

# Cost-Effectiveness Analysis of Intraoperative Frozen Section in Women with Breast Cancer: Evidence from South of Iran

Navid Omidifar<sup>1#</sup>, MD; Elham Chogani<sup>2#</sup>, MSc; Vahid Zangouri<sup>3</sup>, MD; Khosro Keshavarz<sup>4</sup>, PhD; Abdolrasoul Talei<sup>5</sup>, MD

<sup>1</sup>Department of Pathology, School of Medicine, Clinical Education Research Center, Shiraz University of Medical Sciences, Shiraz, Iran;

<sup>2</sup>Student Research Committee, Department of Health Economics, School of Management and Medical Informatics, Shiraz University of Medical Sciences, Shiraz, Iran;

<sup>3</sup>Department of Surgery, School of Medicine, Breast Diseases Research Center, Shiraz University of Medical Sciences, Shiraz, Iran;

<sup>4</sup>Health Human Resources Research Center, School of Management and Medical Informatics, Shiraz University of Medical Sciences, Shiraz, Iran;

<sup>5</sup>Department of Surgery, School of Medicine, Breast Diseases Research Center, Shahid Faghihi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

\*The authors contributed equally to this work.

## Correspondence:

Khosro Keshavarz, PhD;  
Almas Building, Alley 29, Qasrodasht Ave., Postal code: 71336-54361, Shiraz, Iran

Tel: +98 71 32340774

Fax: +98 71 32340039

Email: khkeshavarz2007@gmail.com  
khkeshavarz@sums.ac.ir

Received: 10 November 2020

Revised: 08 February 2021

Accepted: 13 March 2021

## What's Known

- Counseling on intraoperative frozen section is taken into account as one of the reliable and effective approaches. This approach either reduces reoperation or increases effectiveness.

## What's New

- This investigation is the only economic evaluation study in Iran. This study is focused on determining the cost-effectiveness of intraoperative frozen section analysis in women with breast cancer in the south of Iran. The results revealed that performing frozen sections during surgery was more cost-effective than ignoring them.
- Intraoperative frozen section can prevent the costs of subsequent reoperations.

## Abstract

**Background:** Breast cancer is one of the most prevalent malignancies in women worldwide, and the rate of breast cancer is increasing among Iranian women. The purpose of this study is to determine the cost-effectiveness of intraoperative frozen section analysis in women with breast cancer.

**Methods:** This study was a cost-effectiveness analysis, which was implemented as a cross-sectional study from a societal perspective. In this case, total direct and indirect costs were calculated, and the study outcome was involved in preventing reoperation. A data collection form has been used to collect the cost and effectiveness data. The sample size was comprised of all the patients referred to the hospitals of Shiraz University of Medical Sciences for breast cancer surgery in 2019. The patients were studied in two different groups, including individuals who received frozen counseling during surgery, and individuals who did not receive it. A one-way sensitivity analysis was performed for this case. Moreover, the Tree Age and Microsoft Excel Software were employed for analyzing processes.

**Results:** The results demonstrated that the mean costs of frozen and non-frozen patients were 4168\$ and 3843\$ purchasing power parity (PPP), respectively. In addition, the effectivenesses were 0.996 for the former and 0.8 for the latter. Furthermore, the incremental cost-effectiveness ratio (ICER) was 1658.2 PPP\$. This issue revealed that the frozen section procedure during surgery was more cost-effective than the other case. Because, the cost-effectiveness of this option was below the threshold. Besides, the one-way sensitivity analysis confirmed the robustness of the study results.

**Conclusion:** The results showed that performing frozen sections during surgery in women with breast cancer was more cost-effective than ignoring them. Indeed, the frozen section can prevent the costs of subsequent reoperations.

Please cite this article as: Omidifar N, Chogani E, Zangouri V, Keshavarz K, Talei AR. Cost-Effectiveness Analysis of Intraoperative Frozen Section in Women with Breast Cancer: Evidence from South of Iran. *Iran J Med Sci.* 2022;47(2):143-151. doi: 10.30476/IJMS.2021.88887.1960.

