The American Journal of Surgery 220 (2020) 1225–1229

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Evaluation of breast surgical oncology complications after single agent versus dual agent HER2 targeted neoadjuvant chemotherapy

Melissa E. Cullom [a], Amanda L. Amin, MD [b], Christa R. Balanoff, MD [b], Jamie L. Wagner, DO [b], Kelsey E. Larson, MD [b, *]

[a] School of Medicine, University of Kansas, Kansas City, KS, USA
[b] Department of General Surgery, University of Kansas, Kansas City, KS, USA

ARTICLE INFO

Article history:
Received 15 February 2020
Received in revised form
23 April 2020
Accepted 25 June 2020

Keywords:
Breast cancer
Surgical Complications
Neoadjuvant chemotherapy
HER2

ABSTRACT

Background: The aim of this study was to determine whether differing neoadjuvant chemotherapy (NAC) regimens for HER2 positive breast cancer (HER2+ BC) are associated with differing surgical complications. Our goal was to evaluate postoperative complications in HER2+ BC patients receiving NAC with Herceptin (trastuzumab, H) alone versus in combination with pertuzumab (HP).
Methods: Retrospective chart review was performed of patients with Stage I-III HER2+ BC receiving NAC from 2007 to 2016. Demographics, tumor characteristics, surgical procedure, and 60-day postoperative complications were analyzed.
Results: H (n = 101) and HP (n = 132) were similar with respect to tumor characteristics and surgical procedure. Overall operative complications were similar between groups (p = 0.63), as were major versus minor complications (p = 1.0). Subgroup analysis identified a higher rate of complications for lumpectomy patients receiving HP versus H (p = 0.003).
Conclusions: Neoadjuvant chemotherapy with HP is associated with increased complications after lumpectomy. Additional studies are warranted to assess causative factors for this observation.

Introduction

HER2 positive breast cancers (HER2+ BC) historically were associated with poor prognosis and survival before the advent of appropriate systemic medications.[1,2] However the availability of HER2-targeted chemotherapy regimens containing trastuzumab (Herceptin, H) and/or pertuzumab (Perjeta, P) in combination with chemotherapy has significantly improved clinical outcomes in patients with HER2+ BC.[3–5] Herceptin and pertuzumab are recombinant monoclonal antibodies that target different extracellular regions of the HER2 tyrosine kinase receptor, which when combined synergistically inhibit the survival of breast cancer cells through the HER2 oncogenic pathway.[6] In general, chemotherapy regimens with dual HER2 targeted therapy (Herceptin pertuzumab, HP) are associated with longer progression-free and overall survival than single agent (Herceptin H) regimens.[7] Thus, HP-based chemotherapy regimens are commonly used in current practice, particularly in the neoadjuvant setting.

Despite excellent studies detailing overall oncologic outcomes for H and HP regimens, minimal data on surgical outcomes following neoadjuvant use of these regimens exists. A single prior study comparing HER2 targeted regimens and surgical outcomes demonstrated a significant increase in postoperative wound breakdown for patients treated with HP.[8] However this study is limited to patients undergoing post-mastectomy reconstruction and thus may not be applicable to other types of breast cancer operations.

With the limitations in previously published data in mind, the goal of this study was to compare postoperative complications in women with stage I-III HER2+ BC who received H versus HP neoadjuvant regimens and underwent any breast cancer operation.

Materials and methods

A retrospective review was performed to identify women 18–90 years old diagnosed with stage I-III HER2+ breast cancer who underwent both neoadjuvant chemotherapy and subsequent breast surgery at a single academic center between 2007 and 2016.

* Corresponding author. 4000, Cambridge Street Mail Stop 2005, Kansas City, KS, 66160, USA.
E-mail address: klarson6@kumc.edu (K.E. Larson).

https://doi.org/10.1016/j.amjsurg.2020.06.053
0002-9610/

Patients were identified via the tumor registry and electronic medical record query. Patients with recurrent disease were excluded. All patients received the HER2 targeted agent as part of a chemotherapy regimen. Patients receiving HER2 targeted agents alone were excluded. All patients were taken to surgery within 4–6 week timeframe after last chemotherapy, but targeted HER-2 therapy continued throughout this time as per the national standard of care.

