Efficacy of Scaffold Mediated Localized Chemotherapy in Cancer: A Systematic Review

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Abstract:

Aim: To assess the efficacy of scaffold mediated localized chemotherapy in cancer.

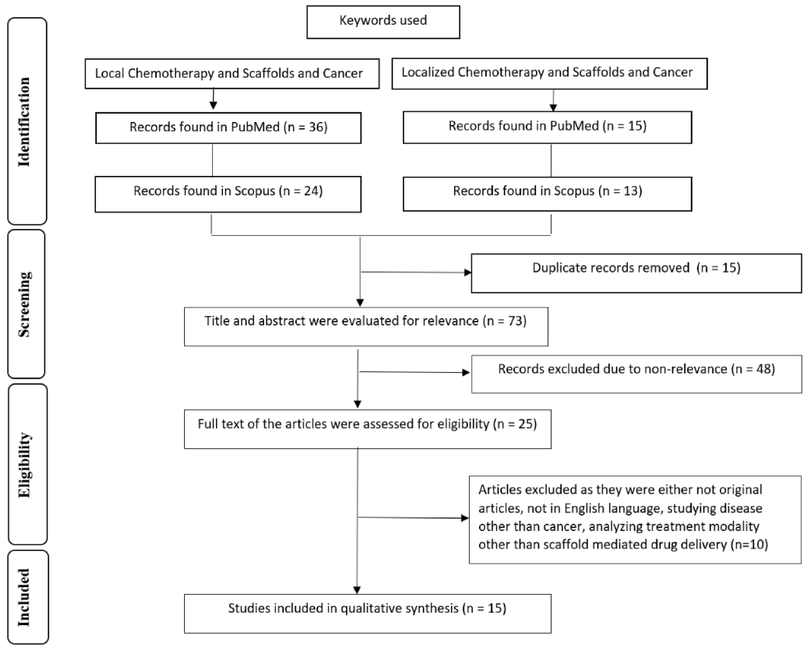
Materials and Methods: PubMed, Cochrane Library, and SCOPUS databses were searched for articles reporting the use of scaffold mediated localized drug delivery in cancer. Essential data including scaffold fabrication material and methods, the drug dosage and release duration, its effect on the cancer cells were extracted.

Results: 15 articles out of 60 screened, fulfilled the eligibility criteria. Among the 15 studies, 5 studies included only cell lines and 2 studies were only on mouse models while 8 studies involved a combination of cell lines and mouse models. The scaffold materials ranged from synthetic polymers such as poly-lactide, polycaprolactone, etc to natural scaffolds including d-periosteum, human micro-fragmented adipose tissue, etc.

Conclusion: Studies differed with respect to a wide number of variables ranging from the type of scaffold material used, the fabrication procedure, the nature of the drug used, and the tools used to assess the effect of the scaffold mediated drug on cancer. Due to these variables, it was not possible to make any direct comparison of the efficacy of therapeutic strategy used in each of these studies. Irrespective of the differences, a common consensus in all the included studies was that scaffold mediated localized drug delivery effectively reduced the cancer cell viability by increasing the bioavailability of the drug to the target tissue, while its localized effect reduces the risk of systemic toxicity.

Keywords: Cancer, chemotherapy, scaffold

Workflow



Conclusion:

Irrespective of the drugs, scaffold materials and assessment tools used, scaffold mediated localized delivery of chemotherapeutics is a potentially exciting method for drug delivery to solid tumours with the aim of preventing or minimising adverse systemic toxicity. However, scaffold placement and other variables discussed in this paper mean that the introduction of this potential method of chemotherapy is dependent on further research and appropriately designed, prospective clinical trials

