

Ana Filipa Santos Pinto

Short-term Morbidity and Ipsilateral Breast Tumor Recurrence Associated to Nipple/
Skin Sparing Mastectomy with Immediate Reconstruction

março, 2019

FMUP

Ana Filipa Santos Pinto

**Short-term Morbidity and Ipsilateral Breast Tumor Recurrence Associated to Nipple/
Skin Sparing Mastectomy with Immediate Reconstruction**

-

Mestrado Integrado em Medicina

Área: Cirurgia

Tipologia: Dissertação

Trabalho efetuado sob a Orientação de:

Professor Doutor José Luís Fougo

Trabalho organizado de acordo com as normas da revista:

Porto Biomedical Journal

março, 2019

FMUP

Eu, Ana Filipa Santos Pinto, abaixo assinado,
nº mecanográfico 201303294, estudante do 6º ano do Ciclo de Estudos Integrado em
Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta
integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão,
assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as
frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou
redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 22/03/2019

Assinatura conforme cartão de identificação:

Ana Filipa Santos Pinto

NOME

Ana Filipa Santos Pinto

NÚMERO DE ESTUDANTE

E-MAIL

201303294 *ana.filipe.pinto95@gmail.com*

DESIGNAÇÃO DA ÁREA DO PROJECTO

Cirurgia

TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

Short-term morbidity and Spilateral breast tumor Recurrence associated to nipple/skin sparing Mastectomy with immediate reconstruction

ORIENTADOR

Jose Luis Fong

COORDENADOR (se aplicável)

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTES TRABALHOS APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☒
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTES TRABALHOS (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTES TRABALHOS.	☐

Faculdade de Medicina da Universidade do Porto, 22/03/2019

Assinatura conforme cartão de identificação: *Ana Filipa Santos Pinto*

Agradecimentos

Todo o trabalho que desenvolvi ao longo do Projeto de Opção é um agradecimento aos meus amigos que acompanharam etapa a etapa esta jornada.

À Sofia B,
à Sofia C,
à Rita R,
à Rita S,
ao Diogo F,
à Caroline S,
e ao Tiago S.

Aprendi o significado de Resiliência e, enquanto houver Memória, haverá quem conte esta história.
It always seems impossible until it's done- Nelson Mandela.

Agradeço também à minha mãe e aos meus sobrinhos.

Este foi um trabalho árduo, de muitas horas, esforço e dedicação. Desde a extensa leitura dos processos das doentes do Centro de Mama e construção da base de dados, até à redação do protocolo de estudo, pesquisa bibliográfica, escrita do trabalho e diligências para sua publicação científica. Na verdade, *não há fama sem suor*. Em todas as fases deste processo, tenho a agradecer ao meu orientador Professor Doutor José Luís Fougo toda a autonomia que me deu.

Short Term Morbidity and Ipsilateral Breast Tumor Recurrence Associated to Nipple/Skin Sparing Mastectomy with Immediate Reconstruction

Ana Filipa Pinto¹, José Luís Fougho^{1,2}

¹Faculty of Medicine, University of Porto, Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal

² Breast Center, São João University Hospital, Oporto, Portugal

*Corresponding author:

Ana Filipa Pinto (electronic address: up201303294@med.up.pt)

Faculty of Medicine, University of Porto, Oporto, Portugal

Alameda Prof. Hernâni Monteiro

4200-319 Porto, Portugal

Abbreviations:

ANED, alive with no evidence of disease
AWC, alive with cancer
BC-CHSJ, Breast Centre of São João University Hospital
BCS, breast-conserving surgery
BMI body mass index
CDC, Clavien-Dindo Classification
CHUSJ, São João University Hospital
CS, Current Status
CT, computed tomography
ChT, Chemotherapy
DI, Direct to Implant
DIEP, Deep inferior epigastric artery perforator
DOC, died of cancer
DOTHER, died of another reason
ER, estrogen receptor
FEC, 5-fluorouracil-epirubicin-cyclophosphamide
HER2, Human epidermal growth factor receptor-2
HT, hormonal therapy
IBR, immediate breast reconstruction
IHC, Immunohistochemistry
ISH, In situ hybridization
LD, Latissimus Dorsi
LN, lymph node
LR, local recurrence
NSABP, National Surgical Adjuvant Breast and Bowel Project
NSM, nipple-sparing mastectomy
NST, No special type
OPBC, Oncoplastic Breast Consortium
PR, progesterone receptor
PT, Primary Tumor
RATFS, retroareolar tissue frozen section
RT, Radiotherapy
SSM, skin-sparing mastectomy
TC, temozolomide and capecitabine
TE, Tissue Expander
TRAM, Transverse Rectus Myocutaneous
UIQ, Upper-Inner Quadrant of breast
UOQ, Upper-Outer Quadrant of breast
Yo, years-old

Abstract

Background: In 2018, an estimated 2.1 million new cases of breast cancer were detected in women worldwide, making it the most commonly diagnosed cancer among females. Skin-Sparing Mastectomy (SSM) and Nipple-Sparing Mastectomy (NSM) are surgical treatment options, but are still faced with some degree of concern regarding their oncological safety and their immediate complications following surgery. In order to add up to already available consecutive case series on the subject, this paper aims to give information on the type and rate of immediate surgical morbidity (within 30 days), local tumor recurrence and the occurrence of new primary breast cancer following risk-reducing SSM/NSM.

Methods: Retrospective analysis of clinical files of patients who underwent SSM or NSM with immediate breast reconstruction at the BC-CHSJ between January 2011 and December 2015.

Results: A total of 186 patients underwent SSM or NSM followed by IBR at CHUSJ Breast Centre between January 2011 and December 2015. Of these, 46 underwent double mastectomy, resulting in a total of 232 surgical procedures. Overall complication rate was 42,2%, and the rate of grade II/III complications using the Clavien-Dindo Classification was 27.1%. Local recurrence rate of breast cancer following these procedures was 1.8% over a 56-months (range, 13-93) follow-up. No cases of primary tumor following prophylactic surgery were reported.

Conclusions: The rate of immediate complications with an impact in patient's clinical course following skin-sparing or nipple sparing mastectomy is low. Recurrence rate following these procedures is comparable to that of traditional mastectomy and after prophylactic procedures there were no primary breast tumors detected.

INTRODUCTION

In 2018, an estimated 2.1 million new cases of breast cancer were detected in women worldwide, making it the most commonly diagnosed cancer among females (11.6% of the total cases).¹ Breast cancer is the leading cause of cancer death among women as well, and its complex approach requires a multi-disciplinary team of professionals consisting of oncologic and plastic surgeons, radiologists, oncologists, pathologists and expertise of other fields, such as Psychology and Nursing.^{1,2}

The publishing of the Milan trials in 1981 and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial in 1985 was considered a landmark, for such projects paved the way for the emergence of breast-conserving surgery (BCS)- quadrantectomy or lumpectomy.^{3,4} These techniques are less mutilating than it had been previously assumed to be necessary for breast cancer treatment, originating a paradigm shift for the surgical management of breast cancer.^{3,4} Nowadays, aesthetic results are a matter under growing awareness in the management of breast cancer due to the psychological effects caused by breast disfigurement.^{5,6} As a result, despite oncological safety being the main focus of treatment, a present-day operation gracefully balances disease control with external appearance outcomes, fitting within the concept of oncoplastic surgery.⁷ Nevertheless, about one-third of women with breast cancer still require a mastectomy, either because BCS is declined or due to the size, site or extent of the tumor.⁸