Patient demographics, pertinent medical history, tumor characteristics and operative intervention and postoperative complications were analyzed. Receipt of radiation in the adjuvant setting was also recorded as it commonly starts in the postoperative timeframe. Breast surgery was identified as lumpectomy (including local tissue rearrangement for cavity closure), lumpectomy with reconstruction (formal oncoplastic reduction or mastopexy), mastectomy (simple), or mastectomy with reconstruction (skin- or nipple-sparing, tissue expander or implant). No patients underwent immediate autologous reconstruction as this is not routinely offered upfront at our institution for patients with an invasive cancer diagnosis. Lumpectomy and mastectomy patients receive standard pre-incision antibiotics but are not discharged on antibiotics. Mastectomy patients with implant-based reconstruction are discharged with 10 days of postoperative antibiotics.

The primary study outcome was surgical complication rate including hematoma, seroma requiring aspiration, infection requiring intravenous (IV) or by mouth (PO) antibiotic administration, reconstruction loss, skin or nipple necrosis, wound dehiscence, and mortality. Complications were divided into major and minor complications for the purposes of analysis. Major complications included hematoma requiring operative (OR) intervention, infection requiring IV antibiotic administration, loss of reconstruction, wound dehiscence, and any ischemia or necrosis. Minor complications included hematoma managed with observation, PO antibiotic administration, and seroma requiring aspiration. Mortality was defined as death within 60 days of the operation. All post-operative complications were assessed within 60 days from the date of surgery as later complications (such as loss of reconstruction) can sometimes occur past the initial 30-day timeframe. Patients having multiple complications were counted in each category for data collection and analysis.

Patients were categorized into two groups according to neoadjuvant chemotherapy regimen: single agent HER2 targeted regimen (H group) versus dual agent HER2 regimen (HP group). Demographics were summarized using counts and percentages or mean and standard deviation where appropriate. Groups were compared using chi-squared analysis with p-value <0.05 considered statistically significant. Complication rates were compared using univariate analysis.

Results

Patient characteristics

A total of 233 patients were included with 101 patients (43%) in the H group and 132 patients (56%) in the HP group. The mean age was 53 years (range 24–86 years). The majority of patients had ER positive (66.1%), PR positive (65.7%) cancer. More patients underwent mastectomy than lumpectomy (71.2% versus 28.8% respectively). Overall 24.5% (n = 50) of patients experienced a complication, 4.3% after lumpectomy and 17.2% after mastectomy.

Groups were similar with respect to baseline demographics and tumor characteristics (Table 1). The average tumor size was 3.1 ± 1.0 cm and did not differ between groups (p = 0.09). While H and HP groups did differ by T-stage distribution (p = 0.003), T1 and T2 were most common throughout. There was no statistically significant difference in clinical N stage (p = 0.22), ER positive status (p = 0.67) or PR positive status (p = 0.57). In addition, there was no significant difference in risk factors for postoperative complications, specifically smoking, diabetes, or the use of an anticoagulant in the perioperative timeframe.

Surgical characteristics

The groups were also similar with respect to their surgical treatment (Table 2). Specifically, there was no significant difference in rates of mastectomy versus lumpectomy between H and HP groups (p = 0.38). Only one patient underwent lumpectomy with reduction, and thus separate analysis could not be performed for this surgical subtype. When considering mastectomy patients, there was no difference in patients undergoing mastectomy with or without reconstruction (p = 0.11) or in laterality (unilateral versus bilateral) (p = 0.87) between H and HP groups.

Post-operative complications

A total of 50 patients out of 233 experienced complications (21.5%). Half of these (n = 26) had multiple complications (range 2–5).Specific types of complications included 24 seromas (10.3%), 24 infections requiring IV antibiotics (2.1%) or oral antibiotics (8.2%), 8 loss of implant or expander (3.4%), 15 skin flap necrosis (6.4%) and 2 delayed wound healing (0.9%). 32 out of 233 patients experienced a major complication (13.7%) and 44 out of 233 patients experienced a minor complication (18.9%). Complications are detailed in Table 3.