Summary of studies

S.no	First author name / Year/ Country	Type of study	Scaffold material/Drug incorporated/Cancer type studies	Study groups	Scaffold mediated drug release duration/dosage	Effect of the scaffold mediated drug on the cancer	Inference/Potential limitations
1	Olga Maria Will/2016/Germany	In-vitro cell line and in-vivo mouse model study	Scaffold: Electrospun nanofibers generated from poly(d,l-lactide-co-glycolide) polymer Drug: Diclofenac Cell Lines: SCC-9	Mouse with SCC-9 cancer was divided into 4 groups: Group 1: no treatment Group 2: implanted scaffolds without diclofenac Group 3: implanted scaffolds loaded with diclofenac Group 4: diclofenac was given orally	Drug release duration: 7 weeks Drug dosage released: 219.8±18.5 (in-vivo); 234.6±17.7 (in-vitro)/or 77.5% (in vivo); 82.7% (in vitro)	7-week survival rate: Group 1- 25%; Group 2- 10%; Group 3- 89%; Group 4- 10% Group 3 recurrence tumor weight was * lower than other groups Ki-67 immunostaining was * lower in group 3 than other groups Caspase 3 immunostaining was the same in all groups	Group 3 showed * greater survival rate and tumor inhibition than other groups/ The limitation was that the in vitro drug release was higher than in-vivo which in turn could have reduced the inhibitory effect on the cancer in-vivo
2.	Maximiliano L. Cacicedo/2016/Argentina	In-vitro cell line	Scaffold: Bacterial (natural) Cellulose-Alginate (BC-Alg) Drug: Doxorubicin (Dox) Cell Lines: H29 Human colorectal adenocarcinoma	Group 1: Soluble free drug in µM (100,150,200) Group 2: Scaffold without drug Group 3: Scaffold with drug 9.55±1.87µmol/gm Group 4: Scaffolds with drug 42.25±3.15 µmol/gm	Drug release duration: 48 hrs max. Drug dosage released: Group 3: 76±5(24hr), 169±5(48hr) Group 4: 77±5(24hr), 181.0±8(48hr)	Cell Viability % at 24 and 48 hrs Group 2: 103±3.1 and 97.4±2.1 Group 3: 59±7.2 and 55±8.2 Group 4: 53±1.6 and 37±0.5	Anti-cancer effect with Dox loaded into BC-Alg films was more prominent than free drug. BC-Alg formulation, drug loading quantities and release kinetic conditions can modulate cytotoxic effect of Dox.
3.	Chuan Chen/2018/China	In-vitro cell line	Scaffold: D – periosteum (natural) Drug: Adriamycin (ADM) Cell Lines: Human Osteosarcoma Cells (HOSs)	Group 1: Control group (medium alone) Group 2: adriamycin free drug Group 3: adriamycin gelatin microspheres (ADM-GMS) Group 4: ADM-GMS D-periosteum Group 5: adriamycin poly (dl-lactide-coglycolide) gelatin microspheres (ADM-PLGA-GMS) Group 6: ADM-PLGA-GMS- D-periosteum Group 7: GMS-D Periosteum	Drug release duration: Maximum of 10 hrs Drug dosage released: Group 2: Released within 1 hr Group 3: Cumulative release of 80% within 10hr Group 4: Cumulative release within 10hr approx. same as group 3 Group 5: the cumulative release of 80% in 48 hrs Group 6: the cumulative release of 76.6% in 48 hrs	The CCK-8 cell counting test Group 2: more HOSs were killed in 2hr and 12hr, with the inhibition rate of 42%, which was higher than those in other groups At 24hr, Group 5 and 6 showed a higher rate of inhibition than other groups Groups 3 and 4 Vs Groups 5 and 6 showed similar cell inhibition rates, respectively at all three-time points	D-periosteum scaffold crosslinked with drug-loaded microspheres showed high porosity slow release of ADM inhibiting HOS cancer cells. Future osteosarcoma animal model studies will be required to investigate the potential of drug-loaded D-periosteum against osteosarcoma and supporting local bone tissue regeneration