**Keywords** • Cost-effectiveness • Breast neoplasms • Frozen sections • Economic evaluation

## Introduction

Despite the achievements in the control and prevention of infectious diseases in recent decades, the incidence and prevalence of non-communicable diseases have remarkably increased.<sup>1</sup> In some countries, cancer is the leading cause of death after cardiovascular diseases.<sup>2</sup> In Iran, cancer has the third rank after cardiovascular diseases and road traffic accidents.<sup>3, 4</sup>

Furthermore, it is taken into account as one of the principal health problems in many developed and developing countries.<sup>5</sup> In the meantime, one-third of all women's cancers are related to breast cancer (BC). After lung cancer, it has the second rank of the cause of cancer death among women.<sup>6</sup> BC is the most prevalent malignancy in women around the world, and the incidence of the disease is increasing among Iranian women.<sup>7</sup> About 2.1 million people around the world have recently been diagnosed with BC. The published reports in 2018 demonstrated that the incidence of the disease in women was about one in four people. According to this global cancer statistics in 2018,<sup>8</sup> the highest incidence of BC was reported in Australia and New Zealand, and the highest mortality rates occurred in Northern European countries (UK, Sweden, Finland, and Denmark), Western European countries (Belgium, Netherlands, and France), Southern Europe (Italy), and North America.<sup>9</sup>

The BC incidence has a rising trend in Iran. The published reports showed that the highest incidences occurred in the age groups of 45-65 and 80-85 years.<sup>10</sup> To deal with this problem, intraoperative consultation (i.e., macroscopic and microscopic tests) is one of the vital services provided by pathologists, which requires knowledge, accuracy, and speed. Frozen section (FS) indications are permanent sections for the tissue involved in the mass. Indeed, it is a basis for pathologic diagnosis. The pathologist reports the type of lesion to the operating room after a microscopic examination of the sample. Moreover, experiments show that performing an FS depends on the type of sample. However, the substantial reasons for using FS are as follows: (I) the need for rapid diagnosis when there is no previous tissue diagnosis available, (II) determining the local and non-local spread of the disease (e.g., lymph node metastasis in BC), (III) Specifying surgical margins in a malignant lesion, (IV) Characterizing the sufficiency of the removed tissue for pathologic diagnosis, and (V) the demands for fresh tissue in specific studies.<sup>11</sup> The FS is currently employed for bile duct atresia, breast lesions, Hirschsprung's disease, liver donor, intrauterine and ectopic pregnancy, lung lesions, lymph nodes, skin, oral mucosa cancer, pancreatic and prostate carcinoma, salivary gland tumors, small intestine, and thyroid.<sup>12</sup> In BC, the sentinel lymph nodes are the first lymph nodes to receive lymphatic drainage from the malignant tumor area. If the sentinel lymph nodes are not involved, the involvement of other axillary lymph nodes rarely occurs.<sup>13</sup> According to the results of some studies, the general survival of the patients, whose sentinel

lymph nodes were not involved and underwent axillary lymph node dissection was similar to that of the patients for whom dissection was not performed.<sup>14, 15</sup>

A frozen section of the sentinel lymph nodes during surgery detects the metastatic disease and allows the dissection of the lymph node in the same surgery. In some patients, the FS of the sentinel lymph nodes is negative in terms of the involvement with cancer cells, while the pathologic examination on the formalin-stabilized sample showed that the sentinel lymph nodes were involved. The FS method can be used in tumor and non-tumor lesions. Indeed, the surgeon does not want to have an immediate effect on the patient during the surgery, but he/she tends to reduce the invasive surgeries and implement fine and sensitive ones based on FS diagnoses. On the other hand, this process can create mutual trust between the surgeon and the pathologist.<sup>16</sup> The purpose of this study is to determine the cost-effectiveness of performing and ignoring intraoperative FS counseling in breast cancer women undergoing protected breast surgery in public and private hospitals of the Shiraz University of Medical Sciences.

## Patients and Methods

This study is an economic evaluation and a cost-effectiveness analysis, which is carried out as a cross-sectional study from a societal perspective in public and private hospitals of the Shiraz University of Medical Sciences. This study has been approved by the Ethics Committee of the Shiraz University of Medical Sciences (Code: IR.SUMS.REC.1398.1159). Besides, informed consent were obtained from all the patients. Moreover, confidentiality and privacy of patients' data were assured.

In this study, total direct costs (i.e., medical and non-medical costs) and indirect costs imposed on the patients and community were calculated.

The sample size is comprised of all the patients referred to public and private hospitals of the Shiraz University of Medical Sciences for BC surgery in 2019. Therefore, no sampling process was considered for this study. The patients were studied in two groups, including people who received FS counseling during the surgery and people who did not receive it. In this study, the inclusion criteria were comprised of primary breast cancer surgery and reoperation within two weeks after the first operation. The exclusion criteria were concerned with other surgeries and re-surgeries performed after two weeks from the first operation.

