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.

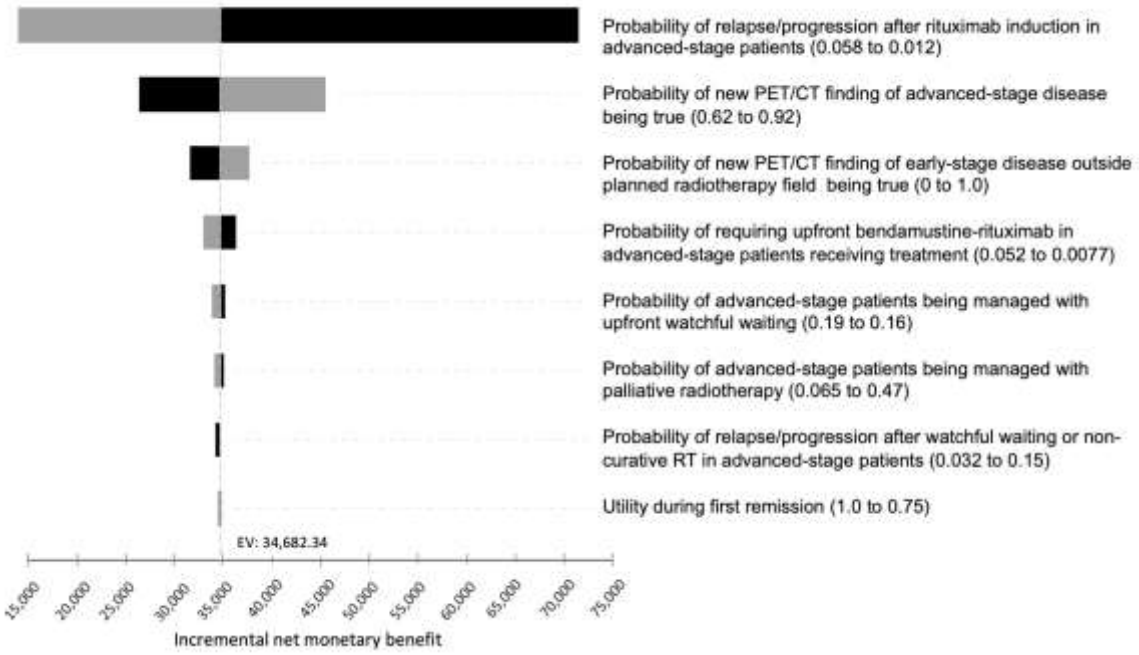
Of early-stage patients who relapse after potentially curative RT, the proportion of patients treated with bendamustine-rituximab was based on a multicenter retrospective study showing that 24% of patients in this setting had systemic therapy (*15*); this estimate was explored in sensitivity analysis. 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

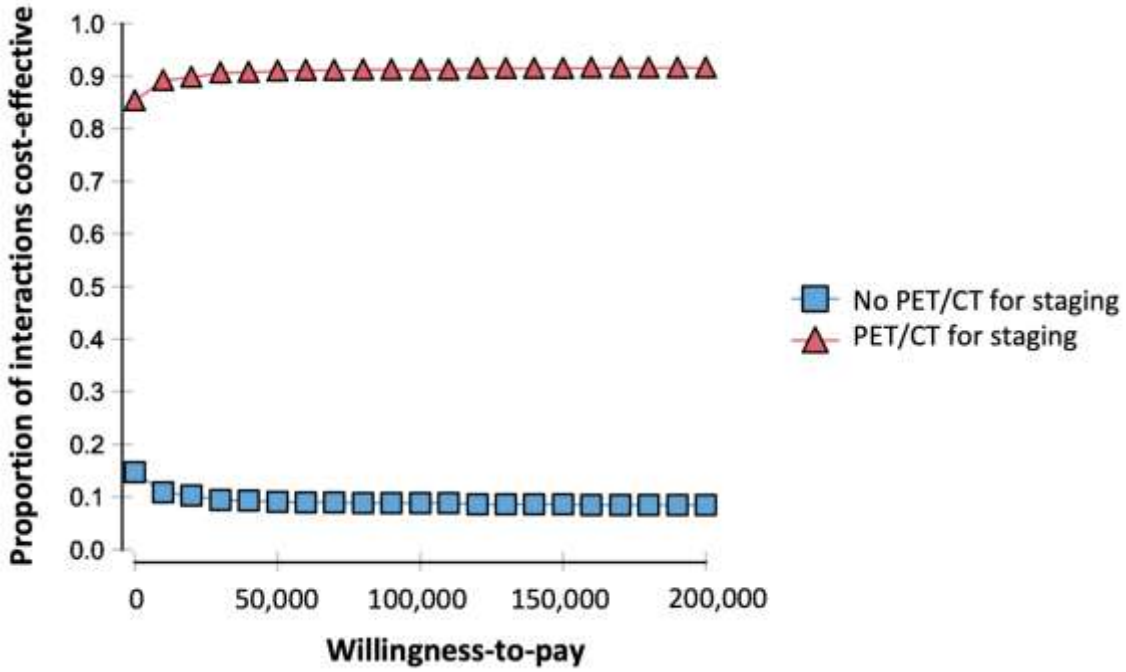
Drug acquisition costs for rituximab and bendamustine were determined from Canadian cost analyses (*33,38*). Supportive drug costs were obtained from hospital pharmacies. Pharmacy and nursing costs were obtained from hospital human resources departments. Resource utilization and overhead costs were extracted 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*).