4.	Hassan Mellatyar/2018/Iran	In vitro Cell Lines	Scaffold: Poly(caprolactone)–poly(ethylene glycol) (PCL/PEG) (Electrospinning) Drug: 17-dimethylaminoethylamino-17-demethoxy geldanamycin (17-DMAG)/ Cell Lines: AS49 lung cancer cells	Group 1: untreated cells Group 2: Cells treated with free drug Group 3: Cells treated with blank scaffolds Group 4: Cells treated with drug-loaded scaffolds	Drug release duration: 7 hrs max. Drug dosage released: 50 – 95% drug is released from 2-6 hrs 96% of the drug was released in 7 hrs	Expression of HSP90 mRNA Group 2: expression levels reduced to about 13, 32, and 48% after 24, 48 and 72h, respectively Group 4: Expression levels reduced to about 39, 57, and 79% after 24, 48 and 72h, respectively Telomerase activity Group 2: The activity was reduced to 31, 51, and 71% after 24, 48 and 72h, respectively. Group 4: Reduced telomerase activity of the cells to about 54, 66, and 83% after 24, 48 and 72h, respectively.	17-DMAG-loaded PCL/PEG nanofibers had more inhibitory effect on cell proliferation, HSP90 mRNA expression, and telomerase activity than free 17-DMAG. Drug-loaded scaffolds can be used for local drug administration and prevention of post-surgical local lung cancer recurrence.
5.	Elizabeth Graham-Gurysh/2018/USA	In vitro cell lines and in-vivo mouse model	Scaffold: Acetalated dextran (Ace-DEX), polyester, poly(L-lactide) (PLA) Dissolution Drug: doxorubicin (DXR) Cell Lines: Human glioma cell lines U87-MG, LN-18, and LN-229	Group 1: No treatment Group 2: Ace-DEX blank Group 3: Ace DEX/10DXR Group 4: PLA/blank Group 5: PLA/10DXR	Drug release duration: 35 days max. Drug dosage released: Ace-DEX/10DXR and PLA/10DXR released similar amounts of DXR (approximately 50%) over 35 days Steady-state release from Ace-DEX scaffolds is faster than that from PLA, which releases the majority of the DXR within the first 24 hours	Survival rate: Ace-DEX/10DXR statistically better compared to Ace-DEX/blank ($p < 0.005$) and 'no treatment' PLA/10DXR statistically better compared to 'no treatment' control group ($p < 0.05$), but was not significant compared to PLA/blank Progression-free survival rates: Ace-DEX/10DXR statistically better compared to Ace-DEX/blank ($p < 0.01$) and 'no treatment' PLA/10DXR statistically better compared to 'no treatment'	Both PLA/10DXR and DXR loaded scaffolds showed sustained release of DXR over same period of time. Higher and sustained amount of DXR release from Ace-DEX scaffolds led to higher suppression of tumor recurrence and complete remission in 43% of mice.
6.	Ziming Yuan/2016/China	In vitro cell lines and in vivo female mice model	Scaffold: poly (L-lactide) (PLLA) fibrous scaffolds blent Electrospinning with the mesoporous silica nanoparticles (MSNs) Drug: doxorubicin (DOX) Cell Lines: MDA-MB-231	Group 1: untreated Group 2: P-F (Blank) Group 3: P-D-F Group 4: P-M/D-F Group 5: P-M/D-S-F (with sodium bicarbonate)	Drug release duration: 100 days Drug dosage released: Lower initial burst and longer release time of P-M/D-F and P-M/D-S-F compared with P-D-F at neutral pH	In-vitro anti-tumor activity: P-M/D-S-F group had the strongest inhibition on tumor cells Residual tumor tissues: Necrosis of P-M/D-S-F was very remarkable among all the groups Expression of Bcl-2 and Bax: P-M/D-S-F showed higher levels of Bax and lower levels of Bcl-2 compared to all other groups Expression of TNF-α and caspase-3: P-M/D-S-F showed highest levels of TNF-α and caspase-3	P-M/D-S-F can kill the post-surgical residual cancer cells as evidenced by reduced expression of Bcl-2 and TNF-α and a increased expression of Bax and caspase-3.