**Costs Inputs**

In this study, the costs were examined from a societal perspective. Therefore, all direct medical costs (DMCs), direct non-medical costs (DNMCs), and indirect costs (ICs) have been considered for analyzing the process. The DMCs were collected through a review of the patients' medical records and self-report by specialists. These costs were comprised of all direct medical costs such as the costs of operating rooms, surgical examinations (pathological samples), clinical examinations, anesthesia, operating room medicine, ward medicine, nursing, surgeon, patient daybed, patient visits, diagnostic services (e.g., radiography, CT scan, ultrasound, ECG) and other costs (e.g., companion's bed, counseling). The DNMCs were comprised of the mean costs of accommodation, intercity, out-of-town travel, and food to receive medical services. In addition, the ICs were concerned with those of the patient's and her companion's absenteeism from work, while being at the hospital or home during the recovery period. We used a data collection form to collect the cost dataset. In this procedure, the first part dealt with the demographic information, and the second part was related to DMC, DNMC, and IC. The human capital approach has been employed to calculate the IC.<sup>17</sup> The purchasing power parity (PPP) for international comparison was used to compute the costs. They were converted into international dollars considering each PPP\$ as 22075.45 Rials (IRR).<sup>18, 19</sup>

**Effectiveness**

In this study, the effectiveness index refers to the probability of success in preventing reoperation in any treatment approach. A data collection form was employed to collect the effectiveness data. The effectiveness form was completed by the authors and a pathologist, as well. It was performed by reviewing the patients'

medical records.

**Decision Tree Structure**

In the present study, a decision tree structure was used to evaluate the cost and effectiveness of performing and ignoring the FS counseling during surgery (figure 1). The decision tree structure is a graphical representation of the diagnosis routes and treatment of various diseases, in which the probabilities, costs, and outcomes of the routes are shown. Analyzing the collected dataset was performed by the TreeAge Pro 2011 and Microsoft Excel Software packages (2016).

**Cost-effectiveness Analysis**

The model was designed in the TreeAge software, and the extracted data were entered into the established model. Then, the costs, effectiveness, and cost-effectiveness were calculated for both methods. Afterward, the incremental cost-effectiveness ratio (ICER) was estimated for each of them using the following equation.<sup>20</sup>

$$ICER = \frac{CostFS - CostNoFS}{OutcomeFS - OutcomeNoFS}$$

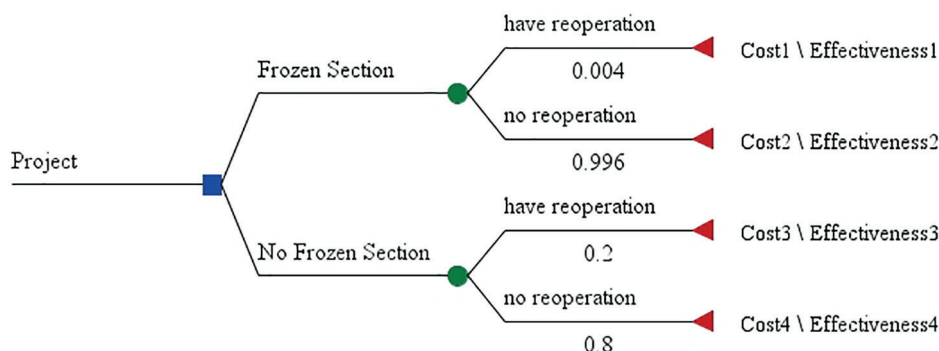
Where FS and no-FS are the Frozen and no-Frozen section, respectively.

**Sensitivity Analysis**

Every economic evaluation study is involved in uncertainty. In this study, the effects of uncertainties were evaluated using a one-way (univariate) sensitivity analysis. Thus, the study variables were changed up to 20%.<sup>21</sup> Moreover, the threshold was considered one gross domestic product (GDP) per capita, which was 17662 PPP\$ in 2019.

**Results**

A total of 247 patients underwent the FS during



**Figure 1:** Schematic diagram of the decision tree structure comparing two treatment strategies of frozen and non-frozen sections in patients with breast cancer.

surgery. In this case, the numbers of 145 and 102 patients underwent surgery in the public and private sectors, respectively. A total of 84 patients did not undergo an FS in which the numbers of 30 and 54 patients were in public and private hospitals, respectively.

According to table 1, the patients who underwent frozen counseling during surgery in the public and private sectors, were categorized into several groups, including housewives 60% and 64%, married 74% and 76%, and literate (high school degree and higher) 62% and 59%, respectively. Furthermore, they had the mean age of 49 and 48 years in the public and private sectors, respectively. The patients, who did not undergo frozen counseling during surgery in the public and private sectors were classified into several groups, including housewives 63% and 74%, married 70% and 74%, and illiterate 60% and 51%, respectively. In addition, they had the mean age of 62 and 47 years in the public and private sectors, respectively.