Skin-Sparing Mastectomy (SSM) and Nipple-Sparing Mastectomy (NSM) are of comparatively recent vintage, rising to surface along the lines of the change in the paradigm.⁹ Indeed, in 1962, Freeman introduced a subcutaneous mastectomy for benign breast lesions with immediate or delayed prosthetic replacement, and five years later he described its complications.^{10,11} In order to avoid the complications of immediate reconstruction, surgeons then started to adopt a technique in which the nipple would be transplanted to the groin and kept there until the final breast reconstruction, which in turn led to reports describing the development of infiltrating carcinoma at the transplantation site, bringing about the disuse of free nipple grafting in oncologic surgeries by most surgeons for many years.^{12,13} In 1991, the term “skin-sparing mastectomy” was used for the first time by Toth and Lappert, and a few years later, despite the opposing views of some analyses, the concept of NSM was revisited in the context of breast surgical oncology, after the results of the NSABP B-06 study- a randomized, prospective, multicenter study, with 20 years of published follow-up- reported no difference in survival among the patients randomized to mastectomy, lumpectomy or lumpectomy with radiation therapy.^{4, 14-19} Jensen points out that safety of NSM is sustained on the fact that, in the face of a nipple recurrence, the patient can be treated without loss of benefit in survival, and not on the assumption that it is not possible for nipple recurrences to occur.²⁰⁻²³ The Oncoplastic Breast Consortium consensus conference panel held in 2018, consisting of 44 breast surgeons and a patient advocate, regards NSM as a safe procedure, if patients meet the recommended criteria and appropriate techniques are performed by a team of specialists.²⁴

On account on some concern still present on the oncological safety of SSM and NSM, and to add up to consecutive case series on the subject already available, in addition to characterizing the patients who underwent SSM or NSM with immediate breast reconstruction (IBR) in the Breast Centre of São

João University Hospital (BC-CHSJ) from January 2011 to December 2015, this paper aims to give information on the type and rate of immediate surgical morbidity (within 30 days), local tumor recurrence and the occurrence of new primary breast cancer following risk-reducing SSM/NSM.

METHODS

Patient and procedure data

All patients who underwent SSM or NSM with IBR at the BC-CHSJ between January 2011 and December 2015 were identified using a retrospective surgery chart review. Patients on this chart were assigned to SSM or NSM by their physician, based on the diagnosis of breast cancer or the identification of oncogenic mutations with increased risk for breast cancer development. SSM was performed if the tumor or the suspicious microcalcifications were within a 10mm distance from the nipple. In case they were more than 20mm away from the nipple, NSM would be the chosen option. Retroareolar tissue frozen section was performed in the cases in which the tumor or the suspicious microcalcifications were within a 10-20 mm range from the nipple. In the event of a positive RATFS result, NAC excision was performed. The medical files of all selected patients were then retrospectively reviewed, and a database was created.

Collected patient data included age at diagnosis and age at surgery, date of last medical observation, weight (kg), height (cm), smoking habits and the need for adjuvant treatments. Regarding tumor features, final pathologic stage, histologic grade, the presence of lymphovascular invasion, the histological subtype, the status of estrogen receptor (ER), progesterone receptor (PR) and Human epidermal growth factor receptor-2 (HER2) protein overexpression were recorded. ER and PR were deemed positive if present in at least 1% of the tumor cells. HER-2 was considered positive in cases of IHC +++ or ISH positivity. Tumor staging was performed according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 7th Edition. Surgical data included mastectomy technique and the reconstruction technique, previous or simultaneous sentinel LN biopsy, and the performance and outcomes of retroareolar tissue frozen section (RATFS).

Immediate surgical morbidity included explantation of prosthesis, hematoma, seroma, partial and total nipple/areola necrosis, wound infection, skin flap necrosis, distant flap necrosis (LD, TRAM, DIEP), wound dehiscence, rehospitalization and reoperation rates (30 days). Complications were graded according to the Clavien-Dindo classification.²⁵ Date and site of first local recurrence (LR) was also analyzed.

After mastectomy, patient's follow-up differed according to tumor stage: stages 1 and 2 were submitted to yearly physical examination, mammography and breast ultrasound; in addition, stages 3 and 4 performed yearly bone scintigraphy, total CT scan and serum tumor markers measurements (CEA and Ca15.3).

This study was approved by the Ethics Committee of CHUSJ.

Statistical analysis

Descriptive statistical analysis was performed using IBM SPSS Statistics 24.0 (SPSS Inc., Chicago, IL, USA).

Rate of immediate complications was calculated by dividing the number of procedures in which a complication occurred in the 30 days following surgery by the total number of procedures. Rate of LR was calculated by dividing the number of recurrences by the total number of procedures with a curative purpose. Rehospitalization rate was calculated by dividing the number of individuals who were readmitted to the hospital in the next 30 days after surgery by the total number of individuals that underwent SSM/NSM.

RESULTS

Patient and Surgery Characteristics

A total of 186 patients underwent SSM or NSM followed by IBR at CHUSJ Breast Centre between January 2011 and December 2015. Of these, 46 underwent double mastectomy, resulting in a total of 232 surgical procedures.

Median age at diagnosis was 48yo (range, 26-80), with a median BMI of 24,7 kg/m² and a 15.6% smoking rate (Table 1). Median waiting time for elective surgery was 47 days (range, 1-2723). The vast majority of patients (91,9%) are currently alive with no evidence of cancer. One patient presented with synchronous hepatic metastases at primary diagnosis of breast cancer and later died of the disease. A large number of patients had stage 0 breast cancer (21,5%), stage 1 cancer (30,6%) or stage 2 cancer (22,0%). Among those with invasive cancer, 88,9% and 79,8% showed positivity for estrogen receptors and progesterone receptors, respectively, and 16.2% had HER2 protein overexpression. In addition, considering that group, the majority underwent adjuvant ChT or endocrine therapy, while only 10,1% received radiation therapy.

More than half of surgical procedures were performed with a curative purpose (163, 70,3%), whereas 69 (29,7%) presented as a risk-reducing surgery (Table 2). A total of 86 SSM and 146 NSM were performed. Only 62 charts clearly stated the adopted surgical excision technique, the most used being blade dissection alone (40 procedures). Mixed excision technique were defined as a combination of sharp dissection and/or scissors and/or electrocautery. The most frequent breast reconstruction techniques were subpectoral expander (two stages technique, 44,8%) and TRAM-flap (23,3%). Surgeons performed 43 RATFS (18,5% of procedures), 10 of which resulted in the detection of a tumor. In those cases, the surgeon proceeded to NAC excision.