7.	Qiuxia Ding/2015/China	In-vitro cell lines and in-vivo mice model study	Scaffold: poly-D,L-lactide (PDLLA) Electrospinning Drug: docetaxel(DTX)/4T1 Cell Lines: breast cancer cells	Group 1: control group Group 2: Unloaded film, Group 3: DTX-loaded film Group 4: Local subcutaneous injection of DTX 15mg/kg Group 5: Intraperitoneal injection of DTX	Drug release duration: 24 days Drug dosage released: Approximately 23.3%, 25.3% and 29.6% of DTX was released in 24 days from the 5, 10 and 20 wt% DTX/PDLLA scaffolds, respectively	Cytotoxicity against 4T1: Group 1 and 2: No cytotoxicity Group 3,4 and 5: cell growth inhibition rates of 20%, 34%, and 54%, respectively Locoregional recurrence: Locally administrated DTX/PLA reduced locoregional recurrence after resection of the primary tumor Overall survival was improved in the DTX/PDLLA group compared with all the other groups	Electrospun DTX-loaded PDLLA nanofibers provide prolonged and sufficient cytotoxic drug locally, preventing local tumor recurrence post-surgically
8.	Feng Chai/2014/France	In vitro cell lines	Scaffold: cyclodextrin polymer (polyCD) functionalized hydroxyapatite (HA) admixing and sublimation Drug: Gentamicin and cisplatin Cell Lines: MG63 osteosarcoma cell lines	Group 1: polyCD-HA/cis Group 2: polyCD-HA/dual Group 3: polyCDHA/genta Group 4: polyCD-HA Group 5: HA granules	Drug release duration: 48 hrs Drug dosage released: in different media: 84, 82, and 74% respectively for Cis loaded scaffolds in human blood plasma, in 10% FBS enriched MEM and serum-free MEM	Cell Vitality against osteosarcoma cells: No difference ($p>0.05$) between polyCD-HA/dual and polyCD-HA/cis, both showed strong cytotoxic effect (20%±3%) to MG63 cells HA, polyCD-HA and polyCD-HA/genta showed no toxic effect to MG63 cells with a similar level of cell vitality (95%±4%) to control group	Biodegradable polyCD functionalized HA material can load higher amounts of one or two selected drugs (antimitotic, antibiotic, etc.) which can be gradually released into tumor surroundings maintaining the therapeutic efficacy of drug
9.	Vishal Gupta/2011/USA	In vitro cell lines and in vivo nude rats	Scaffold: Silk Fibroin(SF)- chitosan(CS) lyophilization Drug: Emodin Cell Lines: Breast cancer cell line GILM2	Group 1: SF only Group 2: SF-CS blank scaffolds Group 3: emodin-loaded SFCS scaffold	Drug release duration: 24 days Drug dosage released: SF scaffolds showed highest emodin release as compared to all SFCS blends However, there was no difference in release between various blends of different concentrations of SF and CS.	Cell Viability: SFCS scaffolds significantly decreased the number of viable cells as compared to cells in culture dishes (no SFCS, no emodin, $p<0.01$) and cells exposed to SFCS scaffolds only In vivo response: emodin-loaded SFCS scaffold group showed decreased tumor presence and size Cell Density: The cell density in remodeled SFCS scaffold (3238 ± 152 cells/mm2) was significantly higher ($p<0.05$) than the emodin loaded SFCS scaffold (2733 ± 118 cells/mm2).	Liposomal emodin-loaded 25:75 SFCS scaffold composites provide good mechanical integrity, optimal drug loading and release over time, and reduced breast cancer cell viability in vitro. Scaffolds were effective in reducing tumor presence, scaffold degradation and increasing remodelling and new tissue deposition in vivo.
10.	Jesse B.Wolinsky/2010/United States	In vitro cell lines and in-vivo mouse model	Scaffold: poly(glycerol stearic acid-co-e-caprolactone)PGC-C18/10, poly(glycerol-co-e-caprolactone)PGC-OH adhered to collagen scaffolds (solution, evaporation and adhering) Drug: hydroxycamptothecin HPCT Cell Lines: Lewis lung carcinoma cells	Group 1: PGC-OH unloaded Group 2: HCPT loaded PGC-OH Group 3: Unloaded PGC-C18 Group 4: HCPT loaded PGC-C18	Drug release duration: 7 weeks/ 3 weeks Drug dosage released: PGC-C18 released in a more controlled manner than PGC-OH	Cytotoxic Studies (in-vitro): HCPT loaded PGC-C18 films exhibited significant cytotoxicity for 7 weeks compared to unloaded PGC-C18 In vivo mouse studies: Local tumor growth was suppressed in loaded PGC-C18 compared with unloaded films and intravenous HPCT	HPCT loaded scaffolds help in controlled and sustained release of drug alongwith complete inhibition of tumor at a dose which is three times lesser compared to required intravenous dose