The complication rates for H and HP patients were 19.8% and 22.7% respectively, and therefore overall the rate of complications between the cohorts was not statistically significant (p = 0.63). The rate of multiple complications also did not differ between H and HP cohorts (p = 0.77). However, the distribution of cases for which complications occurred did differ. Among patients undergoing lumpectomy, complication rates were significantly higher in the HP group (n = 9, 34.6% of lumpectomies) versus the H group (n = 1, 2.3% of lumpectomies) (p = 0.03). These complications were primarily seroma and PO antibiotic use (H seroma n = 1; HP seroma n = 7, PO antibiotics n = 2). The rate of complications for mastectomy did not differ between H and HP groups (p = 0.85), nor did the rate of major (p = 0.83) versus minor (p = 0.73) complications. There was no statistically significant difference in types of complications. Although there were no statistically significant differences in specific types of complications between H and HP cohorts, the HP cohort trended towards increased necrosis (10 patients compared to 5 patients, p = 0.59) and increased wound dehiscence (2 patients compared to 0, p = 0.50). Seroma, infection requiring PO antibiotics, and necrosis were the most common in both groups. In those 50 patients who experienced post-operative complications, potential contributing risk factors (diabetes, smoking, anticoagulation) were similarly distributed between H & HP cohorts.

Discussion

In our cohort, there was not an overall increased rate of complications for breast surgery patients following neoadjuvant chemotherapy when analyzing based on HER2 regimen. However, the lumpectomy subgroup did differ with respect to complications, with the HP group having a higher complication rate.

A single prior publication assessed the impact of HER2 neoadjuvant regimen on surgical outcomes. In 2017, Shammas et al. compared postoperative complications following mastectomy with breast reconstruction in both HER2 negative and HER2+ patients.[8] In their study, HP patients had increased rates of postoperative

Table 1
Patient demographics and tumor characteristics.

Characteristic	All Patients (n = 233)	H (n = 101)	HP (n = 132)	p-values*
Age (mean)	53	54	52	0.22
Race				0.67
Asian	1 (0.4%)	0 (0%)	1 (0.6%)	
African American	19 (8.1%)	9 (8.9%)	10 (7.5%)	
Caucasian	159 (68.2%)	65 (64.4%)	94 (7.1%)	
Unknown	54 (23.1%)	27 (26.7%)	27 (20.4%)	
Insurance				0.05*
Medicaid	3 (1.3%)	0 (0%)	3 (2.3%)	
Medicare	69 (29.6%)	34 (33.7%)	35 (26.5%)	
Private	157 67.4%)	65 (64.4%)	92 (69.7%)	
Unknown	4 (1.7%)	2 (1.9%)	2 (1.5%)	
Primary Tumor Size (mean ± standard deviation, in cm)	3.1 ± 1.0	3.3 ± 2.4	2.9 ± 1.2	0.09
T Stage				0.003*
T1	72 (30.9%)	39 (38.6%)	33 (25.0%)	
T2	114 (48.9%)	36 (35.6%)	78 (59.1%)	
T3	37 (15.9%)	19 (18.8%)	18 (13.6%)	
T4	10 (4.3%)	7 (7.0%)	3 (2.3%)	
N Stage				0.22
N0	129 (55.4%)	51 (50.5%)	78 (59.1%)	
N1	85 (36.5%)	42 (41.6%)	43 (32.5%)	
N2	8 (3.4%)	5 (5.0%)	3 (2.3%)	
N3	11 (4.7%)	3 (2.9%)	8 (6.1%)	
ER+	154 (66.1%)	65 (64.3%)	89 (67.4%)	0.67
PR+	153 (65.6%)	64 (63.4%)	89 (67.4%)	0.57
Smoker	10 (4.5%)	7 (6.9%)	3 (2.3%)	0.71
DM	16 (6.7%)	10 (9.9%)	6 (4.5%)	0.24
Anticoagulation	27 (11.6%)	15 (14.9%)	12 (9.1%)	0.08

*p-values compare H (Herceptin, single agent) versus HP (Herceptin pertuzumab, dual agent) groups. $p < 0.05$ statistically significant.

complications, but their data is limited to a specific operative intervention. Our study contributes to current literature with the inclusion of patients undergoing differing types of breast surgery. This is important because HP lumpectomy patients were noted to have higher surgical complication rates in our analysis, indicating an additional potentially at-risk population not previously identified.