The mean DMC, DNMC, and IC of the patients, who underwent intraoperative FS in the public sector were 1,635\$, 370\$, and 823\$,

respectively. These values were 4,260\$, 424\$, and 825\$ in the private sector, respectively. Moreover, the mean DMC, DNMC, and IC of the patients who did not undergo intraoperative FS in the public sector were 1,481\$, 395\$, and 779\$, respectively. These values were 3,331\$, 396\$, and 782\$ in the private sector, respectively (table 2).

The cost-effectiveness results of the FS method compared to the non-FS one are expressed in table 3 and figure 2. The results demonstrated that the effectiveness in patients with and without intraoperative FS counseling were 0.996 and 0.80, respectively. Besides, the costs were 4,168\$ and 3846 PPP\$, respectively. The FS method has increased the costs by 325 PPP\$ compared to ignoring it. Furthermore, the FS method has reduced reoperation or increased effectiveness by 19.6%. Thus, the calculated ICER indicated that for each unit of decrease in reoperation or increase in effectiveness, FS increased the costs by 1658.21 PPP\$ compared to ignoring FS. Since the ICER value was below the cost-effectiveness threshold, the FS method was cost-effective in this case.

**Table 1: Demographic characteristics for patients undergoing surgery in public and private sectors**

Type of Or ganization	Variable	Items	With Frozen Section	Without Frozen Section
Public	Job	Housewife	87 (60%)	19 (63%)
		Employed	38 (26%)	9 (30%)
		Retired	20 (14%)	2 (7%)
	Marital status	Single	38 (26%)	9 (30%)
		Married	107 (74%)	21 (70%)
	Education	Illiterate	56 (38%)	18 (60%)
		Literate	89 (62%)	12 (40%)
	Age(year) (Mean±SD)	-	49±11.43	62±14.56
	Age at first pregnancy(year) (Mean±SD)	-	15±4.44	17±3.26
	Number of deliveries (Mean±SD)	-	3±2.16	3±1.31
	Number of abortions (Mean±SD)	-	1±.77	1±.87
	Number of children (Mean±SD)	-	3±2.05	2±3.14
	Number of breastfeeding (month) (Mean±SD)	-	49±45.59	52±47.71
	Menopausal status	Menopausal	76 (52%)	18 (61%)
Not menopausal		69 (48%)	12 (39%)	
Private	Job	Housewife	65 (64%)	40 (74%)
		Employed	29 (27%)	9 (17%)
		Retired	10 (14%)	5 (9%)
	Marital status	Single	24 (24%)	14 (26%)
		Married	76 (76%)	40 (74%)
	Education	Illiterate	42 (41%)	51 (51%)
		Literate	60 (59%)	49 (49%)
	Age (Mean±SD)	-	48±10.51	47±9.71
	Age at first pregnancy (Mean±SD)	-	14±3.46	16±2.77
	Number of deliveries (Mean±SD)	-	4±2.51	3±1.31
	Number of abortions (Mean±SD)	-	1±0.03	1±0.51
	Number of children (Mean±SD)	-	4±2.03	3±1.78
	Number of breastfeeding (month) (Mean±SD)	-	50±43.85	48±42.65
	Menopausal status	Menopausal	63 (63%)	31 (57%)
Not menopausal		37 (37%)	23 (43%)	

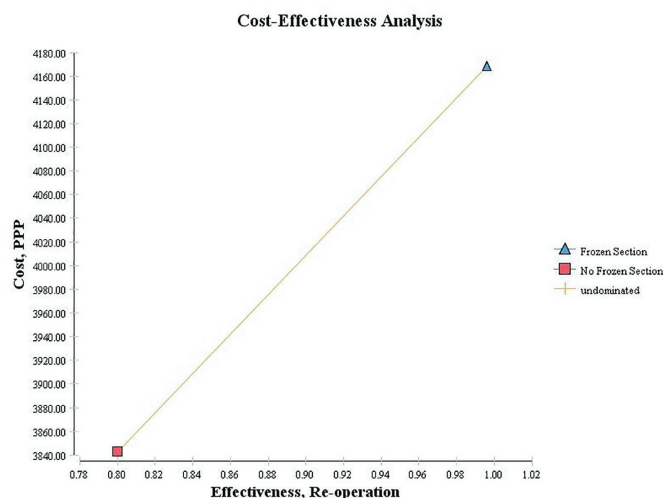
**Table 2:** The mean direct and indirect costs for frozen and non-frozen sections in patients with breast cancer in public and private sectors