TABLE 1. PATIENT CHARACTERISTICS

		Total (n=232)	SSM (n=86)	NSM (n=146)	Curative (n=163)	Risk- reducing (n=69)
Median age at diagnosis, years (n=186)		48 (26-80)	51 (35-80)	46 (26-68)	49 (26-80)	41 (26-72)
Median waiting time, days (n=186)		47 (1-2736)	42 (2-547)	52 (1-2736)	42 (1-383)	95 (18-2736)
Median follow-up time, months (n=186)		52 (13-93)	52 (13-93)	55 (16-91)	55 (16-93)	51 (13-91)
Current Status (n=186)	ANED	171 (91,9%)	67 (90,5%)	104 (92,9%)	128 (92,1%)	46 (97,9%)
	AWC	13 (7,0%)	6 (8,1%)	7 (6,3%)	10 (7,2%)	-
	DOC	1 (0,5%)	1 (1,4%)	-	1 (0,7%)	-
	DOTHER	1 (0,5%)	-	1 (0,9%)	-	1 (2,1%)
Weight median, kg (n=182)		63 (44-93)	64 (44-89)	64 (45-93)	64 (44-89)	63 (47-93)
Height, median, cm (n=162)		160 (134-178)	160 (134-175)	161 (146-178)	160 (134-178)	162 (142-175)
BMI, median (n=162)		24,7 (16,7-38,1)	25,3 (17,3-34,3)	24,1 (16,7-38,1)	24,8 (16,7-34,3)	24,0 (17,3-38,1)
Smoking habits (n=186)	no	115 (61,8%)	43 (58,1%)	72 (64,3%)	87 (62,6%)	28 (59,6%)
	yes	29 (15,6%)	11 (14,9%)	12 (16,1%)	23 (16,5%)	6 (12,8%)
	unknown	42 (22,6%)	20 (27,0%)	22 (19,6%)	29 (20,9%)	13 (27,7%)
Stage of cancer (n=186)	0	40 (21,5%)	18 (24,3%)	22 (19,6%)	40 (28,8%)	-
	1	57 (30,6%)	26 (35,1%)	31 (27,7%)	57 (41,0%)	-
	2	41 (22,0%)	18 (24,3%)	23 (20,5%)	41 (29,5%)	-
	4	1 (0,5%)	1 (1,4%)	-	1 (0,7%)	-
	NA	47 (25,3%)	11 (14,9%)	36 (32,1%)	-	47 (100%)
Tumor grade (invasive cancer n=99)	1	28 (28,3%)	14 (31,1%)	14 (25,9%)	28 (28,3%)	-
	2	41 (41,4%)	20 (44,4%)	21 (38,9%)	41 (41,4%)	-
	3	28 (28,3%)	13 (15,1%)	17 (31,5%)	28 (28,3%)	-
	NA	2 (2%)	-	2 (3,8%)	2 (2,0%)	-
LN metastasis (invasive cancer n=99)	no	86 (86,9%)	37 (82,2%)	49 (90,7%)	86 (86,9%)	-
	yes	13 (13,1%)	8 (17,8%)	5 (9,3%)	13 (13,1%)	-
ER (invasive cancer n=99)	negative	11 (11,1%)	4 (8,9%)	7 (13,0%)	11 (11,1%)	-
	positive	88 (88,9%)	41 (91,1%)	47 (87,0%)	88 (88,9%)	-
PR (invasive cancer n=99)	negative	20 (20,2%)	6 (13,3%)	14 (25,9%)	20 (20,2%)	-
	positive	79 (79,8%)	39 (86,7%)	40 (74,1%)	79 (79,8%)	-
HER2 status (invasive cancer n=99)	negative	81 (81,8%)	34 (75,6%)	47 (87,0%)	81 (81,8%)	-
	positive	16	10	6	16	-

		(16,2%)	(22,2%)	(11,1%)	(16,2%)	
	Undefined	2	1	1	2	-
		(2,0%)	(2,2%)	(1,9%)	(2,0%)	
Chemotherapy	no	41	19	22	41	-
(invasive cancer n=99)		(41,4%)	(42,2%)	(40,7%)	(41,4%)	
	neoadjuvant	2	-	2	2	-
		(2,0%)		(3,7%)	(2,0%)	
	adjuvant	56	26	30	56	-
		(56,6%)	(57,8%)	(55,6%)	(56,6%)	
Radiation therapy	no	89	38	51	89	-
(invasive cancer n=99)		(89,9%)	(84,4%)	(94,4%)	(89,9%)	
	yes	10	7	3	10	-
		(10,1%)	(15,6%)	(5,6%)	(10,1%)	
Antihormonal therapy	no	10	2	8	10	-
(invasive cancer n=99)		(10,1%)	(4,4%)	(14,8%)	(10,1%)	
	adjuvant	89	43	46	89	-
		(89,9%)	(95,6%)	(85,2%)	(89,9%)	

ANED= alive with no evidence of cancer, AWC= alive with cancer, BMI= body mass index; DOTHER= died of other reason, ER= estrogen receptor, HER2= human epidermal growth factor receptor-2, LN= lymph node, DOC=died of cancer, PR= progesterone receptor

TABLE 2. SURGERY CHARACTERISTICS

		Total (n=232)	SSM (n=86)	NSM (n=146)	Curative (n=163)	Risk- Reducing (n=69)
Mastectomy technique	Tumescent technique+ Sharp dissection alone	1 (0,4%)	-	1 (0,7%)	1 (0,6%)	-
	Blade dissection alone	40 (17,2%)	17 (19,8%)	23 (15,8%)	29 (17,8%)	11 (15,9%)
	Scissors dissection alone	7 (3,0%)	2 (2,3%)	5 (3,4%)	6 (3,7%)	1 (1,4%)
	Electric cautery alone	-	-	-	-	-
	Mixed technique	13 (5,6%)	3 (3,5%)	10 (6,8%)	10 (6,1%)	3 (4,3%)
	Unknown	170 (73,3%)	22 (25,6%)	110 (75,3%)	117 (71,8%)	54 (78,2%)
Type of reconstruction	Subpectoral TE	104 (44,8%)	32 (37,2%)	72 (49,3%)	59 (36,2%)	45 (65,2%)
	Prepectoral TE	3 (1,3%)	-	3 (2,1%)	2 (1,2%)	1 (1,4%)
	Subpectoral DI	28 (12,1%)	4 (4,7%)	24 (16,4%)	16 (9,8%)	12 (17,4%)
	Prepectoral DI	3 (1,3%)	-	3 (2,1%)	-	3 (4,3%)
	LD + Implant	19 (8,2%)	12 (14%)	7 (4,8%)	18 (11%)	1 (1,4%)
	Skin Graft + Implant	2 (0,9%)	-	2 (1,4%)	2 (1,2%)	-
	TRAM Flap	54 (23,3%)	26 (30,2%)	28 (19,2%)	49 (30,1%)	5 (7,2%)
	DIEP Flap	18 (7,8%)	12 (14,0%)	6 (4,1%)	16 (9,8%)	2 (2,9%)
	LD + Expander	1 (0,4%)	-	1 (0,7%)	1 (0,6%)	-

DI= Direct to Implant, DIEP= Deep inferior epigastric artery perforator, LD= Latissimus Dorsi, TE= Tissue Expander, TRAM= Transverse Rectus Myocutaneous

Immediate complications

Information regarding the morbidity events in the 30 days following surgery was easily available in all clinical files, except for one patient's file, which did not have sufficient data for assessment of surgical morbidity.

Overall complication rate was 42,2%, and the rate of grade II/III complications using the Clavien-Dindo Classification was 27.1% (Table 3). The most frequent immediate complication after mastectomy was the development of a hematoma (12,9%). The vast majority of the patients (72,8%) suffered no complications or minor, grade I. Serious complications (e.g., CDC grade III) occurred after 13,8% of procedures. Partial and total nipple/ areolar necrosis happened in 14.8% and 8.5% of NSMs, respectively.

Re-hospitalization rate was 5,4% (10/186) and 15,6% of patients were re-operated under general anesthesia.