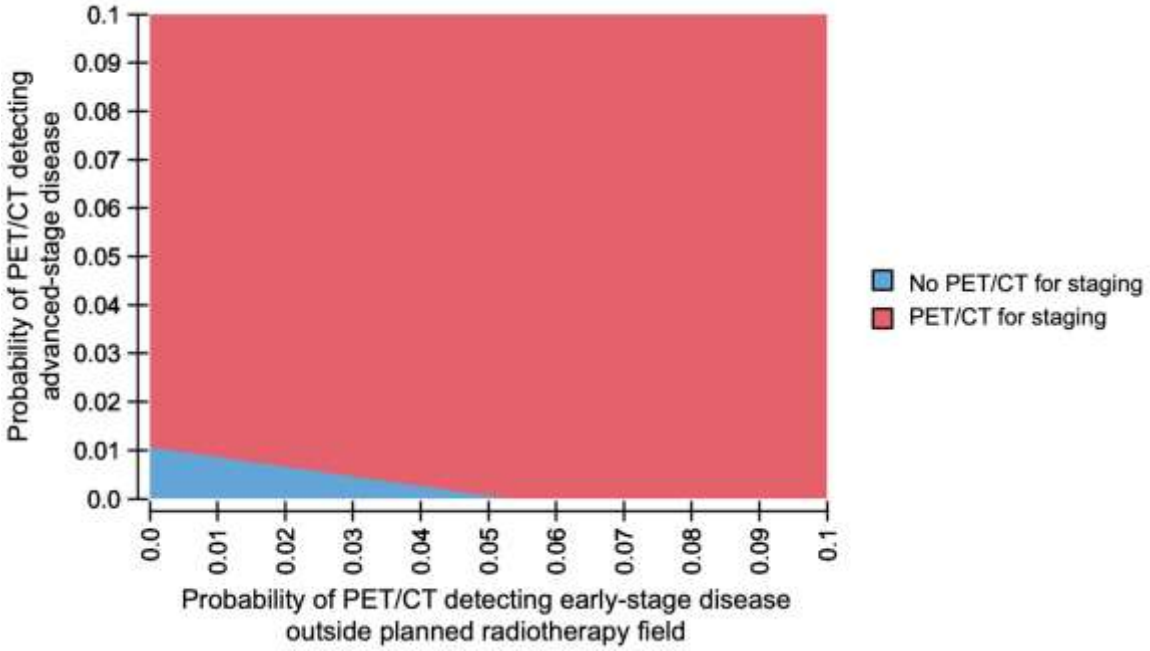
Figures



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
Diagnostic probabilities				
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*)
Disease course probabilities				
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-	0.029	0.015	Beta	(*16*)

curative RT or rituximab induction in early-stage patients				
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*)
Utilities				
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	0.88	0.010	Beta	(*25,26*)

therapy or rituximab induction				
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 chemotherapy	0.53	0.05	Beta	(*29*)
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	(*32,36*)
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