Cost type	Costs items	Frozen section in public sector (PPP\$) (Mean±SD)	Non-frozen section in public sector (PPP\$) (Mean±SD)	Frozen section in private sector (PPP\$) (Mean±SD)	Non-frozen section in private sector (PPP\$) (Mean±SD)
Direct medical costs	Operating room use	81±11.05	84±13.01	317±204.52	261±288.05
	Surgical pathologic evaluation	459±291.21	241±105.41	1,168±309.05	262±109.8
	Laboratory tests	3±2.03	4±1.37	49±35.46	35±1.19
	Anesthesia	143±14.53	126±11.33	163±12.23	303±25.21
	Medication	69±10.12	80±12.31	24±4.1	22±3.02
	Nursing	11±1.07	13±2.14	24±3.22	18±2.31
	Surgeon	349±31.02	314±26.07	963±150.76	784±146.21
	Diagnostic services	165±20.64	234±22.61	440±31.24	440±26.02
	Consumables and equipment	136±12.36	128±8.23	432±36.87	580±45.31
	Surgeon assistant	-	-	193±16.23	139±11.65
	Hospitalization	178±36.12	216±12.31	407±38.47	407±65.79
	Visits to the doctor	4±1.23	4±1.78	56±11.02	56±10.34
	Other cost	37±7.66	38±10.02	25±6.23	25±5.61
	Direct medical cost	1,635±33.77	1,481±20.50	4,260±65.62	3,331±56.78
Direct non-medical costs	Accommodation	71±12.33	84±10.28	144±21.75	93±12.36
	Meals	23±4.06	27±6.54	47±10.31	43±8.07
	Transportation	276±30.21	284±31.03	233±28.05	259±29.07
	Direct non-medical cost	370±15.53	395±15.95	424±20.03	396±16.50
Indirect Costs	Time spent by the patient	415±61.02	387±45.02	387±48.25	387±49.85
	Time spent by the patient's accompany	408±51.05	392±35.02	438±46.02	396±41.56
	Indirect Costs	823±56.03	779±40.02	825±47.13	782±45.70
Total cost	-	2,828	2,656	5,508	4,509
Mean cost Reoperation	-	-	2,712	-	5,447
Mean total cost with reoperation	-	-	5,367	-	9,957

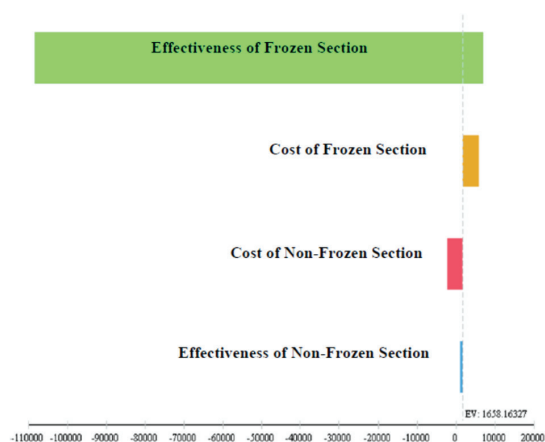
**Table 3:** Results of cost-effectiveness of frozen and non-frozen sections in patients with breast cancer

Strategy	Cost (PPP\$)	Effectiveness	Incremental Cost	Incremental effectiveness	ICER (Incremental cost per extra success) PPP\$
No Frozen Section	3843	0.8	0	0	-
Frozen Section	4168	0.996	325	0.196	1658.2

ICER: Incremental cost-effectiveness ratio



**Figure 2:** A cost-effectiveness analysis indicate the frozen and non-frozen sections in patients with breast cancer



**Figure 3:** Tornado diagram illustrates the cost-effectiveness of frozen and non-frozen sections in patients with breast cancer

### Uncertainty Analysis

The results of a one-way sensitivity analysis (tornado diagram) revealed that the ICER had maximum sensitivity to the effectiveness of FS. However, the ICER did not have such an effect on other parameters (figure 3).