TABLE 3. IMMEDIATE COMPLICATIONS (30 DAYS)

	Total (n=232)	SSM (n=86)	NSM (n=146)	Curative (n=163)	Risk- reducing (n=69)
Immediate Complications					
Explantation of prosthesis	8 (3,4%)	4 (4,7%)	4 (12,3%)	5 (3,1%)	3 (4,3%)
Hematoma	30 (12,9%)	12 (14,0%)	18 (12,3%)	25 (15,3%)	5 (7,2%)
Seroma	25 (10,8%)	14 (16,3%)	11 (7,5%)	18 (11,0%)	7 (10,1%)
Partial nipple/ areolar necrosis	24 (10,3%)	-	24 (16,4%)	15 (9,2%)	9 (13,0%)
Total nipple/ areolar necrosis	13 (5,6%)	-	13 (8,9%)	7 (4,3%)	6 (8,7%)
Wound infection	10 (4,3%)	6 (7%)	4 (2,7%)	9 (5,5%)	1 (1,4%)
Skin flap necrosis	20 (8,6%)	11 (12,8%)	9 (6,2%)	15 (9,2%)	5 (7,2%)
Distant flap necrosis (LD, TRAM, DIEP)	9 (3,9%)	6 (7,0%)	2 (2,1%)	9 (5,5%)	-
Wound dehiscence	14 (6,0%)	10 (11,6%)	2 (2,7%)	12 (7,4%)	2 (2,9%)
Others					
Rehospitalization (30 days)					
Reoperation under general anesthesia					
Clavien-Dindo Classification					
0-I	169 (72,8%)	58 (67,4%)	111 (76,0%)	116 (71,2%)	53 (76,8%)
II	31 (13,4%)	15 (17,4%)	16 (11,0%)	24 (14,7%)	7 (10,1%)
III (A/B)	32 (13,8%)	13 (15,1%)	19 (13,0%)	23 (14,1%)	9 (13,0%)
N° Procedures with complications			98		
Overall Complication Rate			42,2%		
Grade II/III Complications Rate			27,1%		
Rehospitalization rate (30 days)			5,4%		

DIEP= Deep inferior epigastric artery perforator, LD= Latissimus Dorsi, TRAM= Transverse Rectus Myocutaneous

Local recurrence and Primary Tumor after Prophylactic Mastectomy

Three of a total of 163 SSM/NSM with a curative purpose had breast cancer recurrence (Table 4). Therefore, LR rate of breast cancer following these procedures was 1.8% over a 56-months (range, 13-93) follow-up. The median time from treatment to LR was 36 months (mean, 36,7; range, 29-45).

In 2011, patient A underwent bilateral NSM with IBR with expanders and subsequent adjuvant ChT (FEC) and HT (tamoxifen) for a right breast primary tumor. Definitive 355cc implants placed in 2012 were later switched to 435cc implants in 2015, both procedures followed one year later by breast augmentation by lipofilling. In 2017, this patient underwent total mastectomy of the right breast and sentinel LN biopsy. Pathology described a multifocal in-breast recurrence (4 foci, sized from 8 to 14 mm). Then, Patient A received ChT (TC*6), thoracic wall RT and HT (exemestane).

Patient B underwent NSM of the left breast with IBR with DIEP flap in 2011, followed by adjuvant ChT (FEC) and HT (tamoxifen). Subcutaneous LR was diagnosed in 2015, and prompted a tumorectomy plus sentinel node biopsy, and adjuvant breast RT and HT with anastrozole.

In January 2015, patient C was diagnosed with a 9mm tumor in the right breast. This patient had a 16,8 kg/m² BMI and an A breast cup. NSM with IBR with a 245cc implant took place in February 2015, and a week later patient was re-operated due to hematoma and maintained the implant. This patient received 2 cycles of adjuvant TC and later switched to 4 cycles of AC due to multiple systemic reactions to TC. In 2016, implant was switched to a 320 cc one and a lipofilling was performed. In 2017, excision of a cutaneous node on the mastectomy scar revealed a local tumor recurrence. This resulted in a total mastectomy and adjuvant chest wall RT and 8 cycles of capecitabine.

No cases of primary breast cancer were detected after prophylactic mastectomy.

TABLE 4. PATIENTS WITH LOCAL RECURRENCE

	PT: Site, Surgery, Characteristics and Adjuvant therapy	PT treatment-to- recurrence interval	Recurrence: Site, Surgery, Treatment	CS and Follow-up time
Patient A	UOQ, NSM with underpectoral expander, Multifocal Mixed tumor (ductal and mucinous). HR+ (>80%), Her2- pT2 (14mm) N0sn M0 G3 R0 ChT+HT+RT	73 months	UOQ, Subcutaneous/ in- breast, Total Mastectomy (including reconstruction) ChT+RT+HT	ANED 92 months
Patient B	UIQ, NSM with DIEP flap, Unifocal NST carcinoma. HR+ (>90%) HER2- pT2 (22mm) N0sn M0 G2 R0 ChT+ HT	44 months	UIQ, Subcutaneous/ in- breast, Wide Excision + RT+ HT	ANED 82 months
Patient C	UIQ, NSM with underpectoral implant, Unifocal Basal cell carcinoma HR- Her2- pT1 (8mm) N0sn M0 G3 R0 ChT+ RT	28 months	UIQ, Cutaneous (Surgical Scar), Total Mastectomy (including reconstruction) RT + ChT	ANED 54 months

CS= Current Status, ChT= Chemotherapy, HT= hormonal therapy, NST= No special type, PT= Primary Tumor, RT= Radiotherapy, UIQ= Upper-Inner Quadrant of breast cancer UOQ= Upper-Outer Quadrant of breast cancer

DISCUSSION

Authors of this study carried out a retrospective review of patient's clinical files to examine the complications and the oncological safety of SSM/NSM with IBR. In skin-sparing mastectomy, the breast glandular tissue is removed and separated from the subcutaneous fat, but most of the breast skin is retained.⁹ Nipple-sparing mastectomy is in essence the same process, with the exception of the conservation of the nipple-areolar complex.⁹ During the surgery, in case the retroareolar tissue sent for frozen pathology reports the presence of a tumor, the surgeon proceeds to excision of the nipple areolar complex.²

Immediate complications associated with the analyzed conservative mastectomies included breast prosthesis explantation, hematoma, seroma, wound infection or dehiscence, necrosis (nipple, skin-flap, or distant flap necrosis). Rehospitalization and reoperation under general anesthesia were also taken into account in this analysis. The overall complication rate was 42,2%. However, considering the complications that authors of this study find to have a bigger impact on patient's well-being and clinical course (eg Clavien-Dindo grade II/III complications), this rate was 27,1%, which is close to those reported in literature.²⁶ Nipple necrosis rate was 15,9%. A systematic review of the literature from Headon et al. which included 12 358 NSMs and revealed an overall complication rate of 22.3% and overall incidence of partial or total nipple necrosis of 5.9%.²⁶ Partial or full nipple necrosis is reported in 2% to 20% of cases after NSMs.²⁷ Headon et al. suggested that factors that influence the occurrence of nipple necrosis were breast features (large size and ptosis), periareolar incision, tobacco use and re-exposure to radiotherapy.²⁶

Local recurrence rate of breast cancer following skin-sparing or nipple-sparing mastectomy with immediate breast reconstruction was 1.8% over a 56-months follow-up. This indicates that these procedures present as an oncologically safe option for patients that meet the criteria for such procedures. Earlier studies reviewed SSM with IBM and found LR rates equivalent to those of total mastectomy and that ranged from 0% to 8.3%.^{5, 28-31} Likewise, De La Cruz et al. authored a meta-analysis and systematic review that included 5594 patients and concluded that NSM and SSM was not associated with higher LR rates compared to modified radical mastectomy.³² In fact, Mota et al. states that after a traditional mastectomy, there is a 2.3% likelihood after 20 years of breast cancer having a LR.³³ Several factors influence the risk of LR after SSM/NSM, including T2/T3 cancer, triple negative tumors, high-grade tumors and positive lymph nodes.³¹ Vaughan et al. reported that 82% of patients had local recurrence in the same area as the primary tumor.³⁰ This work had similar findings. Specifically, LR mainly occurred subcutaneously and one cutaneous recurrence, and the area of recurrence was the same as that of the primary tumor.

The greatest limitation of this study was the quality of the reporting of complications following mastectomy. Each physician adopted different ways of writing patient's reports, and its interpretation may have affected the results. The nearly five-year follow-up is also a limitation, and future studies with longer follow-ups are advised for better assessment of oncologic outcomes of NSM/ SSM.

This study found no cases of primary breast cancer after risk-reducing NSM/SSM. A systematic review published by Carbine et al. reports that both bilateral and contralateral risk-reducing mastectomies are effective in reducing the incidence of breast-cancer, but recommend the future publications of more prospective studies.

