherapy				
Utility during palliation	0.38	0.05	Beta	(29)
Utility of death	0	-	Fixed	

Abbreviations: RT=radiation therapy; PET/CT= positron emission tomography/computed tomography

Supplemental Table 2: Model parameter cost estimates

Parameter	Mean (CAD\$)	Standard deviation	Distribution	References
Cost of radiation therapy	9,196	920	Gamma	(30)
Cost of PET/CT	1,117	112	Gamma	(31)
Cost of biopsy	250	25	Gamma	(31)
Cost of medical oncology consultation	157	16	Gamma	(32)
Cost of rituximab induction	13,517	14	Gamma	(23,33,34,36)
Cost of follow-up	351	35	Gamma	(32,35,36)
Cost of bendamustine-rituximab after rituximab induction	46,929	4693	Gamma	(19,23,32,34,36-38)
Cost of bendamustine-rituximab after watchful waiting or radiation therapy	47,083	4708	Gamma	(19,23,32,34,36-38)
Cost of rituximab maintenance	10,236	1024	Gamma	(23,32,34,36-38)
Cost of salvage chemotherapy #1	37,839	3784	Gamma	(33,39)
Cost of salvage chemotherapy #2	17,366	1737	Gamma	(39)
Cost of salvage chemotherapy #3	17,366	1737	Gamma	(39)
Cost of palliation	21,918	219	Gamma	(40)
Cost of death	0	-	Gamma	

Abbreviations: PET/CT= positron emission tomography/computed tomography