The reasons for increased complications specifically in HP lumpectomy patients are not clear. Assessing causative factors was not the goal of this project, but certainly collection and consideration of potential risk factors was important. Both H and HP groups were similar in terms of demographics and assessed risk factors. Diabetes and anticoagulation are well defined risk factors for complications, and while there was a trend toward differences in the two groups, these were not statistically significant. In terms of treatment characteristics which may increase risk of complications, tumor burden, type and extent of surgery, reconstruction, and adjuvant radiation are potentially associated factors so were specifically collected for our cohort. The difference between H and HP regimens reflects changes over time, not differences in cancer burden as demonstrated in similar tumor size and N stage between groups. Tumor size also corrects to volume of tissue removed, which could increase surgical risk, but again groups were similar with respect to tumor size. Gross specimen measurements were not analyzed specifically for the purposes of this study but could be considered in future projects. Adjuvant radiation certainly has been associated with complications, so analysis included adjuvant radiation given patients would have started treatment within 60 days postoperatively based on standard timing. While our study does include a similarly large overall patient sample compared to the prior publication (233 versus 214 patients), each individual operative subtype has relatively smaller numbers. This may also be one reason why an association between neoadjuvant regimen and complications was not identified in mastectomy patients in our cohort, since the numbers for this subgroup are smaller than in the previously reported cohort.

Previous medical intermediate and long-term studies have demonstrated that Herceptin is associated with side effects such as cardiotoxicity and lung injury, and may be associated with an increased incidence of thrombotic events.[9–11] These complications are not expected in the immediate postoperative timeframe based on prior data and indeed were not identified in our patients within 60 days of surgery. Pertuzumab has been associated with an increased incidence of infection, rash, pruritis, and skin and nail infections during treatment.[12,13] While patients in both H and HP groups did experience postoperative infections, rates and severity (as judged by IV versus PO antibiotic administration) were not increased for patients receiving dual HER2 agent regimens. Thus patients with HP regimens should not be considered higher risk for

Table 2
Surgical characteristics.

	All Patients (n = 233)	H (n = 101)	HP (n = 132)	p-values*
Lumpectomy	67 (28.8%)	26 (25.7%)	41 (31.1%)	0.38
Mastectomy				0.11
with Reconstruction	124 (53.2%)	61 (60.4%)	63 (47.7%)	
without Reconstruction	42 (18.0%)	14 (13.9%)	28 (21.2%)	
Mastectomy Laterality				0.87
Unilateral	59 (35.5%)	26 (34.6%)	33 (36.3%)	
Bilateral	107 (64.5%)	49 (65.3%)	58 (63.7%)	

*p-values compare H (Herceptin, single agent) versus HP (Herceptin pertuzumab, dual agent) groups. $P < 0.05$ statistically significant.

Table 3
Post-operative complications.

	All Patients (n = 233)	H (n = 101)	HP (n = 132)	p-values*
Any complication	50 (21.5%)	20 (19.8%)	30 (22.7%)	0.63
Multiple Complications	26 (11.1%)	11 (55.0%)	15 (50.0%)	0.77
Surgery				0.03*
Lumpectomy	10 (20.0%)	1 (5.0%)	9 (30%)	
Mastectomy	40 (80.0%)	19 (95.0%)	21 (70%)	
Major complications	32 (64.0%)	13 (65.0%)	19 (63.3%)	0.83
Hematoma (OR)	2 (4.0%)	2 (10.0%)	0 (0%)	0.19
IV Antibiotics	5 (10.0%)	2 (10.0%)	3 (10.0%)	1.0
Loss of Reconstruction	8 (16.0%)	4 (20.0%)	4 (13.3%)	0.73
Necrosis	15 (30.0%)	5 (25.0%)	10 (33.3%)	0.59
Wound Dehiscence	2 (4.0%)	0 (0%)	2 (6.7%)	0.50
Minor complications	44 (88.0%)	18 (90.0%)	26 (86.6%)	0.73
Hematoma (Observation)	1 (2.0%)	1 (5.0%)	0 (0%)	0.43
Seroma	24 (48.0%)	9 (45.0%)	15 (50.0%)	0.65
PO Antibiotics	19 (38.0%)	8 (40.0%)	11 (36.7%)	1.0
Mortality	0	0	0	1.0
Risk Factors				
Smoking	1 (2.0%)	1 (5.0%)	0 (0%)	0.43
Diabetes	7 (14.0%)	5 (25.0%)	2 (6.7%)	0.24
Anticoagulation	6 (12.0%)	5 (25.0%)	1 (3.3%)	0.08