In view of these data, the results of this work suggest that SSM and NSM with immediate breast reconstruction present as a feasible option for patients that meet the indication criteria in regards to oncological safety and immediate complications.²⁴

ACKNOWLEDGMENTS RELATING TO THIS ARTICLE

Assistance with the study: none.

Financial support and sponsorship: none.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

REFERENCES

1. 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: a cancer journal for clinicians*. 2018; **68**(6):394-424
2. Freeman MD, Gopman JM, Salzberg CA. The evolution of mastectomy surgical technique: from mutilation to medicine. *Gland surgery* 2018; 7(3):308-15.
3. Veronesi U, Saccozzi R, Del Vecchio M, et al. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. *The New England journal of medicine*. 1981; 305(1):6-11.
4. Fisher B, Bauer M, Margolese R, Poisson R, et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *The New England journal of medicine* 1985; 312(11):665-73.
5. Cil TD, McCready D. Modern Approaches to the Surgical Management of Malignant Breast Disease: The Role of Breast Conservation, Complete Mastectomy, Skin- and Nipple-Sparing Mastectomy. *Clinics in plastic surgery* 2018; 45(1):1-11.
6. Sherman KA, Woon S, French J, Elder E. Body image and psychological distress in nipple-sparing mastectomy: the roles of self-compassion and appearance investment. *Psycho-oncology* 2017; 26(3):337-45.
7. Silverstein MJ, Mai T, Savalia N, Vaince F, Guerra L. Oncoplastic breast conservation surgery: the new paradigm. *Journal of surgical oncology* 2014; 110(1):82-9.
8. Lee SB, Lee JW, Kim HJ et al. Long-term outcomes of patients with breast cancer after nipple-sparing mastectomy/skin-sparing mastectomy followed by immediate transverse rectus abdominis musculocutaneous flap reconstruction: Comparison with conventional mastectomy in a single center study. *Medicine (Baltimore)* 2018;97(18):e0680.
9. Galimberti V, Vicini E, Corso G, et al. Nipple-sparing and skin-sparing mastectomy: Review of aims, oncological safety and contraindications. *Breast (Edinburgh, Scotland)* 2017; 3 4 Suppl 1:S82-s4.
10. Freeman BS. Subcutaneous mastectomy for benign breast lesions with immediate or delayed prosthetic replacement. *Plastic and reconstructive surgery and the transplantation bulletin* 1962; 30:676-82.
11. Freeman BS. Complications of subcutaneous mastectomy with prosthetic replacement, immediate or delayed. *Southern medical journal* 1967;60(12): 1277-80.
12. Cucin R GJ. Case report: implantation of breast cancer in a transplanted nipple a plea for preoperative screening. *CA: a cancer journal for clinicians* 1981; 31(5):281-3.
13. Allison AB, Howorth MG, Jr. Carcinoma in a nipple preserved by heterotopic auto-implantation. *The New England journal of medicine* 1978; 298(20):1132.
14. Toth BA, Lappert P. Modified skin incisions for mastectomy: the need for plastic surgical input in preoperative planning. *Plastic and reconstructive surgery* 1991;87(6):1048-53.

15. Simmons RM, Brennan M, Christos P, King V, Osborne M. Analysis of nipple/areolar involvement with mastectomy: can the areola be preserved? *Annals of surgical oncology* 2002; 9(2):1 65-8.
16. Cense HA, Rutgers EJ, Lopes Cardozo M, Van Lanschot JJ. Nipple-sparing mastectomy in breast cancer: a viable option? *Eur J Surg Oncol.* 2001;27(6):521-6.
17. Fisher B, Redmond C, Poisson R, Margoless R, Wolmark N, Wickerham L, et al. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *The New England journal of medicine.* 1989; 320(13):822-8.
18. Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *The New England journal of medicine.* 1995; 333(22):1456-61.
19. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *The New England journal of medicine* 2002;347(16):1233-41.
20. Jensen JA. When can the nipple-areola complex safely be spared during mastectomy? *Plastic and reconstructive surgery.* 2002;109(2):805-7.
21. Jensen JA. Breast Cancer: Is Nipple Sparing Mastectomy Safe? *Annals of Surgery.* 2009;250(4):657-8.
22. Jensen JA. Nipple-sparing mastectomy: what is the best evidence for safety? *Plastic and reconstructive surgery.* 2009;124(6):2195-7; author reply 7.
23. Jensen JA. Nipple-Sparing Mastectomy. *Journal of the American College of Surgeons.* 2018; 226(1):108.
24. Weber WP, Haug M, Kurzeder C, Bjelic-Radisic V, Koller R, Reitsamer R, et al. Oncoplastic Breast Consortium consensus conference on nipple-sparing mastectomy. *Breast Cancer Res Treat.* 2018.
25. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004; 240(2):205-13.
26. Headon HL, Kasem A, Mokbel K. The oncological safety of nipple-sparing mastectomy: a systematic review of the literature with a pooled analysis of 12,358 procedures. *Arch Plast Surg* 2016;43(4): 328e38.
27. Murthy V, Chamberlain RS. Defining a place for nipple sparing mastectomy in modern breast care: an evidence-based review. *Breast J* 2012; 19(6): 571–81.
28. Agrawal A, Sibbering DM, Courtney C-A. Skin sparing mastectomy and immediate breast reconstruction: a review. *Eur J Surg Oncol* 2013;39(4):320–8.
29. Drucker-Zertuche M, Robles-Vidal C. A 7 year experience with immediate breast reconstruction after skin sparing mastectomy for cancer. *Eur J Surg Oncol* 2007;33(2):140–6.

30. Vaughan A, Dietz JR, Aft R, et al. Scientific Presentation Award. Patterns of local breast cancer recurrence after skin-sparing mastectomy and immediate breast reconstruction. *Am J Surg* 2007; 194(4): 438–43.
31. Medina-Franco H, Vasconez LO, Fix RJ, et al. Factors associated with local recurrence after skin-sparing mastectomy and immediate breast reconstruction for invasive breast cancer. *Ann Surg* 2002; 235(6):814–9.
32. De La Cruz L, Moody AM, Tappy EE, et al. Overall survival, disease-free survival, local recurrence, and nipple-areolar recurrence in the setting of nipple-sparing mastectomy: a meta-analysis and systematic review. *Ann Surg Oncol* 2015;22(10): 3241–9.
33. Mota BS, Riera R, Ricci MD, Barrett J, de Castria TB, Atallah ÁN, Bevilacqua JLB. Nipple- and areola-sparing mastectomy for the treatment of breast cancer. *Cochrane Database of Systematic Reviews* 2016, Issue 11. Art. No.: CD008932.
34. Carbine NE, Lostumbo L, Wallace J, Ko H. Risk-reducing mastectomy for the prevention of primary breast cancer. *Cochrane Database Syst Rev*. 2018 Apr 5; 4:CD002748.

ANNEX

Porto Biomedical Journal - Instructions for Authors

Note: These instructions comply with those formulated by the International Committee of Medical Journal Editors (ICMJE). For further details, authors should consult the following article: International Committee of Medical Journal Editors. "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" *New Engl J Med* 1997, 336:309–315. The complete document appears at <http://www.icmje.org>. Manuscripts that do not comply with these Instructions cannot be considered for publication and will be sent back to the authors.

The Editorial Office is pleased to answer any questions you may have about preparing your manuscript in accordance with our guidelines.

Email: andremoreira@med.up.pt

SCOPE

Porto Biomedical Journal (PBJ) is an online free-to-submit and open-access journal devoted to the publication of top-quality original research conducted in the biomedical fields, especially within the clinical and basic medical settings. The project aims to provide a valuable collection of generalist biomedical literature freely accessible to the international community, in order to become a reference in the current scientific landscape.