11.	Giulio Alessandri/2019/Italy	In vitro cell lines and In-vivo mice model	Scaffold: human micro-fragmented adipose tissue (MFAT) Drug: Paclitaxel(PTX) Cell Lines: human Pancreatic Adenocarcinoma cell line, human Glioblastoma cell line U87MG and human, wild type and luciferase (Luc) transfected Neuroblastoma (NB) (IMR-32, SHSY5Y, HTLA-230, NB1691) cell lines/ orthotopic animal model of Neuroblastoma (NB)	Group 1: MFAT untreated Group 2: MFAT-PTX Group 3: Devitalised MFAT (DMFAT) untreated Group 4: DMFAT-PTX Group 5: Condition medium of MFAT-PTX and DMFAT-PTX	Drug release duration: Total duration 60 days Drug dosage released: after 1 day, the PTX released by DMFAT-PTX was double (p-EC= 124.8 ±15.59 ng/ml) compared to MFAT-PTX The concentration of PTX derived from DMFAT-PTX was always higher than that released by MFATPTX	Anti-tumor activity: MFAT-PTX, DMFAT-PTX and condition media derived from both resulted in more than 90% of CFPAC-1 growth inhibition. Anticancer activity was also effective against IMR-32 and U87MG, (NB) and (GBM) cell lines Anti-angiogenesis: MFAT-PTX, DMFAT-PTX and condition media derived from both are cytotoxic in all concentrations against Human Umbilical Vein ECs In vivo: local administration of DMFAT-PTX at tumor site after its surgical resection blocked or delay NB relapse	Both MFAT and DMFAT work as natural biological scaffolds and help in efficiently killing cancer cells both in vito and in vivo by absorbing releasing significant amount of PTX
12.	Qian Zhan/2013/China	In vitro cell lines and In vivo female mice	Scaffold: PGA-TMC and porcine gelatin (electrospinning) Drug: Flofirinox Cell Lines: Pancreatic Cancer cells	Group 1: Drug-eluting scaffold Group 2: Non-eluting scaffold Group 3: Non-eluting scaffold/phosphate-buffered solution group in which the cell medium was supplemented with phosphate-buffered solution as a control	Drug release duration: for 3 weeks Drug dosage released: The release of FOLFIRINOX from scaffold could be attributed to the combined effect of physical disintegration and chemical decomposition/	MTT: Proliferation of pancreatic cancer cells on the drug-eluting scaffolds was arrested during the 3-week period of observation Apoptosis assay: Apoptosis of the pancreatic cancer cell populations on the drug-eluting scaffolds escalated through week 3. However, no significant apoptosis was observed in cancer cell populations on either the non-eluting scaffolds or the tissue culture plates during the 3-week study period In vivo tumor volume: Group 1: 302.24 ± 103.59 mm3 Group 2: 434.22 ± 132.98 mm2 Group 3: 951.78 ± 178.21 mm2	The ability to destroy CD133+ and CXCR4+ cells in cancer tissue helped FOLFIRINOX loaded scaffolds in stabilizing tumorigenesis and preventing hepatic metastasis Limitations: heterogeneous distribution of chemotherapeutic agents in fibers and shorter shelf-life of the scaffold