*p-values compare H (Herceptin, single agent) versus HP (Herceptin pertuzumab, dual agent) groups. $P < 0.05$ statistically significant.

infection in the postoperative period based on our data.

Interestingly, our HP cohort trended towards increased necrosis and wound dehiscence, which are the specific complications identified by Shammas et al. in their HP group. Their study evaluated women receiving chemotherapy and post-mastectomy reconstruction who received either targeted HER-2 therapy with trastuzumab and/or pertuzumab within 6 weeks before reconstruction versus patients who did not receive HER-2 therapy and assessed post-operative complications in order to determine if targeted HER-2 therapy is associated with breast reconstructive outcomes. Their results showed that 22% of patients who received HP experienced wound breakdown requiring operative intervention as compared to 9% in those who received no targeted HER-2 therapy ($p = 0.07$). Unfortunately detailed report of adjuvant factors such as receipt of radiation was not reported. They concluded that HP prior to post-mastectomy breast reconstruction was independently associated with an increased risk of wound breakdown requiring operative intervention as compared to those not undergoing targeted HER-2 therapy.[8] It is interesting that in both their cohort and our currently reported cohort, HP cohort complications trended towards wound breakdown.

There is a potential theoretical explanation for this clinical observation. Epidermal growth factor receptor (EGFR) plays a vital role in wound healing, and prior publications have documented that pertuzumab downregulates EGFR with a differing molecular mechanism when combined with Herceptin than when utilized alone.[14–16] These studies have been performed in the basic science setting, so applicability to patients is not proven. However, based on this basic science data the addition of pertuzumab to a neoadjuvant chemotherapy regimen may have a negative impact on healing, resulting in increased wound breakdown and necrosis. Prior clinical studies examining the side effects of pertuzumab alone did not comment on significant adverse effects on healing, but it is unclear if an association between HER2 regimen and surgical complications was not seen versus not assessed in these prior studies.[7,17,18] Since these studies focus on patients in the metastatic setting who would be unlikely to have primary site surgery, most likely these studies did not have data on surgical complications. H alone may also negatively impact wound healing independently of pertuzumab. It is known that the HER2 protein is found in the epidermis and plays key function in epithelial cells,[19] and therefore there has been concern whether suppression of HER with single targeted HER2 therapy such as Herceptin impacts the integrity of the skin, including healing. Thus the combination of multiple HER2 targeted medications with differing mechanisms of action may explain the higher risk of wound breakdown in the HP cohort, understanding a risk still exists in the H cohort as well. Additional translational and clinical studies would help to clarify this potential basic science explanation with respect to clinical outcomes.

Our study is limited by its retrospective nature based on availability of tumor registry and electronic medical record data. While the assessed demographics, tumor characteristics and risk factors were well matched between H and HP groups, it is certainly possible that non-identified factors may have differed. Second our goal was to answer the question of whether or not there was an association between regimen and complications, not to assess the potential cause for any association. Additional basic science and clinical work to identify possible causative factors is required. Specifically larger patient numbers would increase the power of the results, potentially leading to opportunities for subgroup analysis such as evaluation based on type of breast operation and helping to delineate the impact of trending but not statistically significant factors such as diabetes and anticoagulation use. Also, our study was performed at a single institution, and therefore may not apply to all surgical practices and patient populations. However, the fact that our publication is the second to identify an association between HP neoadjuvant chemotherapy regimen and surgical complications indicates this question warrants further investigation.