In addition, to ensure the quality and scientific relevance of PBJ, the journal counts with a diversified and international editorial board, and only accepts original research and review articles that undergo a strict revision process in a double-blind refereeing system, a procedure that safeguards the fairness of the article selection process.

As a generalist journal, PBJ accepts both original works and reviews in all biomedical areas, be they basic or clinical research. If you believe in a free and open scientific community and want to take your work one step further and closer to your peers, please consider submitting your work to *Porto Biomedical Journal*, the place "where Science meets Knowledge".

JOURNAL POLICIES

Originality

The Editors require that each manuscript is an original contribution and that it has not been, and will not be, submitted elsewhere while it is under consideration for publication in *Porto Biomedical Journal*. Editors may subject any manuscript submitted for consideration of publication in *Porto Biomedical Journal* to plagiarism-detection software. Manuscripts dealing with material that has appeared or is in press, in brief or preliminary form in other publications will not be considered unless the prior publication is a meeting abstract reporting only summarized information and does not exceed one printed page. The ICMJE has provided details of what is and what is not duplicate or redundant publication. If you are in doubt (particularly in the case of material that you have posted on a web site), we ask you to proceed with your submission but to include a copy of the relevant previously published work or work under consideration by other journals. Authors must draw attention to any published work that concerns the same patients or subjects as the present paper in a covering letter with their article.

Authorship

The Journal expects that each person listed as an author has participated sufficiently in the intellectual content, the analysis of data, and/or the writing of the manuscript to take public responsibility for it. Each author must have reviewed the manuscript, believes it represents valid work, and approves it for submission. Moreover, should the Editors request the data upon which the manuscript is based, the authors shall produce it. We ask all authors to confirm that they have met the criteria for authorship established by the ICMJE, believe that the paper represents honest work, and are able to verify the validity of the results reported.

All persons designated as authors should qualify for authorship and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. One or more authors should take responsibility for the integrity of the work as a whole, from inception to published article. Authorship credit should be based only on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be published. Conditions 1, 2 and 3 must all be met. Acquisition of funding, the collection of data or general supervision of the research group, by themselves, do not justify authorship. All others who contributed to the work who are not authors should be named in the Acknowledgements section. Any change in authorship/contributions after submission must be approved in writing by all authors and submitted to the Editorial Office for final consideration.

English Language Assistance

Authors who are not native speakers of English who submit manuscripts to international journals often receive negative comments from referees or editors about the English-language usage in their manuscripts, and these problems can contribute to a decision to reject a paper. To help reduce the possibility of such problems, we encourage such authors to consider using Wolters Kluwer Author Services*.

Wolters Kluwer Author Services

Wolters Kluwer, in partnership with Editage, offers a unique range of editorial services to help you prepare a submission-ready manuscript:

- **Premium Editing:** Intensive language and structural editing of academic papers to increase chances of journal acceptance.
- **Advanced Editing:** A complete language, grammar, and terminology check to give you a publication-ready manuscript.
- **Translation with Editing:** Write your paper in your native language and Wolters Kluwer Author Services will translate it into English, as well as edit it to ensure that it meets international publication standards.
- **Plagiarism Check:** Helps ensure that your manuscript contains no instances of unintentional plagiarism.

- **Artwork Preparation:** Save precious time and effort by ensuring that your artwork is viewed favorably by the journal without you having to incur the additional cost of purchasing special graphics software.

For more information regarding Wolters Kluwer Author Services, please visit <http://wkauthorservices.editage.com>.

*Note that the use of such a service is at the author's own expense and risk, and does not guarantee that the article will be accepted.

Ethics

All articles dealing with original human or animal data must include a statement on ethics approval at the beginning of the Methods section. This paragraph must contain the following information: the name and address of the ethics committee responsible; the protocol number that was attributed by this ethics committee; and the date of approval by the ethics committee.

The paragraph could read, for example:

Ethical approval for this study (Ethical Committee N° NAC 207) was provided by the Ethical Committee NAC of Geneva University Hospitals, Geneva, Switzerland on 12 February 2015.

In addition, for studies or case reports conducted on human participants you must state clearly in the text that you obtained written informed consent from the study participants; please also look at the latest version of the Declaration of Helsinki. Similarly, for experiments involving animals you must state the care of animal and licensing guidelines under which the study was performed and report these in accordance with the ARRIVE (Animals in Research: Reporting In Vivo Experiments) statement. If ethics clearance was not necessary, or if there was any deviation from these standard ethical requests, please state why it was not required. Please note that the editors may ask you to provide evidence of ethical approval. If you have approval from a National Drug Agency (or similar) please state this and provide details, this can be particularly useful when discussing the use of unlicensed drugs.

Patient's Privacy

The protection of a patient's right to privacy is essential. Please collect and keep copies of patients' consent forms on which patients or other subjects of your experiments clearly grant permission for the publication of photographs or other material that might identify them. If the consent form for your research did not specifically include this, please obtain it or remove the identifying material.

A statement to the effect that such consent had been obtained must be included in the 'Methods' section of your paper. If necessary the Editors may request a copy of any consent forms.

Data Reporting

The European Journal of Anaesthesiology adheres to the guidelines on adequate data reporting that were established by The Enhancing the QUALity and Transparency Of health Research (EQUATOR) network (<http://www.equator-network.org/home/>).

Financial Support and Competing Interests

A financial disclosure questionnaire must be completed by the corresponding author and all co-authors at initial submission. Co-authors will receive a link to complete the questionnaire via email. Please

ensure each co-author's email address is properly listed at the 'Add/Edit/Remove Authors' submission step in Editorial Manager, to avoid delays in reaching co-authors.

The primary purpose of the disclosure section is to determine whether authors have received any commercial financial support that could create a conflict of interest. In addition to monetary interests, a potential for conflict of interest can exist whether or not an individual believes that a relationship (such as dual commitments, competing interests, or competing loyalties) affects his or her scientific judgment. Please review ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals at the following link: <http://www.icmje.org/conflicts-of-interest>.

In addition to completing the financial disclosure questionnaire authors must clearly state all relevant conflicts of interest in the Acknowledgements section of the submitted manuscript.

Retractions

Porto Biomedical Journal is a member of the Committee on Publication Ethics (COPE), and also refers to the ICMJE advice on Scientific Misconduct, Expressions of Concern, and Retraction as well as on Overlapping Publications.

Article Types

Original *articles*

These should describe fully, but as concisely as feasible, the results of original clinical, laboratory or biomedical research. *Special note regarding case studies:* Case studies will be considered for publication only in the Letters to the Editor section of the Journal. The average Original Article fills 7 pages in the printed journal, although manuscripts that exceed this may be occasionally accepted for publication at the Editors' discretion. In general, an Original Article should not exceed 3500 words, not including the abstract, figure legends, and references. Abstracts should be 250 words or less. If possible, each figure legend should be held to 60 words or less. Each Original Article may be accompanied by no more than 8 graphic presentations (tables and/or figures)-for example, 3 tables + 5 figures. (Additional text, tables, or figures can be designated as "supplemental" material, which will be included in the PBJs Online Repository. Please note: Original Article manuscripts that are determined to significantly exceed these limits, or that do not include all of the elements listed below, may be returned to the authors for revision prior to review.

Letters to the Editor

Letters to the Editor are brief reports of clinical or laboratory observations, substantiated by controlled data but limited in scope, and without sufficient depth of investigation to qualify as Original Articles. These may include a brief description of a particular condition that provides insights into diagnosis and clinical management or images that impart important clinical information. Like Original Articles, these manuscripts are subject to peer review. A Letter to the Editor must:

- 1) Be brief. The average Letter to the Editor fills 2 pages in the printed journal, although manuscripts that exceed this may be occasionally accepted for publication at the Editors' discretion. In general, a Letter to the Editor should not exceed 1000 words, not including the figure legend(s) and references. If possible, the figure legend(s) should be held to 60 words or less. Please note: Letter to the Editor manuscripts that are determined to significantly exceed these limits may be returned to the authors for shortening prior to review.