### Discussion

This study is the only economic evaluation study regarding intraoperative FS counseling to patients with BC in Iran. The results showed that performing FS was a more expensive method, however, it was a more effective method. The ICER outputs showed that for each unit of increase in the effectiveness, the cost increased by 1658.21 PPP\$. Since the ICER value was below the cost-effectiveness threshold, the FS method was preferable and more cost-effective. Although few studies have been published on the cost-effectiveness of FS, the achieved results are consistent with those of the present study.<sup>22, 23</sup> Osborn and colleagues compared the cost-effectiveness of routine frozen-section analysis for breast margins with reoperation in positive margins. The results showed that the reoperation rate for margin control could be decreased by routine use of frozen-section analysis of lumpectomy margins. Therefore, it is a cost-effective method from the provider and payer viewpoints.<sup>22</sup>

In terms of effectiveness, the results of the study showed that performing FS was more effective than ignoring it. It has reduced reoperation or increased effectiveness by 19.6%. Therefore, performing intraoperative FS counseling was a reliable and effective approach. Many studies have been published in this context. The results of the present study are consistent with those of other published

ones. Almarzooq and colleagues conducted a study in Bahrain, and the results indicated that intraoperative FS was a reliable approach, and they assessed the SLNB status for BC patients. Besides, it prevented a second surgery in most cases.<sup>24</sup> Boughey and colleagues performed a study in the United States, and the results indicated that FS counseling during BC surgery reduced the number of reoperations. This issue has been led to some important outcomes, including patient satisfaction and reduced patient care costs.<sup>25</sup> Similarly, the results of studies conducted by Tang and colleagues in the UK and Stuart and colleagues in the United States<sup>26</sup> showed that the recurrence of the local tumor could be prevented by practicing the FS. Moreover, the re-excision rate might be decreased by performing this procedure.<sup>26, 27</sup> Barakat and colleagues found that the sensitivity of FS in the diagnosis of metastasis was 84%, and its diagnostic accuracy was 93%. Furthermore, they suggested that using FS was effective for patients.<sup>28</sup> The results of those studies are consistent with the current study, and these studies confirm the effectiveness of FS during surgery. Jorns and others represented that although there might be some changes in surgical practices, FS was still a successful method for reducing the re-excision rate.<sup>29</sup>

In terms of cost, Boughey and others carried out a study in the United States. The results showed that in the cases of breast lumpectomy and minimizing reoperation, the widespread use of FS margin evaluation through surgery to guide surgical removal of the mass saved money for patients and payers, and in most cases, it was affordable for service providers.<sup>23</sup> This study is consistent with the results of the present study. Indeed, the mean total costs per patient for those who underwent FS during surgery, were 2,828\$ and 5,508 PPP, respectively. These values were 2,656\$ and 4,509\$ for the patients without intraoperative FS in the public and private sectors, respectively. As observed, the costs in the private sector were almost twice as much as the public sector.

It is necessary to note that the total cost of each reoperation was 2,712\$ in the public sector and 5,447\$ in the private one. In this study, eight patients in the public sector and nine patients in the private one underwent reoperations. If FS was performed during surgery, it would have led to a cost reduction of 1415.9\$ and 5,900\$ per patient in the public and private sectors, respectively. These reduced values were due to the prevention of reoperations. It is noteworthy that the tariffs for performing FS were 119.6\$ and 1167.58\$ in the public and private sectors, respectively.

As stated, other articles emphasized the importance and necessity of performing FS during surgery due to its high accuracy and its effect on reducing treatment costs. Indeed, it would reduce the stress of reoperation and costs of service-providing centers.

The results of one-way sensitivity analysis showed that ICER had the highest sensitivity to the FS effectiveness and a low sensitivity to the other parameters. These results confirm the robustness of the results of this study.

The study results can be generalized considering other factors such as cost coverage by insurance companies, disease prevalence, threshold, and disease epidemiology.

This study had some limitations. The first limitation was the problem of the exact recall of the cost information by the patients. This problem was solved by asking questions as accurately as possible and considering multiple options. The second problem was to determine other outcomes of the disease (e.g., recurrence) or evaluate the patients' life quality. It was necessary to spend a long post-surgery time for at least one year. However, the time of the research was too short to evaluate such outcomes. Probably, different results may be obtained, if the research is conducted for longer periods. The third limitation refers to the lack of data and studies. It was not possible to use a more complex decision tree or Markov models.

## Conclusions

The results of this study showed that although performing intraoperative FS in BC women was more costly, it was a more cost-effective option than ignoring it. It was because of preventing reoperation that imposed more costs on patients. Thus, it provides higher effectiveness and more satisfaction. Moreover, this approach reduces the costs of future patient care. It is recommended that all patients should undergo FS counseling during surgery. Since the FS tariffs are different in the public and private sectors, it is essential to reduce the costs and make frozen counseling tariffs more reasonable. Thus, the pathologists are motivated to provide FS counseling to health system policymakers, insurance organizations, and health-providing centers. Furthermore, it is necessary to guide doctors to prevent reoperations.