13.	Ceren Kutlu/2014/Turkey	In vitro cell lines	Scaffold: poly-lactic-co-glycolic acid (PLGA)-chitosan (emulsion–diffusion–evaporation) Drug: 5-fluorouracil (5-FU) and bevacizumab Cell Lines: Human Glioblastoma cell line T98G and Human Umbilical vein Endothelial Cells (HUVECs)	Group 1: Chitosan blank scaffold Group 2: Chitosan scaffold loaded with 5-FU-PLGA nanoparticles Group 3: bevacizumab loaded scaffold Group 4: 5-FU- and bevacizumab-loaded scaffold	Drug release duration: 80 days Drug dosage released: Burst release was observed in the first 24h with release of 15% of encapsulated 5-FU. 5-FU has continued in a controlled manner during the following days/	Cell Viability: Group 1 and Group 3: No effect Group 2 and Group 4: Antiproliferative against T98G Anti-angiogenesis: HUVECs are viable in the presence of blank and only bevacizumab-loaded scaffold. In group 2 and 4, 5-FU prevented cell proliferation	Double effective chitosan scaffold containing anticancer and antiangiogenic agent inhibits tumor cells, T98G glioblastomas, by releasing 5-FU, and prevents proliferation of HUVECs, by releasing bevacizumab
14.	Dong Gao/2017/China	In vivo mice	Scaffold: Purine-scaffold TLR7 agonist (GD5) Drug: Doxirubicin Cell Lines: EL4 T cell lymphoma cells injected in a mouse model	Group 1: Control Group 2: DOX intratumoural Group 3: GD5 intratumoural Group 4: GD5 intraperitoneal Group 5: Both GD5 and DOX intratumoural Group 6: DOX intratumoural GD5 intraperitoneal	----------	Survival Time: Mice treated with GD5 have more survival than control or DOX treated groups. Group 5 and 6 significantly improved survival compared with Group 3 and 4 Amongst group 5 and 6: Group 5 showed a notable increase in survival compared with group 6 Systemic antitumor effect: Either Co i.t. or Co i.p. group exhibited improved tumoricidal effectiveness compared with single-drug treatment groups Anti-tumor Immunity in Long-term Surviving Mice: EL4 tumor cells were significantly more sensitive to the effector cells from the drugs administration groups than Ctrl group; but no significant difference among GD5 i.t., GD5 i.p. and Co i.p. groups were observed. Only Co i.t. group and supra three groups have a significant difference	Combination therapy including TLR7 agonist GD5 and conventional drugs, like DOX can enhance antitumor effectiveness by generating strong cytokines and increasing immune response. This will help in eradicating both local and distant tumors enhancing local and systemic immune response
15.	Jacob H. Swet/2013/North Carolina	In-vivo rat model	Scaffold: Silica-calcium-phosphate nanocomposite (SCPC75) (solution and dried) Drug: Cisplatin Cell Lines: A rat model of Hepatocellular Carcinoma (HCC)	Group 1: Control Untreated Group 2: Systemic Cisplatin (sCis) Group 3: Blank SCPC75 placed adjacent to tumor (ADJ-SCPC75) Group 4: Cis-SCPC75 placed adjacent to tumor (ADJ-SCPC75-Cis) Group 5: Blank SCPC75 within tumor mass IT-SCPC75 Group 6: Cis-SCPC75 placed within tumor IT-SCPC75-Cis	Drug release duration: 14 days Drug dosage released: In vivo SCPC75-Cis released 55% of the loaded cisplatin. ADJ-SCPC75-Cis or IT-SCPC75-Cis compared with control show similar serum platinum concentration. sCis-treated animals showed increased levels of platinum compared with all other groups Platinum content in tumor tissue: IT-SCPC75-Cis showed significantly increased intratumoral platinum greater than other treatment groups	Tumor Growth: ADJ-SCPC75-Cis and IT-SCPC75-Cis demonstrated slower tumor growth compared with both control and sCis-treated animals Histological analysis: No detectable necrosis in untreated, control tumors. Small areas of necrotic cell death were detected in animals receiving sCis Significant areas of tissue necrosis were observed in tumors receiving ADJ-SCPC75-Cis or IT-SCPC75-Cis treatment No significant difference was measured between the necrotic area in animals treated with ADJ-SCPC75-Cis and ITSCPC75-Cis	Loocal cisplatin delivery to the tumor mass using SCPC75 nano scaffold helps in overcoming the systemic toxicity of the drug which is associated with daily injection of cisplatin. This also increases the intratumoral drug delivery to inhibit the tumor growth