- 2) Have a short, relevant title. Please see the suggestions that appear above (under "A. Original Articles").
- 3) Have a complete title page (see section A1).
- 4) Be accompanied by a short summary that encapsulates the report's findings for a clinically oriented audience (see above).
- 5) Begin with the salutation "To the Editor:"
- 6) Close with the author's name(s), academic degree(s), institutions(s), and location(s).
- 7) Have no more than nine references.
- 8) List the references as complete bibliographic citations following the closure of the letter (see section above for formatting).
- 9) Present lists of Key words, as relevant (see sections above).
- 10) Be limited to a total of 2 figures and/or tables. (Additional figures or tables may be placed in the article's Online Repository; please see the relevant section below.)

Correspondence and replies

Correspondence concerning recent publications in the Journal will be considered for publication and accepted based on their pertinence, their scientific quality, and available space in the Journal. If the correspondence is considered acceptable, a response will be requested from the authors of the referenced PBJ article. Upon review and approval by the Editor, the Correspondence and relevant Reply will both be published together. Both Correspondence and Reply manuscripts must:

- 1) Be no longer than 500 words.
- 2) Have a short, relevant title, distinct from the title of the referenced article. Please note that all Replies should have the title "Reply to [Corresponding author's name]."
- 3) Have a complete title page (see section above).
- 4) List the references as complete bibliographic citations at the end of the letter with the journal article being discussed as the first reference (see section above). The total number of references should be no more than seven. Replies should include the Correspondence to which they are replying as one of the references.
- 5) Have no more than one graphic presentation (table or figure). (See the section on Graphic Presentations below).
- 6) Begin with the salutation "To the Editor:" and close with the author's name(s), academic degree(s), institutions(s), and location(s).

Review

articles

Definitive, in-depth, state-of-the-art reviews of clinical and research subjects. Unsolicited reviews are not generally published in PBJ. Before submitting any unsolicited reviews, please forward an outline to the Editor for consideration. Systematic reviews and meta-analyses should follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see <http://www.prisma-statement.org/>). A PRISMA flow diagram (<http://www.prisma-statement.org/documents/PRISMA%202009%20flow%20diagram.pdf>) should be used to describe the steps of the systematic review, and a complete PRISMA checklist (<http://www.prisma-statement.org/documents/PRISMA%202009%20checklist.pdf>) should be used to ensure that all relevant information is included in the review.

statement.org/documents/PRISMA%202009%20checklist.pdf) should be provided during submission.

Clinical

Guidelines

Official recommendations from professional organizations on issues related to clinical practice and health care delivery. PBJ is most interested in publishing the primary guideline documents but will also consider synopses of guidelines when the primary document is published elsewhere. Synopses should focus on those issues of most relevance to generalist clinicians. Manuscripts must:

- 1) Have an equal or less than 275 words, structured abstract (use the following subheadings: Description, Methods and Recommendations)
- 2) Include the name of the responsible organization in the title and identify the article as a clinical guideline.
- 3) Primary Guideline Reports: PBJ is flexible with length, reference, and other format requirements given the variability in the format of guidelines developed by different organizations. However, if guidelines are lengthy (more than 4000 words), we may require the production of an executive summary document with the full document published as a digital-only appendix. A concise table or concise graphic summarizing the recommendations and other key points is desirable.

Guideline Synopses

Text of synopses include the following sections and subheads:

Rationale, Guideline Focus, Target Population, Guideline Development Process, Evidence Review and Grading, Comments and Modification, Clinical Recommendations, Research Recommendations, Applicability and Implementation Issues, and Summary. Guideline Group members followed by key references should be listed at the end.

Rostrum

articles

Opinion articles about subjects of particular interest and/or debate may be accepted for peer review after preliminary review by the Editor. Proposals for rostrum articles may be emailed to the Editorial Office; they will be evaluated based on level of interest, novelty, and the current needs of the Journal.

MANUSCRIPT PREPARATION AND FORMATTING INSTRUCTIONS

Manuscripts must be written in clear, grammatical English (see English Language Assistance above). Manuscripts not conforming to Journal format will be returned to authors for modification. Please double space the entire main body document and number each page. Do not add line numbers as the system will generate those when the PDF is built.

Title page, footnotes, abbreviations, and abstract pages must be included in the main body file. Please do not upload separate copies of these documents.

Acceptable document file types for text and tables include .DOC and .DOCX; do not submit a PDF.

Page 1:

Title Page. The following elements are required for every submission:

Title. Include a descriptive title of the work; the title should not be a sentence. No proprietary or brand names for drugs or agents may be used in article titles. Please, include the study design in the title; for instance, “randomised controlled trial”, or “systematic review”. Titles should be as informative and complete as possible.

Authors. The full first name, middle initials, and family name of each author, as well as the name(s) of the department(s) and institution(s) to which the work should be attributed.

Address for Correspondence. A current email and full mailing address for the corresponding author must be provided.

Page 2:

Abstract. Original articles should include a structured abstract of no more than 300 words using the following headings: Background; Methods; Results; and Conclusions. They should briefly describe, respectively, the problem being addressed in the study, how the study was performed, the salient results, and what the authors conclude from the results. Conventional non-systematic reviews should include an unstructured abstract of no more than 250 words.

Main Body: Introduction. The introduction contains a statement of the purpose of the work, the problem that stimulated it, and a brief summary of relevant published investigations.

Methods. Avoid detailed description of previously published methods and cite the appropriate reference. Include appropriate ethical and statistical information.

Results. The results should be concise, avoiding redundant tables and figures illustrating the same data.

Discussion. This section should follow the results and is used to interpret results, with minimal recapitulation of findings.

Acknowledgments: The acknowledgements section should be headed 'Acknowledgements relating to this article' and contain the following distinct statements in separate paragraphs:

- Assistance with the study. Acknowledgements should be made only to those who have made a substantial contribution to the study. Authors are responsible for obtaining written permission from people acknowledged by name in case readers infer their endorsement of data and conclusions. If there was no assistance state: 'Assistance with the study: none.'
- Financial support and sponsorship. You must make reference to all relevant sources of funding concerning this article. If there were no sources of funding please state: 'Financial support and sponsorship: none.'
- Conflicts of interest. You must make reference to all relevant conflicts of interest concerning this article including financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest. If there are no conflicts of interest please state: 'Conflicts of interest: none.'
- Presentation (for original articles only). Presentations of preliminary data at, for example, international meetings should be acknowledged separately. If preliminary data was not previously presented please state: Presentation: none.

References: Use the Vancouver reference system as adopted by the U.S. National Library of Medicine ensuring that all journal titles conform to Index Medicus approved abbreviations. Number references consecutively in the order in which they are first mentioned in the text. Identify references in the text, tables and legends using superscripted Arabic numerals that are placed after the punctuation. References cited only in tables or in legends to figures should be numbered in accordance with the sequence established by the first identification in the text of the particular table or illustration.

Avoid citing abstracts unless from a MEDLINE or EMBASE indexed journal. Unpublished observations and personal communications should not be used as references, although references to written (not verbal) communications may be inserted (in parentheses) in the text. Manuscripts that have been accepted but not yet published (e.g. Epub ahead of print) should be included in the list, followed by (in press). Information from manuscripts not yet accepted may be cited only in the text as (unpublished observations). Authors should verify references against the original documents before submitting the article.