## Acknowledgment

This manuscript is supported and approved by Shiraz University of Medical Sciences with ID number (1398-01-07-20392). In addition, the

authors would like to thank Shiraz University of Medical Sciences, Iran Center for Development of Clinical Research of BC and also Center for Development of Clinical Research of Namazi Hospital and Dr. Nasrin Shokrpour for her editorial assistance.

## Authors' Contribution

N.O: Study concept and design, revising manuscript critically for important intellectual content; E.Ch: acquisition, analysis, and interpretation of data, drafting the manuscript; V.Z: Study design, revising manuscript critically for important intellectual content; Kh.K: Study design, the acquisition, analysis and interpretation of data, drafting the manuscript; A.T: Study concept, revising it critically for important intellectual content; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Conflict of interest:** None declared.

## References

- 1 Etemadi A, Sadjadi A, Semnani S, Nouriae SM, Khademi H, Bahadori M. Cancer registry in Iran: a brief overview. *Arch Iran Med.* 2008;11:577-80. PubMed PMID: 18759534.
- 2 Ha M, Lim HJ, Cho SH, Choi HD, Cho KY. Incidence of cancer in the vicinity of Korean AM radio transmitters. *Arch Environ Health.* 2003;58:756-62. doi: 10.3200/AEOH.58.12.756-762. PubMed PMID: 15859510.
- 3 Amirkhah R, Naderi-Meshkin H, Mirahmadi M, Allahyari A, Sharifi HR. Cancer statistics in Iran: Towards finding priority for prevention and treatment. *Cancer Press.* 2017;3:27-38. doi: 10.15562/tcp.42.
- 4 Mousavi SM, Gouya MM, Ramazani R, Davanlou M, Hajsadeghi N, Seddighi Z. Cancer incidence and mortality in Iran. *Ann Oncol.* 2009;20:556-63. doi: 10.1093/annonc/mdn642. PubMed PMID: 19073863.
- 5 Cabanes A, Vidal E, Aragones N, Perez-Gomez B, Pollan M, Lope V, et al. Cancer mortality trends in Spain: 1980-2007. *Ann Oncol.* 2010;21:14-20. doi: 10.1093/annonc/mdq089. PubMed PMID: 20427355.
- 6 Berek J, Novak E. *Woltersk. Female Genital Disease.* Philadelphia: Lippincott Williams & Wilkins; 2012.
- 7 Yavari P, Mosavizadeh M, Sadrol-Hefazi