When counseling women on surgical risk following neoadjuvant chemotherapy, it is important to take HER2 regimen into consideration. We do not advocate for a change in neoadjuvant chemotherapy regimen based on these results particularly given the improvement in progression free and overall survival with dual agent regimens.[7] Our data does not show a difference in overall complication rates between patients who undergo breast surgery following H versus HP neoadjuvant chemotherapy regimens. It does confirm surgical complications are increased in lumpectomy patients receiving dual agent versus single agent HER2 targeted neoadjuvant chemotherapy regimens. More studies are needed to delineate the observed association between neoadjuvant HER2 regimen and surgical risk for the purposes of improved informed consent and decision making at the time of surgery.

Conclusion

There is no statistical difference in overall surgical complication rates between patients who receive neoadjuvant chemotherapy with H versus HP regimens. However, in the subgroup of lumpectomy patients, a higher complication rate was seen in those individuals receiving HP, in agreement with previously reported data from a differing institution and patient population. Additional studies are warranted to evaluate the observed association between dual HER2 targeted neoadjuvant chemotherapy regimens and surgical complications in breast cancer patients.

Declaration of competing interest

The authors have no relevant conflicts of interest to disclose.

Acknowledgement

The authors thank Holly R. Zink, MSA of the Department of Surgery, University of Kansas, Kansas City, KS, for providing medical writing and editorial support for this research.

References

1. Press MF, et al. HER-2/neu gene amplification characterized by fluorescence in situ hybridization: poor prognosis in node-negative breast carcinomas. *J Clin Oncol*. 1997;15(8):2894–2904.
2. Slamon DJ, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*. 1987;235(4785):177–182.
3. Amiri-Kordestani L, et al. First FDA approval of neoadjuvant therapy for breast cancer: pertuzumab for the treatment of patients with HER2-positive breast cancer. *Clin Canc Res*. 2014;20(21):5359–5364.
4. Bullock K, Blackwell K. Clinical efficacy of taxane-trastuzumab combination regimens for HER-2-positive metastatic breast cancer. *Oncol*. 2008;13(5):515–525.
5. Gianni L, et al. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet Oncol*. 2014;15(6):640–647.
6. Nahta R, Hung MC, Esteva FJ. The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells. *Canc Res*. 2004;64(7):2343–2346.
7. Swain SM, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015;372(8):724–734.
8. Shammas RL, et al. Association between targeted HER-2 therapy and breast reconstruction outcomes: a propensity score-matched analysis. *J Am Coll Surg*. 2017;225(6):731–739 e1.
9. Iams W, et al. Thrombotic microangiopathy during docetaxel, trastuzumab, and carboplatin chemotherapy for early-stage HER2+ breast cancer: a case report. *Med Oncol*. 2013;30(2):568.
10. Keefe DL. Trastuzumab-associated cardiotoxicity. *Cancer*. 2002;95(7):1592–1600.
11. Siau K, Varughese M. Thrombotic microangiopathy following docetaxel and trastuzumab chemotherapy: a case report. *Med Oncol*. 2010;27(4):1057–1059.
12. Drucker AM, et al. Risk of rash with the anti-HER2 dimerization antibody pertuzumab: a meta-analysis. *Breast Canc Res Treat*. 2012;135(2):347–354.
13. Mortimer J, et al. Skin/nail infections with the addition of pertuzumab to trastuzumab-based chemotherapy. *Breast Canc Res Treat*. 2014;148(3):563–570.
14. Hughes JB, et al. Pertuzumab increases epidermal growth factor receptor down-regulation by counteracting epidermal growth factor receptor-ErbB2 heterodimerization. *Mol Canc Therapeut*. 2009;8(7):1885–1892.
15. Repertinger SK, et al. EGFR enhances early healing after cutaneous incisional wounding. *J Invest Dermatol*. 2004;123(5):982–989.
16. Nami B, Maadi H, Wang Z. The effects of pertuzumab and its combination with trastuzumab on HER2 homodimerization and phosphorylation. *Cancers*. 2019;11(3).
17. Baselga J, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366(2):109–119.
18. Tiwari SR, et al. Retrospective study of the efficacy and safety of neoadjuvant docetaxel, carboplatin, trastuzumab/pertuzumab (TCH-P) in nonmetastatic HER2-positive breast cancer. *Breast Canc Res Treat*. 2016;158(1):189–193.
19. Wernick Brian, Stawicki Stanislaw P. *"Impaired Wound Healing." StatPearls*. StatPearls Publishing; 2020.