Electronic or online references should be cited in the reference list only if the material referenced is a specific article (e.g. a paper published in a web-based journal); see below for correct style. Less specific references (e.g. the web pages of societies, organisations and university departments) should not appear in the references; instead the URL should be cited in full in the text.

Authors must confirm that the details of these references are accurate and complete. In the full list of references give the names and initials of all authors. If there are more than six, cite only the first three names followed by et al. The authors' names are followed by the title of the article: the title of the journal (*italics*) abbreviated according to the style of Index Medicus: the year of publication: the volume number (in **bold**): the first and last page numbers in full followed by a full stop. Titles of books should be followed by the town and country of publication, the publisher, the year and inclusive page numbers. See the following examples:

Journal articles:

Pollard BJ, Bryan A, Bennett D et al. Recovery after oral surgery with halothane, enflurane, isoflurane or propofol anaesthesia. *Br J Anaesth* 1994; 72:559–566.

Books:

Korttila K. Recovery period and discharge. In: White P, ed. *Outpatient Anaesthesia*. New York, USA: Churchill Livingstone Inc, 1990: 369–395.

Chapter in a book:

Pessayre D, Feldmann G, Haouzi D, Fau D, Moreau A, Neumann M. Hepatocyte apoptosis triggered by natural substances (cytokines, other endogenous molecules and foreign toxins). In Cameron RG, Feuer G (editors): *Apoptosis and its Modulation by Drugs*. Handbook of Experimental Pharmacology. Berlin: Springer-Verlag; 2000, pp. 59-108.

Electronic articles:

Margolis PA, Stevens R, Bordley WC, Stuart J. From concept to application: the impact of a community-wide intervention to improve the delivery of preventive services to children. *Pediatrics* [online serial] 2001; 108:e42.

<http://www.pediatrics.org/cgi/content/full/108/3/e42>. [Accessed 20 September 2001].

Tables: References to tables should be made in order of appearance in the text and should be in Arabic numerals in parentheses, e.g. (Table 1). Each table should be typed on a separate sheet in 1.5 spacing. Tables should not be submitted as photographs. Each table should have a brief title as a heading. Vertical rules should not be used. Place explanatory matter in footnotes, not in the heading. Authors are discouraged from using abbreviations in tables. If abbreviations are necessary then please explain

them in the table's footnotes. Be sure that each table is cited in the text. If you use data from another published or unpublished source, obtain permission and acknowledge the source fully.

Authors are encouraged to submit non-essential tables as supplemental digital content for publication online only. See Supplemental Digital Content section for more details.

Figures and Legends: Figures should be uploaded in the highest resolution available. Legends should be supplied for all figures. They are numbered to correspond with the figures and typed double-spaced on a separate page. Figure legends for any supplemental figures being submitted are to be provided separately; see section, Supplemental Digital Content (SDC).

Acceptable figure file formats

- Do not embed figures into the main body file
- All final digital figures for accepted manuscripts must be submitted in EPS, TIFF, JPG. PowerPoint PPT format is permitted when the image resolution is very high.
- Each figure must be uploaded as a separate file.
- Diagrams, drawings, graphs and other line art should be prepared at a resolution of 1200 DPI.
- Halftones images (black/white or color) should be prepared at a resolution of 300 DPI.
- Combination halftones (images containing both pictures and text labeling) should be prepared at 600 DPI.
- Your manuscript may be returned to you for correction if the images are of insufficient quality.
- If photographs of people are used, their identities must be obscured or their written consent to use the photograph must have been obtained. If necessary the Editors may request copies of any consent forms.
- If a figure has been published before, the original source must be acknowledged and written permission from the copyright holder for both print and electronic formats should be submitted with the material. Permission is required regardless of authorship or publisher, except for documents in the public domain.
- Figures may be reduced, cropped or deleted at the discretion of the editor.

Artwork submitted to the Journal will be checked for quality. Authors submitting a revised paper will have the opportunity to check the quality of their images and make the necessary changes. This step is required for all revisions.

Supplemental Digital Content (SDC): Authors may submit Supplemental Digital Content to supplement the information provided in the manuscript. It is preferable to include all significant figures and tables in the manuscript, since there is not a limit on the number of items in this online journal. Nonetheless, SDC may include the following types of content: text, tables, figures, references peripheral to information provided as SDC, audio, and video. SDC should be consecutively cited in the Main Body text of the submitted manuscript. SDC files will be available via URL(s) placed at the citation points within the article and are not copyedited by the publisher. Note that Journal policies for manuscript submission relating to peer review, patient anonymity, ethics, financial disclosure, copyright, and permissions also apply to SDC. Authors should mask patients' eyes and remove patients' names from supplemental digital content unless they obtain written consent from the patients and submit them as supplemental files at the time of the manuscript submission. See also Case Study Reports, above.

Format, File Type and Size Requirements: SDC must be provided in one Word or PowerPoint file. Each SDC in the file should have a visual header in the following name format (e.g., "SDC, Figure 1"; "SDC, Materials and Methods") and a corresponding citation must appear in the Main Body text. Note that SDC is numbered separately from non-SDC material. If providing SDC figure(s), a figure legend should be included on the figure itself. When uploading SDC select "Supplemental Digital Content" as the file designation. For audio and video files, also include the author name, videographer, participants, length (minutes), and size (MB). Video files should be formatted with a 320x240 pixel minimum screen size. For each submission, the SDC file cannot exceed a total size of 10 MB.

ONLINE

MANUSCRIPT

SUBMISSION

New

Submissions

Once the manuscript has been created, visit the submission site at www.editorialmanager.com/pbj to upload the manuscript. Once the manuscript has been vetted for compliance to the Journal's requirements, a manuscript number will be assigned to the submission. Failure to adhere to these guidelines will result in your manuscript being returned to you for correction. Faxed, scanned or emailed copies of manuscripts will not be accepted.

Mandatory License to Publish Forms

Upon first revision, authors will be required to complete a License to Publish (LTP) form. Authors can also provide these at the original submission stage. LTP forms may be signed by the Corresponding Author on behalf of all authors. Authors retain copyright for all articles. Authors grant the journal a license to publish the article and identify itself as the original publisher. Manuscripts will not pass to production without completed forms. LTP forms are available from the submission site homepage www.editorialmanager.com/pbj.

Article Processing Charges

This is an open access journal: all articles will be immediately and permanently free for everyone to read and download. *Porto Biomedical Journal* does not charge authors for Open Access publishing.

Creative Commons license

Open access articles will be freely available to read, download and share from the time of publication. Articles are published under the terms of the Creative Commons License Attribution-NonCommercial No Derivative 4.0 which allows readers to disseminate and reuse the article, as well as share and reuse of the scientific material. It does not permit commercial exploitation or the creation of derivative works without specific permission. To view a copy of this license visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

Compliance with NIH and other research funding agency accessibility requirements

A number of research funding agencies now require or request authors to submit the post-print (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. As a service to our authors, Wolters Kluwer identifies to the National Library of Medicine (NLM) articles that require deposit and transmits the post-print of an article based on research funded in whole or in part by the National Institutes of Health, Howard Hughes Medical Institute, or other funding agencies to PubMed Central. The License to Publish provides the

mechanism. Wolters Kluwer ensures that authors can fully comply with the public access requirements of major funding bodies worldwide.

Authors funded by RCUK, Wellcome Trust, Austrian Science Fund (FWF), or World Health Organization (WHO) must sign a license giving the publisher the right to publish the article. The authors retain copyright but anyone may reuse the article and create derivatives, even for commercial purposes, with proper attribution to *Porto Biomedical Journal* as the original publisher. Authors will be required to publish, as per the RCUK mandate and the Wellcome Trust, FWF, and WHO policies, under the Creative Commons: Attribution (CC-BY) License.