- B, Mehrabi Y. Reproductive characteristics and the risk of breast cancer--a case-control study in Iran. *Asian Pac J Cancer Prev*. 2005;6:370-5. PubMed PMID: 16236002.
- 8 Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Pineros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*. 2019;144:1941-53. doi: 10.1002/ijc.31937. PubMed PMID: 30350310.
  - 9 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424. doi: 10.3322/caac.21492. PubMed PMID: 30207593.
  - 10 Rafiemanesh H, Salehiniya H, Lotfi Z. Breast Cancer in Iranian Woman: Incidence by Age Group, Morphology and Trends. *Asian Pac J Cancer Prev*. 2016;17:1393-7. doi: 10.7314/apjcp.2016.17.3.1393. PubMed PMID: 27039778.
  - 11 Acs G, Baloch ZW, LiVolsi VA. Intraoperative consultation: an historical perspective. *Semin Diagn Pathol*. 2002;19:190-1. PubMed PMID: 12469786.
  - 12 Rosai J. *Rosai and Ackerman's Surgical Pathology Mosby*. Amsterdam: Elsevier Inc. 2004.
  - 13 Manca G, Tardelli E, Rubello D, Gennaro M, Marzola MC, Cook GJ, et al. Sentinel lymph node biopsy in breast cancer: a technical and clinical appraisal. *Nucl Med Commun*. 2016;37:570-6. doi: 10.1097/MNM.0000000000000489. PubMed PMID: 26886421.
  - 14 Veronesi U, Viale G, Paganelli G, Zurrada S, Luini A, Galimberti V, et al. Sentinel lymph node biopsy in breast cancer: ten-year results of a randomized controlled study. *Ann Surg*. 2010;251:595-600. doi: 10.1097/SLA.0b013e3181c0e92a. PubMed PMID: 20195151.
  - 15 Wood WC. Close/positive margins after breast-conserving therapy: additional resection or no resection? *Breast*. 2013;22:S115-7. doi: 10.1016/j.breast.2013.07.022. PubMed PMID: 24074771.
  - 16 Wong J, Yong WS, Thike AA, Iqbal J, Salahuddin AS, Ho GH, et al. False negative rate for intraoperative sentinel lymph node frozen section in patients with breast cancer: a retrospective analysis of patients in a single Asian institution. *J Clin Pathol*. 2015;68:536-40. doi: 10.1136/jclinpath-2014-202799. PubMed PMID: 25855801.
  - 17 Brahmbhatt M, Dutta A. On SARS type economic effects during infectious disease outbreaks. *World Bank Policy Research Working Paper*. 2008. doi: 10.1596/1813-9450-4466.
  - 18 Bank W [Internet]. *World Development Indicators*. [cited 12October 2020]. Available from: <http://databank.worldbank.org/data/reports.aspx?source=2&series=NY.GDP.PCAP.PP.CD&country>
  - 19 Bank W, Metrics Evaluation IfH. *The cost of air pollution: strengthening the economic case for action*. Washington: World Bank; 2016.
  - 20 Gray AM, Clarke PM, Wolstenholme JL, Wordsworth S. *Applied methods of cost-effectiveness analysis in healthcare*. Oxford: Oxford University Press; 2011.
  - 21 Rezaee M, Izadi S, Keshavarz K, Borhani-haghighi A, Ravangard R. Fingolimod versus natalizumab in patients with relapsing remitting multiple sclerosis: a cost-effectiveness and cost-utility study in Iran. *J Med Econ*. 2019;22:297-305. doi: 10.1080/13696998.2018.1560750. PubMed PMID: 30561242.
  - 22 Osborn JB, Keeney GL, Jakub JW, Degnim AC, Boughey JC. Cost-effectiveness analysis of routine frozen-section analysis of breast margins compared with reoperation for positive margins. *Ann Surg Oncol*. 2011;18:3204-9. doi: 10.1245/s10434-011-1956-0. PubMed PMID: 21861234.
  - 23 Boughey JC, Keeney GL, Radensky P, Song CP, Habermann EB. Economic Implications of Widespread Expansion of Frozen Section Margin Analysis to Guide Surgical Resection in Women With Breast Cancer Undergoing Breast-Conserving Surgery. *J Oncol Pract*. 2016;12:e413-22. doi: 10.1200/JOP.2015.005652. PubMed PMID: 26907452.
  - 24 Almarzooq R, Alrayes A, Saeed A, Abdulla H. Accuracy of intraoperative frozen section evaluation of sentinel lymph node biopsy in breast cancer: Our experience in Bahrain. *Gulf J Oncolog*. 2018;1:46-51. PubMed PMID: 30344134.
  - 25 Boughey JC, Hieken TJ, Jakub JW, Degnim AC, Grant CS, Farley DR, et al. Impact of analysis of frozen-section margin on reoperation rates in women undergoing lumpectomy for breast cancer: evaluation of the National Surgical Quality Improvement Program data. *Surgery*. 2014;156:190-7. doi: 10.1016/j.surg.2014.03.025. PubMed PMID: 24929768.
  - 26 Schnitt SJ, Morrow M. Should intraoperative frozen section evaluation of breast



- lumpectomy margins become routine practice? *Am J Clin Pathol.* 2012;138:635-8. doi: 10.1309/AJCPPQ1JGV0GJIAB. PubMed PMID: 23086762.
- 27 Tang SS, Kaptanis S, Haddow JB, Mondani G, Elsberger B, Tasoulis MK, et al. Current margin practice and effect on re-excision rates following the publication of the SSO-ASTRO consensus and ABS consensus guidelines: a national prospective study of 2858 women undergoing breast-conserving therapy in the UK and Ireland. *Eur J Cancer.* 2017;84:315-24. doi: 10.1016/j.ejca.2017.07.032. PubMed PMID: 28865259.
- 28 Barakat FH, Sulaiman I, Sughayer MA. Reliability of frozen section in breast sentinel lymph node examination. *Breast Cancer.* 2014;21:576-82. doi: 10.1007/s12282-012-0431-5. PubMed PMID: 23192628.
- 29 Jorns JM, Daignault S, Sabel MS, Myers JL, Wu AJ. Frozen sections in patients undergoing breast conserving surgery at a single ambulatory surgical center: 5 year experience. *Eur J Surg Oncol.* 2017;43:1273-81. doi: 10.1016/j.ejso.2017.01.237. PubMed PMID: 28215733.